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3

Final Report on the Safety Assessment of Dioctyl Adipate and Diisopropyl Adipate

Dioctyl Adipate, the diester of octyl alcohol and adipic acid, and Diisopropyl Adipate, the diester of isopropyl alcohol, are used in cosmetics as emollients and bases. These two ingredients have a low acute oral and percutaneous toxicity. Undiluted Dioctyl Adipate and Diisopropyl Adipate were, at most, only very mild, transient eye irritants. Primary dermal irritation tests indicated that Dioctyl Adipate was a very mild irritant and Diisopropyl Adipate was minimally irritating. Dioctyl Adipate was not a skin sensitizer in guinea pigs.

An Ames test for the mutagenic potential of Dioctyl Adipate was negative. An assay of the carcinogenic potential of Dioctyl Adipate produced no untoward effects and was noncarcinogenic to rats. Mice studies indicated a dose-related body weight reduction and a higher incidence of hepatocellular adenoma and carcinoma than controls. In a lifetime study Dioctyl Adipate caused no skin tumors when 10 mg was applied weekly to the back skin of mice. The teratogenicity potential of Dioctyl Adipate is reviewed.

Clinical assessment of Dioctyl Adipate in formulations showed, at most, minimal erythema and papules when applied under occlusion. No UV sensitization occurred. Undiluted Diisopropyl Adipate produced no irritation in 24 h patch tests, but was moderately irritating in a 21-day cumulative irritancy test. Formulations containing up to 20% Diisopropyl Adipate caused minimal to mild irritation, no sensitization and no photosensitization. On the basis of available data, it is concluded that Dioctyl Adipate and Diisopropyl Adipate are safe as presently used in cosmetics.

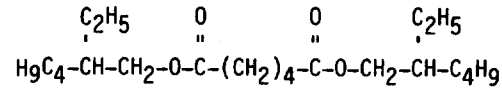
INTRODUCTION

Dioctyl Adipate and Diisopropyl Adipate are common plasticizers and emollient esters. In cosmetics they are used as emollients and as the base of many different types of products.[1-3]

CHEMICAL AND PHYSICAL PROPERTIES

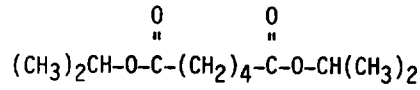
Structure

1. Dioctyl Adipate is the diester of octyl alcohol and adipic acid. It conforms generally to the formula:



CAS Number: 103-23-1
Synonyms include: Di-(2-Ethylhexyl)Adipate and Wickenol 158.[3]

2. Diispropyl Adipate is the diester of isopropyl alcohol and adipic acid. It conforms generally to the formula:



CAS Number 6938-94-9
Other names include:

Beta DIA
Ceraphyl 230
Crodamol DA
Iso-Adipate 2/043700
Prodipate
Schercemol DIA
Standamul DIPA
Tegester 504-D
Wickenol 116.[3]

Production

Dioctyl Adipate is produced by the reaction of adipic acid and 2-ethylhexanol in the presence of an esterification catalyst such as sulfuric acid, p-toluenesulfonic acid or a proprietary catalyst. Purification of the reaction product includes removal of the catalyst, alkali refining and stripping.[4,5] Diisopropyl Adipate is produced by esterification of adipic acid with an excess of isopropanol. The excess alcohol is removed by vacuum stripping and the ester is then alkali-refined and filtered.[6]

Properties

Dioctyl Adipate and Diisopropyl Adipate are clear, colorless to light yellow viscous liquids with an aromatic odor. They are soluble in most organic solvents and insoluble in water. For other properties, see Table 1.

Analytical Methods

Diisopropyl Adipate and Dioctyl Adipate can be identified through standard Infrared (IR) spectroscopy.[7] Gas-liquid chromatography, liquid–liquid extraction, mass spectrometry, and high-pressure liquid chromatography are also methods of analysis for the Adipates.[8-10]

Reactivity/Stability

Dioctyl Adipate and Diisopropyl Adipate are considered stable; however,

TABLE 1. Properties of Dioctyl and Diisopropyl Adipate.

Property	*Dioctyl Adipate*	*Ref.*	*Diisopropyl Adipate*	*Ref.*
Form	Oily liquid	2	Oily liquid	7
Color	Colorless to light yellow	2,4	Colorless, clear	7
Boiling point (°C)	417	2	—	—
Specific gravity (20/20°C)	0.9268	2	0.950 to 0.965	7
Flash point, °C, (°F)	204.4 (400)	11	—	—
Melting point (°C)	−67.8	4	—	—
Molecular weight	370.56	11	230.34	4
Refractive index at 20°C	1.4474	11	1.4200–1.4245	7
Acid value	1.0 (max.)	5	2.0 (max.)	7
Saponification value	298–308	5	465–500	7
Iodine value	0.5 (max.)	5	1.0 (max.)	5
Viscosity (20°C)	13.7 cps	—	—	—
Vapor pressure σ 200°C	2.4 mm Hg	—	—	—
Soluble in:	Alcohol	4	—	—
Ether				
Acetone				
Acetic acid				
Most organic solvents				
Insoluble in:	Water	2,4	—	—
Glycerin and glycols				

hydrolysis of the ester groupings may occur in the presence of aqueous acids or bases.[5,6]

Impurities

No known minor impurities occur in either Dioctyl Adipate or Diisopropyl Adipate, although the acid values imply the presence of adipic acid or of the monoester in both.[5,6]

USE

Non-Cosmetic Uses

The Adipates are used primarily as plasticizers in food wraps, vinyl blood bags and hemodialysis bags. Adipates are also used as solvents and aircraft lubes.[1,2,4,12,13] Dioctyl Adipate has Indirect Food Additive (IFA) Status for use in food wrapping.[14]

Cosmetic Use

The Adipates are used as components of cosmetic bases and as solvents and emollients in other cream-type skin preparations.[1] They are also used to modify the tactile and flow properties of emollient blends, especially in bath products.[15]

The cosmetic product formulation computer printout which is made available by the Food and Drug Administration (FDA) is compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of

Federal Regulations.[14] Ingredients are listed in prescribed concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the true, actual concentration found in the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA. Since data are submitted only within the framework of preset concentration ranges; this presents the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus, introducing the possibility of a two- to 10-fold error in the assumed ingredient concentration.

According to the industry's 1981 submission of product formulation data to the FDA, Dioctyl Adipate was used in 27 products in concentrations of ≤ 0.1%–1% in some facial makeup, and up to 10%–25% in bath preparations[16] (see Table 2).

Diisopropyl Adipate was used in 112 cosmetic formulations according to the 1981 FDA product formulation data. Its concentrations of use ranged from less than 0.1% up to 25%[16] (see Table 2).

Surfaces to Which Commonly Applied and Frequency of Application

Dioctyl and Diisopropyl Adipates are found in cosmetics which may come in contact with the skin of the face, hands, and the general body surface, the mucous membranes, nails, scalp, and hair. Thus, cosmetics containing Adipates may be applied to the body once every few days to several times daily[16] (see Table 2).

TABLE 2. Product Formulation Data.[a]

Product category[b]	*Total no. containing ingredient*	*No. of product formulations within each concentration range (%)*[b]				
		>10–25	*>5–10*	*>1–5*	*>0.1–1*	*≤0.1*
Dioctyl Adipate						
Bath oils, tablets, and salts	4	4	—	—	—	—
Colognes and toilet waters	6	—	—	6	—	—
Blushers (all types)	1	—	—	—	—	1
Makeup foundations	4	—	2	1	1	—
Lipstick	5	—	—	5	—	—
Other makeup preparations (not eye)	1	—	—	1	—	—
Nail polish and enamel remover	2	—	—	2	—	—
Deodorants (underarm)	1	—	—	—	1	—
Aftershave lotions	1	—	—	1	—	—
Face, body, and hand skin care preparations (excluding shaving preparations)	1	—	—	1	—	—
Other suntan preparations	1	—	—	—	1	—
1981 TOTALS	27	4	2	17	3	1

TABLE 2. (Continued.)

Product category[b]	Total no. containing ingredient	No. of product formulations within each concentration range (%)[b]				
		>10–25	>5–10	>1–5	>0.1–1	≤0.1
Diisopropyl Adipate						
Bath oils, tablets, and salts	7	5	1	1	—	—
Bubble baths	1	—	—	1	—	—
Eyeliner	1	—	—	1	—	—
Eye shadow	1	1	—	—	—	—
Colognes and toilet waters	15	—	—	12	3	—
Perfumes	20	3	13	4	—	—
Sachets	1	1	—	—	—	—
Other fragrance preparations	9	1	1	6	1	—
Hair conditioners	3	—	—	—	1	2
Hair sprays (aerosol fixatives)	1	—	—	1	—	—
Tonics, dressings, and other hair grooming aids	4	—	—	4	—	—
Wave sets	2	—	—	1	1	—
Blushers (all types)	1	—	—	1	—	—
Face powders	1	—	—	1	—	—
Makeup foundations	1	—	—	—	1	—
Other personal cleanliness products	1	—	—	—	1	—
Aftershave lotions	16	—	—	9	7	—
Preshave lotions (all types)	1	—	1	—	—	—
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	5	—	—	—	5	—
Foot powders and sprays	1	—	—	—	1	—
Moisturizing skin care preparations	2	—	—	1	1	—
Night skin care preparations	1	—	1	—	—	—
Skin fresheners	11	—	3	—	6	2
Other skin care preparations	2	—	1	1	—	—
Suntan gels, creams, and liquids	2	—	2	—	—	—
Indoor tanning preparations	2	—	—	2	—	—
1981 TOTALS	112	11	23	46	28	4

[a] Data from Ref. 16.

[b] Preset product categories and concentration ranges in accordance with federal filing regulations (21 CFR 720.4).

BIOLOGICAL PROPERTIES

General Studies

Subcellular and Enzyme Effects

Dioctyl Adipate was fed to male rats in a dietary concentration of 2% for three weeks. Effects included hepatic peroxisome proliferation, increased size of the liver, and increase in the hepatic activities of the peroxisome-associated enzymes catalase and carnitine acetyl transferase. Hypolipidemia and a decrease

in serum lipids were also observed in Dioctyl Adipate-treated animals. The authors postulated that the active portion of the compound, in the induction of hepatic peroxisome proliferation, may be the metabolite 2-ethylhexyl alcohol.[17]

Effect on Cultured Cells

When contracting chick embryo heart cells were maintained in tissue culture and exposed to Dioctyl Adipate at a level of 1.5 μg/ml (4 μm), the number of cardiac contracting cells was reduced to 50% of control levels.[18] In cultures of human diploid cells of the WI38 strain, the ID_{50} (dose that inhibits cell growth to 50% of the control culture) for Dioctyl Adipate was 32 μM.[19]

Animal Toxicology

Acute Toxicity

Oral

Dioctyl Adipate was administered by gavage to nine groups of five male and five female F344 rats at doses of 0.08, 0.16, 0.31, 0.63, 1.25, 2.5, 5.0, 10, or 20 g/kg of the substance in corn oil. Two of five males of the 10 g/kg group died and one male and one female of the 20 g/kg group died.[20]

Five groups of five male and five female mice were given Dioctyl Adipate in corn oil in single doses of 1.25, 2.5, 5.0, 10.0, or 20.0 g/kg. Mortality observations were: one male of the 1.25 g/kg group died "accidentally," two males of the 10.0 g/kg group, three at the 20.0 g/kg group, one female of the 20 g/kg group. The estimated LD_{50} for male mice was 15.0 g/kg, and for females it was 24.6 g/kg.[20]

In an acute oral toxicity study using rats, Andreeva[21] reported a no effect dose of Dioctyl Adipate in rats of 6 g/kg. Doses greater than this resulted in central nervous system (CNS) stimulation followed by depression which lasted for the five- to seven-day observation period.

The single oral toxic dose of Dioctyl Adipate for the rat over an observation period of 14 days was 9.11 g/kg.[22]

A group of five male and five female albino rats was fasted overnight, intubated with a dose of 7.4 g/kg Dioctyl Adipate, and then observed daily for 14 days. One animal died on Day 14, but other observations were not recorded.[23]

A product containing 0.175% Dioctyl Adipate was administered in a single undiluted 6.5 g/kg dose to five male and five female Harlan Wistar rats. During the seven observation days, no signs of toxicity were observed and body weight gains were normal.[24]

A face cream containing 0.7% Diisopropyl Adipate was intubated into groups of five male and five female Wistar rats per dose concentration. Animals were observed for 14 days; one male rat of the highest dose group (76.8 g/kg of the formulation) died on Day 4 of observation. At necropsy of this animal, the findings included urinary staining of the abdomen, prominent serosal blood vessels in the stomach, cecum and intestines, and red fluid in the intestines. No other deaths or abnormal findings were reported.[25]

A perfume containing 1.08% Diisopropyl Adipate was administered in a single 5 g/kg dose of the preparation to five male and five female Sprague–Dawley rats. The animals were observed for 14 days; one female died on Day 2.

Necropsy findings of this animal were dark and mottled lungs and liver, reddened pylorus, and gas-filled GI tract. Other surviving animals showed signs of decreased activity, ataxia, diarrhea, gasping, and urinary incontinence.[26]

In a similar study a perfume containing 1.08% Diisopropyl Adipate was studied. Five male and five female Sprague–Dawley rats were given by oral intubation a single 5 g/kg dose of the formulation; animals were observed for 14 days. No animals died, but three males and five females had decreased activity and ataxia.[27]

A product containing 5% Diisopropyl Adipate was administered as a single 5 g/kg dose of the formulation by intubation to five female albino rats; the animals were observed for seven days. No deaths or abnormal behavior were observed.[28]

A dose of 15 g/kg of a product containing 20.75% Diisopropyl Adipate was administered orally by stomach tube to five female rats. After seven observation days, no deaths or abnormal responses were observed and the LD_{50} was >15 g/kg dose[29] (see Table 3).

14-day oral study

A 14-day repeated dose study of Dioctyl Adipate was conducted using six groups of five male and five female F344 rats and of the same number of B6C3F1 mice. Dosages of 0 (control), 3,100, 6,300, 12,500, 25,000, and 50,000 ppm in the diet were fed to male rats and mice for 14 days. Female rats and mice were fed 0 (control), 6,300, 12,500, 25,000, 50,000, and 100,000 ppm Dioctyl Adipate in the diet. Weight gain was depressed in male rats fed 50,000 ppm and in female rats fed 25,000 ppm or more. Females fed 100,000 ppm lost weight and one died. All female mice receiving 100,000 ppm died, and males at 50,000 ppm and females at 25,000 or more lost weight.[20]

Intravenous

The intravenous LD_{50} of Dioctyl Adipate to rats and rabbits was 900 mg/kg and 540 mg/kg, respectively.[30]

The acute intravenous LD_{50} of Diisopropyl Adipate to rats was 640 mg/kg.[30]

Percutaneous

The acute dermal toxicity of Dioctyl Adipate was tested using eight albino rabbits. The trunk of each animal was clipped of all hair and half of the rabbits received longitudinal epidermal abrasions over the clipped area. The rabbits were immobilized and plastic sleeves were slipped over the shaved areas. The animals were placed into groups of two each and received doses of 0 (control), 3.6, 5.6, and 8.7 g/kg of pure Dioctyl Adipate under the sleeve. After 24 h, the sleeves were removed, the volume of unabsorbed material was cleaned from each animal and measured, and skin reactions were evaluated. The animals were observed for signs of toxicity for two weeks. Daily observation included body weights, food consumption, and behavior. Urinalysis, hematologic features, and skin changes were also observed and skin changes were rated according to standard Draize scores. The animals had only slight erythema which increased in duration with increasing concentration. However, all irritation disappeared several days before the end of the observation period. Weight gain, feed consumption, urine and hematologic values, as well as behavior were normal in all animals. Dioctyl Adipate produced mild irritation, but no systemic toxic effects.[23]

TABLE 3. Acute Oral Toxicity.

Ingredient	*Species and No. of Animals*	*Ing. Conc. (%)*	*Dose/kg*	*LD_{50}/kg*	*Observation period*	*Comments*	*Ref.*
Dioctyl Adipate							
Ingredient	F344 rats 45 male, 45 female	—	0.08–20.0 g	45.0 g for males[a] 26.0 g for females[a]	14 days	2 of 5 males died in the 10 g/kg dose group; 1 of 5 males and 1 of 5 females died in the 20 g/kg dose group.	20
	B6C3F1 mice 25 male, 25 female	—	1.25–20.0 g	15.0 g for males[a] 24.6 g for females[a]	15 days	2 of 5 males died in the 10 g/kg dose group; 3 males and 1 of 5 females died in the 20 g/kg group.	20
	rats	—	6 g	—	7 days	6 g/kg = "No effect level." Greater doses cause CNS disturbance.	21
	5 male rats	—	—	9.11 g (7.28–11.4)	14 days	—	22
	5 male, 5 female rats	—	7.4 g	—	14 days	One animal died on Day 14.	23
Formulation	5 male, 5 female Wistar rats	(0.175)	6.5 g	—	7 days	No signs of toxicity; weight gains normal.	24
Diisopropyl Adipate							
Formulation	5 male, 5 female Wistar albino rats per dosage	0.7	up to 76.8 g	—	14 days	One male rat at the 80 ml/kg level died on Day 4 of observation.	25
	5 male, 5 female Sprague–Dawley rats	1.08	5.0 g	—	14 days	On Day 2 of observation, one animal died. Necropsy showed red, mottled lungs and liver, gas-filled G.I. tract.	26
	5 male, 5 female Sprague–Dawley rats	1.08	5.0 g	—	14 days	3 males and 5 females showed decreased activity and ataxia. No deaths.	27
	5 female albino rats	5.0	15.0 g	—	7 days	No deaths occurred and all animals appeared normal.	28
	5 female albino rats	20.75	15.0 g	—	7 days	No deaths occurred and all animals appeared normal.	29

[a] Extrapolated by author.

Immersion test

A product containing 20.75% Diisopropyl Adipate was tested for dermal irritation and percutaneous toxicity in a whole-body immersion test using six albino guinea pigs. The product was diluted to 0.5% w/v with water so that the actual concentration of the Adipate was 0.10%. The animals were clipped of all abdominal hair and placed in restraining cylinders. The lower parts of the body were immersed in the 37°C test solution for 4 h per day for three consecutive days. Forty-eight hours after the last exposure, the skin of the abdomen was graded according to a scale from 10 (normal) to 1 (moribund as determined by skin injuries). Clinical signs were recorded daily, and products with a score less than seven are considered potential irritants. On observation, four animals were normal (score = 10) and two had a "first hint of scaling" (score = 9). There were no signs of systemic toxicity and the degree of skin irritation was considered minimal.[31]

Ocular

Undiluted Dioctyl Adipate (0.1 ml) was instilled into one eye of each of six albino rabbits. The untreated eye served as control. The eyes were graded at 24, 48, and 72 h on a scale of 0 (normal) to 4 (corneal opacity, iridial destruction, red conjunctivae, and swelling). No irritation (all scores = 0) was found at any of the observation periods.[23]

Each of six albino rabbits was treated in one eye with 0.1 ml of a cosmetic moisturizer containing 0.175% Dioctyl Adipate. The animals were observed up to seven days following instillation. After 1 h, slight conjunctival redness was observed, but it had disappeared after 24 h. No other effects were noted.[24]

A 0.1 ml sample of a rouge product containing 0.01% Dioctyl Adipate was instilled into one eye of each of six albino rabbits. The untreated eye served as the control and all eyes were graded after 24, 48, and 72 h. This product produced no conjunctival redness or chemosis, keratitis, or iritis and it was considered nonirritating.[32]

Two lots of undiluted Diisopropyl Adipate were tested for ocular irritation using six albino rabbits per lot. One eye of each animal received 0.1 ml of the ingredient and examinations for irritation were made daily until all scores were negative or up to seven days. One lot caused neligible irritation on Day 1, which disappeared by Day 2. No irritation was caused by the second lot.[33]

A face cream formulation containing 0.7% Diisopropyl Adipate was tested on nine albino rabbits for ocular irritation. One-tenth milliliter of the undiluted test material was placed in one eye of each animal; the other eye served as the control. Thirty seconds after instillation, the treated eyes of three rabbits were rinsed with 20 ml of deionized water. Observations for ocular reactions were made at 24, 48, and 72 h, and four and seven days after administration. In rabbits with unwashed eyes, two had conjunctival redness for 72 h and one had some presence of corneal stippling for 48 h. No other reactions were noted. The washed eyes of two rabbits had some corneal stippling up to Day 4; no other reactions were noted.[34]

Two products, one containing 5.0% Diisopropyl Adipate and one containing 20.75%, were each tested for ocular irritation using six albino rabbits. The products were instilled into one eye of each animal; the untreated eye served as the control. Observations were made until all eyes were negative for up to seven

days. The 5.0% product produced minimal irritation (score = 6 out of 110) on Day 1 and the irritation had disappeared by Day 2.[35] The second product produced minimal irritation (score = 2 out of 110) on Day 1 and the irritation had disappeared by Day 2[36] (see Table 4).

Primary skin irritation

The primary cutaneous irritation of undiluted Dioctyl Adipate was studied using six albino rabbits. An intact and an abraded site on each rabbit received 0.5 ml of the Adipate under an occluded patch. After 24 h of exposure, the patches were removed and the sites evaluated for irritation according to the Draize method. A second observation was made 48 h after patch removal. Only very slight, barely perceptible erythema was observed in all animals at 24 h. After 72 h, the irritation had decreased in severity in all animals and had disappeared in one. The Primary Irritation Index (PII) was 0.83, indicating that Dioctyl Adipate was a very mild irritant.[23]

The primary skin irritation of a moisturizing cream containing 0.175% Dioctyl Adipate was tested using three albino rabbits. The formulation was applied in four single daily 0.5 ml applications to the shaved backs of the animals and observations were made for seven days. After 24 h, slight erythema was observed which persisted throughout the seven-day period. One animal had well defined erythema with edema, and mild desquamation was seen on day seven. The irritation index was 1.6.[24]

The primary skin irritation of three lots of Diisopropyl Adipate was investigated according to the Draize method. In each experiment, 0.1 ml of the undiluted product was applied under occlusion to the clipped back skin of nine albino rabbits. After 24 h of contact, the dressing was removed and the sites scored on a Primary Skin Irritation (PSI) scale of 0 (no effect) to 4 (severe erythema with or without edema). The PII was the average score of the total number of test subjects. The first lot had a PII of 1.6 and the second, 1.3. These scores indicated that the material was a mild irritant.[37] The third lot caused no irritation in eight rabbits and only barely perceptible erythema in one. The PII score of 0.06 indicated that this compound was minimally irritating.[38]

Two products containing Diisopropyl Adipate at 5.0% and 20.75% were tested by the Draize technique. The undiluted product (0.1 ml) was applied under occlusion to the shaved skin of nine albino rabbits for 24 h. Observations were made 24 and 72 h after contact. The product with 5.0% Diisopropyl Adipate had a PII of 0.33, indicating that the product was minimally irritating.[39] The product with 20.75% Diisopropyl Adipate had a PII of 0.11 and was minimally irritating[40] (see Table 5).

Sensitization

The skin sensitizing potential of Dioctyl Adipate was studied using 10 white male guinea pigs. An area on the backs and flanks, clipped free from hair, was injected intracutaneously with 0.1% Dioctyl Adipate in olive oil. Injections were made every other day, three times weekly, until 10 had been given. The first injection was 0.05 ml and all subsequent ones were 0.1 ml each. Two weeks after the last injection, a challenge dose of 0.05 ml was injected. Observations were made 24 h after each injection as to area, height, and color of reaction. The retest or challenge injection reaction was compared with an average of the scores taken after the original 10 doses. The area and height of the retest area was

TABLE 4. Ocular Irritation.

Ingredient	Species and no. of animals	Conc. (%)	Applied amount (ml)	Observation period	Irritation score Max. score	Comments	Ref.
Dioctyl Adipate							
Ingredient	6 albino rabbits	100	0.1	72 h	0/4	Nonirritating to rabbit eyes.	23
Formulation	6 albino rabbits	0.175	0.1	7 days	—	Slight conjunctival redness after 1 h; cleared after 24 h.	24
Formulation	6 albino rabbits	0.01	0.1	72 h	—	No irritation.	32
Diisopropyl Adipate							
Ingredient							
Lot 75	6 albino rabbits	100	0.1	72 h	1/110	Negligibly irritating on Day 1. Irritation disappeared on Day 2.	33
Lot 76	6 albino rabbits	100	0.1	72 h	0/110	Nonirritating.	33
Formulation	9 albino rabbits (6 unwashed eyes) (3 washed eyes)	0.7	0.1	7 days	—	Unwashed eyes; 2 showed conjunctival redness for 72 h, 1 had corneal stippling for 48 h. Washed eyes; 2 showed corneal stippling to Day 4.	34
	6 albino rabbits	5.0	0.1	2 days	6/110	Minimal irritation occurred on Day 1 and disappeared on Day 2.	35
	6 albino rabbits	20.75	0.1	2 days	2/110	Minimal irritation occurred on Day 1 and disappeared on Day 2.	36

TABLE 5. Primary Dermal Irritation.

Ingredient	Ingr. Conc. (%)	Applied amount (ml)	Species and no. of animals	Time		PII/Max.	Comments	Ref.
				Contact	Observ.			
Dioctyl Adipate								
Ingredient	100	0.5	6 albino rabbits	24 h	48 h	0.83/8.0	Very slight, barely perceptible erythema in all animals.	23
Product-moisturizer	0.175	0.5	3 albino rabbits	4 days	7 days	1.6/4.0	After 24 h, slight erythema persisting to Day 7 with desquamation.	24
Diisopropyl Adipate								
Ingredient	100	0.1	9 albino rabbits	24 h	—	1.6/4.0	Mild irritant.	37
	100	0.1	9 albino rabbits	24 h	—	1.3/4.0	Mild irritant.	37
	100	0.1	9 albino rabbits	24 h	—	0.06/4.0	Minimally irritating.	38
Products	5.0	0.1	9 albino rabbits	24 h	72 h	0.33/4.0	Minimally irritating.	39
	20.75	0.1	9 albino rabbits	24 h	72 h	0.11/4.0	Minimally irritating.	40

smaller and lower than the average induction reactions; therefore, Dioctyl Adipate was not a sensitizer.[23]

Phototoxicity

Primary dermal phototoxic irritation studies were conducted on two perfumes both containing 1.1% Diisopropyl Adipate. Four male and three female New Zealand white rabbits were clipped of all back hair and 200 mg of the undiluted product was applied to gauze patches which were then affixed to the shaved areas. Six patches were applied to the back of each test rabbit and one rabbit received two positive control patches. After a 2 h exposure, the patches on the right-hand side of each animal were removed and the skin irradiated for 15 min with four F40BLB bulbs (wavelength of 320–420 nm, peaking at approximately 360 nm), 24 in from the skin. The left-hand side was not irradiated. The patches were replaced on the right side and sealed with an occlusive wrap. All patches were removed 48 h after the initial application and 1 h after removal, sites were scored according to the Draize criteria. Scores were again recorded 72 and 96 h postdose. Both perfumes scored 0 (no irritation) for primary dermal irritation as well as primary dermal phototoxic irritation.[41,42]

Mucous membrane irritation

Six female albino rabbits were used to test the mucous membrane irritancy of a product containing 0.175% Dioctyl Adipate. The animals were given a single 0.1 ml topical application of the product to the genital mucosa. During the seven-day observation period, no irritation was noted.[24]

Subchronic Toxicity

Oral

Diets containing 0, 1,600, 3,100, 6,300, 12,500, or 25,000 ppm Dioctyl Adipate were fed for 13 weeks to six groups of ten F344 rats and ten B6C3F1 mice of both sexes. Observations were made twice daily and animals were weighed weekly. After 91 days, all survivors were sacrificed, necropsy was performed, and tissues were examined histopathologically. Weight gain was depressed for male rats at the 12,500 and 25,000 ppm dosage levels. No other compound-related abnormalities were found. Weight gain depression occurred in male mice fed 3,100 ppm or more and in female mice fed 6,000 or 25,000 ppm. No other compound-related abnormalities occurred.[20]

Chronic Toxicity

Oral

Intragastric doses of Dioctyl Adipate of 0.4, 1.0 or 2.0 g/kg given for six months to rats caused no enzymatic changes, but did increase the level of sulphydryl compounds in the blood. Hepatic detoxification appeared depressed at the onset of the study, but it was accelerated after six months. Administration of 0.1 g/kg for 10 months decreased CNS excitability.[21] (See Carcinogenesis Section of this report for additional chronic test results.)[20]

Special Studies

Mutagenesis

Dioctyl Adipate (5 mg/plate or the dose which gave a toxic response, whichever was lower), was tested in the Ames *Salmonella*/microsome assay. The compound was nonmutagenic when *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 were exposed to the chemical with and without metabolic activation systems from rat livers.[43]

Carcinogenesis

Oral administration

Groups of 50 male and 50 female F344 rats and 50 male and 50 female B6C3F1 mice were fed diets containing 12,000 or 25,000 ppm Dioctyl Adipate for 103 weeks. Fifty untreated rats and mice of both sexes were used as controls, and all surviving animals were sacrificed at 104–107 weeks. In rats, mean body weights of the 25,000 ppm group were lower than those of the controls. Males had survival rates of 68% in both the control and low-dose (12,000 ppm) group and 80% in the high-dosed (25,000 ppm) group. In females, 58% of controls, 78% of the low-dose group, and 88% of the high-dose group survived the study. Neoplastic and nonneoplastic lesions were seen with equal frequency in treated and control groups and none appeared related to administration of the compound. Dioctyl Adipate was not carcinogenic in F344 rats.[20]

In the prechronic studies a dose level of 12,500 ppm and 25,000 ppm caused a weight change in male mice, relative to controls, of minus 15% and minus 25%, respectively. In female mice, the same low and high dose concentrations caused a plus 5.6% and minus 13% weight loss, respectively. In three of these four dose concentrations, the weight loss exceeded the criteria for selecting the Maximum Tolerated Dose.[44]

In treated mice, mean body weights of either sex were lower than those of controls. Males had survival rates of 72% in controls, 64% in the low-dose group, and 82% in the high-dose group. In females, 84% of controls, 78% of the low-dose group, and 73% of the high-dose group survived. Incidence of hepatocellular adenomas in male mice were dose-related and statistically significant in the high-dose group. The incidence of hepatocellular carcinomas in male mice was higher in dosed groups, but was not statistically significantly increased. In female mice, there was a significant, dose-related trend and significantly higher incidence of hepatocellular adenomas or carcinomas in each of the dosed groups than in the control group (see Table 6). Since hepatocellular tumors were induced in this bioassay, Dioctyl Adipate was considered carcinogenic in B6C3F1 mice.[20]

Hodge and associates[45] fed rats a diet containing 0%, 0.1%, 0.5%, or 2.5% Dioctyl Adipate for two years. A total of 33 tumors were found which were mainly lymphomas and adenomas; one fibroma occurred. Also two carcinomas of the mammary gland and one carcinoma of the kidney were found, but the incidence of these tumors was not different from controls and not related to dietary treatment. They concluded the compound was not carcinogenic.

No tumors were found when dogs were maintained for one year on diets containing 0%, 0.07%, 0.15%, or 0.2% Dioctyl Adipate.[45]

TABLE 6. Hepatocellular Tumors in Mice.[a]

Tumor	Dose (ppm)	Time to First observed tumor (weeks)		Incidence (%)	
		F	M	F	M
Adenoma	0	106	46	4	12
	12,000	103	37	10	16
	25,000	84	101	12	31
Carcinoma	0	106	86	2	14
	12,000	85	68	28	24
	25,000	79	65	24	24

[a] Data from Ref. 20.

Subcutaneous and skin application

Dioctyl Adipate was included in a study which tested the carcinogenic potency of six chemicals by subcutaneous implantation and by repeated skin application. Three compounds, aminotriazole, Aramite [2-(p-tert-butylphenoxy) isopropyl 2-chloroethyl oulfite] and Flectol H (a polymer of 1,2,dihydro-2, 2,4-trimethylquinoline) were chosen as carcinogens or suspected carcinogens. Two additional reported noncarcinogenic compounds, butylated hydroxyanisole and dioctyl adipate, were included in the study. Groups of 50 male and 50 female C3H/AnF strain mice were used for each chemical and for each dosing method and dose concentration. A single 10 mg subcutaneous injection dose was used for one group of animals. A weekly application of either 0.1 or 10 mg of each chemical in acetone was applied for life to the clipped skin of the back in two separate groups of animals. All animals were observed for life. No significant adverse treatment-related effects were reported, nor were any of the compounds tested considered to be carcinogenic by the test methods used. The authors concluded that methods used are not substitutes for tests by other routes of administration.[45]

Teratogenesis/Dominant Lethal Study

Dioctyl Adipate was injected i.p. to each of 10 male albino Swiss strain mice at doses of 0.47, 0.93, 4.7, or 9.3 g/kg. Two groups of controls were injected with distilled water. Immediately after injection, two virgin female mice were caged with each male mouse. Females were replaced weekly for eight weeks. Pregnant mice were sacrificed on Day 15 (± 2) of gestation and necropsy was performed to determine the number of corpora lutea, implantations, preimplantation losses, early and late fetal deaths, and viable fetuses. The antifertility effect was considered a function of the reduction in the number of pregnancies; the dominant lethal mutation was determined directly from the number of early fetal deaths in individual females and indirectly from the number of implantations. The results indicated no compound-related changes in the incidence of late fetal deaths. The 10 ml/kg dose of Dioctyl Adipate reduced the number of pregnancies, but the lower doses had values comparable to controls. The compound caused a dose-dependent and time-dependent decrease in implants per pregnancy, and there was a dose-related increase in early fetal death, a direct measure of dominant lethal mutation. A dose- and time-related decrease in the number of live fetuses

TABLE 7. Embryonic-Fetal Toxicity of Dioctyl Adipate on Rat Fetuses.[a,b]

Treatment groups	Dose injected (g/kg)	Number of corpora lutea	Number of resorptions (percent)	Dead fetuses	Live fetuses (percent)	Mean weight of fetuses (g)[c]
Blunt needle (injection)	—	69	4(6.0)	0	63 (94.0)	3.91 ± 0.02
Distilled water	10.00	59	4(6.8)	0	55 (93.2)	4.40 ± 0.33
Normal saline Control	10.00	62	7(11.5)	0	54 (88.5)	4.10 ± 0.13
Cottonseed oil	9.2	71	5(7.5)	0	62 (92.5)	3.89 ± 0.09
Di-2-ethylhexyl adipate	0.93	62	3(5.3)	0	54 (94.7)	3.90 ± 0.09
	4.7	65	2(3.1)	0	63 (96.9)	3.83 ± 0.03[d]
	9.3	60	4(7.0)	0	53 (93.0)	3.49 ± 0.14[d]

[a] Data from Ref. 48.
[b] Five pregnant female rats were injected in each group on Days 5, 10, and 15 of pregnancy.
[c] Numbers represent the average values (g) ± the standard error of the mean for each group.
[d] $p \leq 0.05$.

occurred in groups treated with Dioctyl Adipate. The authors concluded that the mutational effects occurred mainly during the postmeiotic stage of spermatogenesis.[46] A comment received on this study questioned the author's conclusions, noting that additional data on the number of pregnancies per treated male were required. It was also suggested the number of corpora lutea was necessary if one is to determine whether the differences in implantations per pregnancy are associated with male infertility or are a dominant lethal effect. The comment also stressed the need for historical control data on the test species, as well as the need to have included a positive control in the experiment.[47]

Singh et al.[48] studied the embryonic-fetal toxicity and teratogenic effect of Dioctyl Adipate in rats. The compound was administered i.p. at 0.93, 4.7, and 9.3 g/kg to pregnant rats on the 5th, 10th, and 15th days of gestation. The diluents at each dose level were water, saline and cottonseed oil, respectively. Animals were sacrificed on Day 20. Resorption rates were 5.3%, 3.1%, and 7.0% for each increasing dose; each control had similar or greater rates (Tables 7 and 8). One

TABLE 8. Gross, Skeletal, and Visceral Malformations.[a]

Treatment groups	Dose injected (g/kg)	Resorptions[b] (%)	Abnormalities Gross[c]	skeletal[d]	Visceral[e]
Blunt needle (injection)	—	4(6.0)	0	1(3.0%)	0
Distilled Water	10.00	4(6.8)	0	0	—
Normal saline	10.00	7(11.5)	1(1.9%)	4(14.3%)	—
Cottonseed oil	10.00	5(7.5)	1(1.6%)	2(6.3%)	0
Di-2-ethylhexyl adipate	0.93	3(5.3)	0	1(3.6%)	0
	4.7	2(3.1)	1(1.6%)	3(9.4%)	1(3.2%)
	9.3	4(7.0)	2(3.8%)[f]	2(7.1%)	1(4.0%)

[a] Data from Ref. 48.
[b] Percent resorptions are based on total number of resorptions and dead and live fetuses.
[c] Percent gross abnormalities are based on total number of fetuses.
[d] Percent skeletal abnormalities are based on total number of stained fetuses (50% of total fetuses).
[e] Percent visceral abnormalities are based on total number of unstained fetuses.
[f] Values greater than the 95% confidence interval of the "pooled volume control."

malformed fetus occurred at the 4.7 g/kg dose and two at the 9.3 g/kg dose. The equivalent control had one abnormality. Skeletal abnormalities occurred at rates of 3.6%, 9.4%, and 7.1% as compared with 6.3% in the control. Visceral abnormalities of 0%, 3.2%, and 4.0% were observed for each increasing dose. No similar results were seen in the control. The investigator concluded that Dioctyl Adipate depressed the mean body weight of the developing fetus. Further, there was a significant increase of gross fetal abnormalities in the high-dose group as compared with the pooled controls. However, the available data did not indicate teratogenic effect when the same results were compared to control groups for each dose concentration. The lack of data on historical controls, and the failure to include a positive control in the study, make it difficult to accept the validity of the statistical procedures used and the conclusions made by the investigator.

Clinical Assessment of Safety

Dioctyl Adipate

Patch tests

A Schwartz–Peck prophetic patch test was used to assess the irritation and sensitization potential of a rouge product containing 0.01% Dioctyl Adipate. A 48 h patch impregnated with the formulation was applied under occlusion to the cleansed upper backs of 100 panelists. Simultaneously, an open patch was affixed for 48 h to the inside of the right upper arm and after the allotted time, the sites were scored. After a 14-day rest, a second open and closed insult was applied and graded 48 h later. The sites on the backs were then irradiated for 1 min at a distance of 12 in with a UV source (Hanovia Tanette Mark I Lamp) at a wavelength of 360 nm. These sites were read 48 h after irradiation. Two of the 100 subjects had a weak erythematous reaction at the open patch site after the first patch and one individual had a strong edematous or vesicular reaction after the second open patch. No reactions occurred after the UV exposure. The investigators concluded the product was nonirritating, nonsensitizing and nonphotosensitizing.[49]

A Shelanski and Shelanski repeated insult patch test was conducted on the same rouge product discussed above. A series of 10 successive 24 h open and closed patches was applied to the skin of 49 panelists and each site was graded after patch removal. After a two- to three-week rest, an 11th challenge patch was applied for 48 h and read after patch removal. Ultraviolet light sensitization was evaluated after removal of patch numbers 1, 4, 7, 10, and 11 by irradiating the sites for 1 min at a distance of 12 in with a Hanovia Tanette Mark I Lamp. No photosensitivity was indicated by this test, but weak reactions were produced in three, one, and four panelists, after the fourth, fifth, and tenth open patch exposures, respectively. Strong reactions occurred in one panelist after the sixth open patch, and in another after the 11th (challenge) open patch.[49]

A liquid makeup product containing 9.0% Dioctyl Adipate was assayed in a Modified Draize–Shelanski patch test on 209 men and women. The undiluted product was applied under occlusion to sites on the upper back on Monday, Wednesday, and Friday for three consecutive weeks. Patches were removed and sites scored on the next patch replacement day. After a two-week rest, two consecutive 48 h challenge patches were applied to adjacent sites on the back and these areas were scored 48 and 96 h after application. Three subjects had moderate to strong erythematous reactions, with or without infiltration and

vesicles, and one subject had a macular faint erythema over 25% of the test area after the second challenge.[50]

Another makeup product containing 9.0% Dioctyl Adipate was tested as above in a Modified Draize–Shelanski patch test. The product caused irritant reactions in two of the 151 men and women tested, but no significant sensitization or primary irritation occurred.[51]

A Shelanski–Jordan repeated insult procedure was used to evaluate primary irritation and allergic sensitivity of a moisturizing product containing 0.7% of a 25% solution of Dioctyl Adipate (0.175% actual concentration). Patches containing the material were affixed to the cleansed back for 24 h on each Monday, Wednesday, and Friday for 3½ consecutive weeks for 10 insults. A 10- to 14-day rest followed removal of the 10th insult, at which time a 48 h challenge patch was applied. The challenge site was scored and seven to 10 days later, a second 48 h challenge patch was applied and graded immediately and 24 h after patch removal. One subject had erythema and papules on the test site after the ninth and tenth inductions. The second challenge patch caused erythema and papules in one subject. No other reactions were noted.[52]

Cumulative irritancy test

A similar moisturizing product containing 0.175% Dioctyl Adipate was tested in a 21-day cumulative irritation assay. The product, 0.2 ml, was applied under cotton patches to the backs of 11 female panelists for 21 consecutive days. The patches were removed 23 h after application and the sites were scored 1 h after patch removal. New patches were applied immediately. The cumulative irritation score for this product was 72 out of a possible 630. This product was slightly irritating.[53]

Photopatch test

A photopatch test was conducted using a formulation containing 9.0% Dioctyl Adipate. Each of 25 panelists received patches containing 0.1 ml of the product. Twenty-four hours later, the patches were removed and the sites were irradiated with a Xenon Arc Solar Simulator (150 W) with a continuous emission in the UVA and UVB range (290–400 nm). Forty-eight hours later, the irradiated sites were scored for irritation. This entire procedure was repeated twice weekly for a total of six exposures. After a 10-day rest, a challenge patch was applied for 24 h and then irradiated for 3 min. This site was then scored 0.25, 24, 48, and 72 h after irradiation. Two control sites, one with the test product with no irradiation, and a second receiving irradiation but no product, were included in the test program. None of the 25 individuals had phototoxic or photoallergic reactions[54] (see Table 9).

Diispropyl Adipate

24-hour patch tests

Diisopropyl Adipate, alone and in a formulation, was assayed for skin irritation potential in 24 h patch tests. Occlusive patches containing 0.1 ml of the substance were affixed to the volar surface of the forearm and/or the medial aspect of arm. The patches were removed 24 h later, and the sites read 2 and 24 h later. The sites were scored on a scale of 0 (no irritation) to 4 (severe deep red

TABLE 9. Clinical Assessment of Safety.

Ingredient	Test	No. of subjects	Conc. (%)	Applied amount (ml)	Time		Irrit. score	Comments	Ref.
					Contact	Observ.	Max.		
Dioctyl Adipate									
Formulation	Schwartz–Peck prophetic patch	100 M,F	0.01	—	2 24-h	48 h	—	Two panelists showed a mild reaction after the first open patch. 1 panelist showed a strong reaction after the 2nd open patch.	49
Formulation	Shelanski–Shelanski RIPT	49 M,F	0.01	—	11 24-h + UV	—	—	Ten induction patches; 14-day rest; challenge patch (11th). UV irradiation after patch nos. 1,4,7,10,11. Weak reaction in 3/49 after patch 4; in 1/49 after patch 5; in 4/49 after patch 10. Strong reaction in 1/49 after patch 6; in 1/49 after patch 11. No UV reaction.	49
Formulation	Modified Draize–Shelanski RIPT	209 M,F	9.0	—	See comments	48, 96 h	—	Nine 48 h inductions; 14-day rest; one 48 h challenge. Three moderate to strong erythematous reactions during induction. One faint erythematous reaction from challenge patch. Not a sensitizer or irritant.	50
	Modified Draize–Shelanski RIPT	151 M,F	9.0	—	See comments	48, 96 h		Nine 48 h inductions; 14-day rest; one 48 h challenge. Two subjects had irritant reactions; no sensitization.	51

TABLE 9. (Continued.)

Ingredient	Test	No. of subjects	Conc. (%)	Applied amount (ml)	Time		Irrit. score	Comments	Ref.
					Contact	Observ.	Max.		
Formulation	Shelanski-Jordan RIPT	210 M,F	0.225	—	See comments	See comments	—	Ten 24 h inductions; 14-day rest; one 48 h challenge; 7- to 10-day rest and 2nd 48 h challenge. Results: Insults 1–8 caused no reaction. Insults 9,10 caused erythema, papules in 2/210. Challenge 1 caused no reaction. Challenge 2 caused erythema, papules in 1/210 after 72 h.	52
Formulation	21-day cumulative irritant test	11 F	0.175	0.2	21 23-h	—	72/630	Sites scored 1 h after patch removal. Maximum irritation occurred in 3 panelists after insults 3,7,18; slight irritation occurred in 1 after patch 16.	53
Formulation	Photopatch test	25 M,F	9.0	0.1	See comments	—	—	Six 24 h patches (twice weekly for 3 weeks). Sites irradiated (Xenon UV lamp) on patch removal and read 48 h later; 10-day rest; one 24 h patch to new site; irradiation after patch removal; readings taken 0.25, 24, 48, and 72 h after irradiation. Results: No phototoxicity or photoallergenicity.	54
Diisopropyl Adipate									
Ingredient	24 h patch	19 M,F	100	0.1	24 h	2, 24 h	0/4	No irritation.	55
	24 h patch	19 M,F	100	0.1	24 h	2, 24 h	0/4	No irritation.	55
	24 h patch	15 M,F	100	0.1	24 h	2, 24 h	0/4	No irritation	56
	24 h patch	15 M,F	100	0.1	24 h	2, 24 h	0/4	No irritation.	56

Formulation	24 h patch	19 M,F	0.26	0.1	24 h	2, 24 h	0.16/4.0	13 subjects had no irritation; 6 had barely perceptible erythema. Minimal irritation.	57
	24 h patch	19 M,F	5.0	0.1	24 h	2, 24 h	0/4	No irritation.	58
Formulation	Maibach–Marzulli RIPT	235 M,F	1.08	0.5	See comments	—	—	Ten 48 h patches; 14-day rest; One 48 h patch. Erythema occurred in one person after induction. Hyperpigmentation occurred in 17/235, but no sensitization reactions occurred.	59
Formulation	RIPT	50 M,F	3.0	—	See comments	See comments	—	Ten 24 h patches, 7-day rest, one 24 h challenge and observation after 24 and 48 h. No irritation or sensitization reactions.	60
	Modified Draize RIPT	108 M,F	5.0	0.4	See comments	See comments	—	Nine 24 h induction patches; 14-day rest; one 24 h challenge read 48 and 96 h after application. No irritation was seen in any panelist.	61
	RIPT	116 M,F	1.04	0.1	See comments	See comments	—	Nine 24 h inductions, 3-week rest, one 24 h challenge scored 24 and 48 h after removal. If a challenge reaction occurred, a 2nd 24 h challenge was applied. Results: Induction No. 1—faint erythema in 2/116; mild erythema in 1/116. Induction No. 2—faint erythema in 4/116; inductions 3 and 5—faint erythema in 1/116; and induction 4—mild erythema in 1/116. Challenge produced faint erythema in 2/116. No potential for allergic sensitization.	62
Formulation	Kligman maximization test	25 M,F	0.7	—	See comments	See comments	—	Five 48 h induction patches; eight 10-day rest; 1 h pretreatment with SLS; 48 h challenge patch read at patch removal and after 24 and 48 h. No contact sensitization occurred.	63

TABLE 9. (Continued.)

Ingredient	Test	No. of subjects	Conc. (%)	Applied amount (ml)	Time		Irrit. score	Comments	Ref.
					Contact	Observ.	Max.		
Ingredient	21-day cumulative irritation test	16 M,F	100	0.3	21 22-h patches	—	26.33/630	All but one panelist showed erythema. Ingredient is "moderately irritating."	64
Formulation	21-day cumulative irritation test	10 F	0.7	0.3	21 23-h patches	—	2/630	One panelist showed minimal erythema after patch no. 18. Product is "essentially nonirritating."	65
	21-day cumulative irritation test	17 F	1.08	0.5	See comments	—	0.29/84	Application of material was made on 5 consecutive days during 3 consecutive weeks. Continuous contact was made on Sat./Sun. to allow for 21-day continuous exposure. Two panelists had questionable erythema, one had vesiculation. Low irritation.	66
	21-day cumulative irritation test	17 F	1.08	0.5	See comments	—	0.24/84	Procedure as above. One panelist had questionable erythema, 2 had definite erythema. Low irritation.	66
	21-day cumulative irritation test	7 M,F	20.75	—	21 24-h patches	—	8/84	—	67
Formulation	Schwartz-Peck prophetic patch + UV	98 M,F	0.7	—	2 24-h + UV	48 h	—	All patch tests were negative. UV test was negative.	68

Formulation	Draize-Shelanski RIPT + UV	49 F	0.7	—	See comments	48 h	—	Ten 48 h inductions; 14-day rest; one 48 h challenge. UV irradiation after patch nos. 1,4,7,10,11. All patch tests + UV tests were negative.	68
Formulation	Modified maximization + UV	50 M,F	3.0	—	See comments	—	—	Patch test sites pretreated with 5% aq. SLS for 30 min. Six to 8 h later, the first test patch was applied and read 48 h later. A second 48 h patch was then applied. This procedure was repeated twice and followed by a 5-day rest. An SLS pretreatment preceded the 48 h challenge patch. Duplicate sites were exposed to a Hanovia UV Lamp after patches 1,3,5, and 7 (challenge) and read 48 h later. No photoallergic responses occurred.	69
	Modified maximization + UV	49 M,F	3.0	—	See comments	—	—	Test performed as directly above. Product is not a photosensitizer or phototoxic.	70
	Modified maximization + UV	50 M,F	17.0	—	See comments	—	—	Test performed as directly above. Product is not a photoallergic sensitizer.	71
	Modified maximization + UV	50 M,F	17.0	—	See comments	—	—	Test performed as directly above. Product is not a photoallergic sensitizer or a primary irritant.	72

erythema, vesiculation). Two different lots of the undiluted ingredient were tested on 15 men and women. Neither product caused irritation.[55] Additionally, 19 individuals were tested with two different lots of the undiluted ingredient. None of the 19 had signs of irritation.[55,56]

Product formulations containing Diisopropyl Adipate were tested as discussed in the preceding paragraph. One formulation containing the ingredient at 20.75% was diluted to 1.25% in water (actual ingredient concentration = 0.26%) and tested on 19 individuals. Thirteen subjects had no irritation and six had minimal faint erythema. The PII was 0.16 (possible score of 4.0).[57] Another formulation containing 5.0% Diisopropyl Adipate was tested undiluted on 19 panelists and produced no irritation.[58]

Repeated insult patch tests

A Marzulli–Maibach repeat insult sensitization study was performed using a perfume containing 1.08% Diisopropyl Adipate (18% of a 6% solution). The perfume (0.5 ml) was applied under occlusion to the skin of the upper backs of 235 women for 48 h (72 h on weekends). The sites were scored on a scale of 0 (no reaction) to 5 (erythema with induration and bullae). New patches were applied to the same sites; this procedure was repeated for a total of 10 applications. A two-week rest was followed by a challenge patch applied to an adjacent, untreated site for 48 h. During the induction series, one individual had erythema covering the entire test site and one had erythema with induration and vesiculation. This patient had no reaction when challenged. Seventeen subjects had slight hyperpigmentation, but no sensitization reaction occurred in any of the 235 volunteers.[59] A similar test was conducted using a suntan lotion containing 3.0% Diisopropyl Adipate. No reactions were produced in the 50 men and women panelists. The product was neither a sensitizer nor a contact irritant.[60] A hair grooming preparation containing 5.0% Diisopropyl Adipate was tested as above on 108 men and women. This product caused no reactions and gave no evidence of sensitization.[61] A 5.0% aqueous dispersion of a bath oil containing 20.75% Diisopropyl Adipate was tested as above on 116 men and women. The first insult produced minimal faint to pink erythema in four panelists. Minimal faint erythema occurred in four panelists after insult 2, in one after insult 3, and in one after insult 5. Pink, uniform erythema occurred in one person after insult 4. The challenge patch produced minimal, faint erythema in two persons after 24 h, and no reactions occurred after 48 h.[62]

Maximization test

A facial cream containing 0.7% Diisopropyl Adipate was evaluated for contact-sensitization potential in a maximization test. The material was applied under occlusion to the skin of the volar forearm or back of 25 subjects for five consecutive 48 h periods. The patch site was then treated with 2.5% sodium lauryl sulfate for 24 h under occlusion. A challenge patch was then applied for 48 h and the site read immediately after patch removal and 24 h later. The product produced no reactions indicative of contact-sensitization.[63]

Cumulative irritancy test

Twenty-one day cumulative irritancy tests were performed on Diisopropyl Adipate alone and in a formulation. The undiluted ingredient was tested on 16 men and women. No irritation was observed until after the sixth patch was ap-

plied (sixth day). After this time, irritation was reported in 14 of 16 panelists where erythema and papules were the most severe reaction. The undiluted ingredient had a total irritation score of 395 out of a possible 945; it was classified by the authors as "moderately irritating." The formulation, a face cream product containing 0.7% Diisopropyl Adipate, was tested on 13 individuals. Minimal erythema occurred in one person after the third patch (third day), and in one person after patch 18 (18th day). This product had a score of 2 out of a possible 630; the product was classified as nonirritating.[64,65]

A cumulative irritancy test of two products containing 1.1% Diisopropyl Adipate was tested on 17 subjects using procedures similar to that previously noted for Dioctyl Adipate.[53] The first product had a score of 0.5 (questionable erythema) in two subjects, 1.0 (definite erythema) in one, and 3.0 (vesiculation) in one. The mean score was 0.29 (possible 84). The second product had a score of 0.5 in one person, 1.0 in two people, and 1.5 (definite erythema and possible induration) in one person. The mean score for this product was 0.24 (possible 84). These product scores indicate a low potential for hazard to the consumer.[66] In a similar test, a bath oil containing 20.75% Diisopropyl Adipate was tested on seven patients. The bath oil caused an average score of 8 (possible 84).[57]

Photopatch tests

A face cream containing 0.7% Diisopropyl Adipate was evaluated for irritation potential by a Schwartz–Peck prophetic patch test followed by UV exposure and by the Draize–Shelanski repeated insult patch test which was also followed by UV exposure. In the Schwartz–Peck Procedure, 98 panelists were patch tested with the product on the back and on the volar surface of the right arm for 48 h. A second patch was applied 12–14 days later and graded 48 h after application. After the patch site was scored, the same site was irradiated with a UV source (Hanovia Tanette Mark I Lamp) at 12 in for 1 min. The site was graded 48 h after exposure. Reactions were not observed at the induction patch, the challenge patch, or the irradiation sites.[68] In the Draize–Shelanski test, 10 consecutive 48 h inductions were applied for 48 h to each of 49 panelists and an 11th challenge patch was applied for 48 h approximately 14 days later. Skin sites which received patches 1, 4, 7, 10, and 11 also were exposed to UV radiation (Hanovia Tanette Mark I Lamp) at 12 in for 1 min. These light-exposed sites were graded 48 h after irradiation. No reactions occurred after any induction patch, challenge patch, or UV exposure. The product was neither a primary irritant nor a sensitizer.[68]

Several products were used in modified maximization tests with UV exposure. The procedures followed were: on Day 1 of the test (Monday), patch test sites were pretreated for 30 min with 0.5 ml of 5.0% aqueous sodium lauryl sulfate. The test material was then applied to the test site 6–8 h later for a period of 48 h. On Wednesday, the sites were graded immediately after patch removal, and a new patch was then applied for 48 h. On Friday, this site was graded and left untreated over the weekend. This regimen was repeated for two more weeks. After the last induction patch was graded (Friday of the third week), a five-day nontreatment period followed and a patch of sodium lauryl sulfate was again applied for 30 min. After 6–8 h, a challenge test patch was applied and graded 48 h later. A control site was treated with sodium lauryl sulfate, but no test material was applied to it. To assess UV sensitization, skin sites which received patches 1, 3, 5, and 7 were also exposed to a UV source (Hanovia Tanette Mark I Lamp) at 12 in for 1 min. Sites were graded 48 h later. A suntan product containing 3.0%

Diisopropyl Adipate was tested on 50 people. There were no reactions and the product was not a photoallergic sensitizer.[69] A sunburn lotion containing 3.0% Diisopropyl Adipate was similarly tested on 49 individuals. No reaction occurred and the product was not a photosensitizer or a phototoxic agent.[70] Two sunburn foam bases, each containing 17.0% Diisopropyl Adipate, were tested on two panels of 50 subjects. Neither material caused any reaction and the products were not photoallergic sensitizers or primary irritants[71,72] (see Table 9).

SUMMARY

Dioctyl Adipate, the diester of octyl alcohol and adipic acid, and Diisopropyl Adipate, the diester of isopropyl alcohol and adipic acid, are plasticizers and emollients. They are produced by the esterification of adipic acid and the appropriate alcohol in the presence of an esterification catalyst. Both Adipates are clear, colorless to light yellow viscous liquids, with an aromatic odor.

In noncosmetic products, the two Adipates are used in plastic food wraps, blood and hemodialysis bags, solvents, and lubricants. Dioctyl Adipate has Indirect Food Additive status for use in food wrapping materials. The Adipates are used in cosmetics as emollients and bases. Dioctyl Adipate is used in 27 products in concentrations of $\leq$ 0.1%–25%, and Diisopropyl Adipate is used in 112 formulations, ranging in concentration from $\leq$ 0.1%–25%.

Dioctyl Adipate had low acute oral toxicity, with the LD_{50} ranging from 9.11 g/kg to 45.0 g/kg (estimated). Likewise, Diisopropyl Adipate had low oral toxicity. Estimated LD_{50}s ranged from greater than 5 g/kg to greater than 76.8 g/kg. In a 14-day study, rats and mice fed up to 50,000 ppm (for males) and 100,000 ppm (females) had weight loss and weight gain reduction at the highest concentrations. Females fed the 100,000 ppm diet died. The intravenous LD_{50} of Dioctyl Adipate to rats and rabbits was 900 mg/kg and 540 mg/kg, respectively. Diisopropyl Adipate had an intravenous LD_{50} of 640 mg/kg for rats. A percutaneous absorption test on rabbits showed that Dioctyl Adipate had an LD_{50} of 16 g/kg, but up to 8.7 g/kg for 24 h was not toxic to rabbits in another test. An immersion test of a formulation containing Diisopropyl Adipate (20.75%) indicated no toxicity to guinea pigs. The intraperitoneal LD_{50} of Dioctyl Adipate in mice was 1.0 g/kg; in rats, 47.0 g/kg; and 38.0 g/kg in rabbits.

In ocular irritation studies, undiluted Dioctyl Adipate was nonirritating; formulations containing up to 0.175% of the ingredient were, at most, mild, transient irritants. Undiluted Diisopropyl Adipate was a very mild, transient irritant; formulations containing the ingredient produced minimal irritation. The results of primary dermal irritation tests indicated that Dioctyl Adipate, when administered alone and in formulations, was a very mild irritant and Diisopropyl Adipate was minimally irritating. Dioctyl Adipate was not a skin sensitizer in guinea pigs. Two perfumes containing 0.108% Diisopropyl Adipate were neither irritating nor phototoxic to rabbits and a product with 0.175% Dioctyl Adipate caused no mucous membrane irritation in rabbits.

Mice and rats fed up to 25,000 ppm Dioctyl Adipate for 91 days had weight gain depression, but no other abnormalities.

An Ames test for the mutagenic potential of Dioctyl Adipate was negative. An assay of the carcinogenic potential of Dioctyl Adipate showed that administration

of up to 25,000 ppm of the compound for 103 weeks produced no untoward effects and was noncarcinogenic to rats. Mice fed the same amount for 103 weeks had dose-related body-weight reductions and a higher incidence of hepatocellular adenoma and carcinoma than controls. Hodge and associates reported that rats fed up to 2.5 Dioctyl Adipate for two years had a tumor incidence similar to that of the control group. They also found no tumors in dogs fed up to 0.2% Dioctyl Adipate for one year. A single 10 mg dose of Dioctyl Adipate given by subcutaneous injection was not carcinogenic in mice. In a lifetime study Dioctyl Adipate caused no skin tumors when 10 mg was applied weekly to the back skin of mice.

The teratogenicity of Dioctyl Adipate was studied in mice. According to the author, intraperitoneal injection of up to 9.3 g/kg of the ingredient to male mice caused antifertility effects in females to which they were mated. Intraperitoneal injections of up to 9.3 g/kg Dioctyl Adipate were administered to pregnant rats on the 5th, 10th, and 15th days of gestation. The investigator reported that resorption rates were similar; however, there was a greater incidence of skeletal and visceral abnormalities. The experimental design and interpretation have been questioned by some.

Clinical assessment of Dioctyl Adipate at concentrations of 0.01%–9.0% in formulation showed, at most, erythema and papules when applied under occlusion for extended periods of time. No UV sensitization occurred. Undiluted Diisopropyl Adipate produced no irritation in 24 h patch tests, but was moderately irritating in a 21-day cumulative irritancy test. Formulations containing concentrations of 0.26%–20.75% Diisopropyl Adipate caused minimal to mild irritation, no sensitization and no photosensitization.

DISCUSSION

The Expert Panel, in reviewing the animal and human test data on Dioctyl Adipate and Diisopropyl Adipate, found them adequate to evaluate the safety of these ingredients as used in cosmetic products. No human data were available for Dioctyl Adipate as a pure ingredient; however, data were available on formulations up to a concentration of 9.0%. These data, plus animal test data at a concentration of 100% of the ingredient, indicated Dioctyl Adipate is, at most, a weak irritant. Sensitization and phototoxicity tests were negative. In a formulation Diisopropyl Adipate at a concentration of 0.1% was neither an irritant or phototoxic agent to rabbits.

Two studies by the same investigator, one which reported on fetal toxicity and teratogenic effects, and the second on mutation and antifertility effects of Dioctyl Adipate, were reviewed. The author concluded a statistically significant effect in each study, but there were several deficiencies noted in each study which made the author's conclusions questionable.

Several carcinogenic studies have been reported. All but one were negative; one oral feeding study conducted by the National Toxicology Program indicated that Dioctyl Adipate was carcinogenic in female mice and was probably carcinogenic in male mice. The Expert Panel noted that the Maximum Tolerated Dose was significantly exceeded in this chronic study; thus, these test data may not be relevant in a safety assessment for humans.

CONCLUSION

On the basis of available data, the Panel concludes that Dioctyl Adipate and Diisopropyl Adipate are safe as presently used in cosmetics.

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