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Final Safety Assessment of Thiodipropionic Acid and Its Dialkyl Esters as Used in Cosmetics

Catherine Diamante[1], Monice Zondlo Fiume[2], Wilma F. Bergfeld, MD, FACP[3], Donald V. Belsito, MD[3], Ronald A. Hill, PhD[3], Curtis D. Klaassen, PhD[3], Daniel C. Liebler, PhD[3], James G. Marks Jr, MD[3], Ronald C. Shank, PhD[3], Thomas J. Slaga, PhD[3], Paul W. Snyder, DVM, PhD[3], and F. Alan Andersen, PhD[4]

Abstract

Dilauryl thiodipropionate (DLTDP), dicetyl thiodipropionate, dimyristyl thiodipropionate, distearyl thiodipropionate, and ditridecyl thiodipropionate are dialkyl esters of their respective alcohols and thiodipropionic acid (TDPA) used in cosmetics. Ingested DLTDP was excreted in the urine as TDPA. Single-dose acute oral and parenteral studies and subchronic and chronic repeated dose oral studies did not suggest significant toxicity. Neither DLTDP nor TDPA was irritating to animal skin or eyes and they were not sensitizers. TDPA was neither a teratogen nor a reproductive toxicant. Genotoxicity studies were negative for TDPA and DLTDP. Clinical testing demonstrated some evidence of irritation but no sensitization or photosensitization. The Cosmetic Ingredient Review Expert Panel considered that the data from DLTDP reasonably may be extrapolated to the other dialkyl esters and concluded that these ingredients were safe for use in cosmetic products that are formulated to be nonirritating.

Keywords

safety, cosmetics, dilauryl thiodipropionate

The Cosmetic Ingredient Review (CIR) Expert Panel previously considered the safety of dilauryl thiodipropionate (DLTDP), finding it safe for use in cosmetic products at concentrations not to exceed 0.05%.[1]

In 2007, the Expert Panel reviewed this safety assessment and determined that there were sufficient data to reopen it and to add thiodipropionic acid (TDPA), as the base acid, and that other dialkyl esters of TDPA were sufficiently similar to DLTDP to be added as well. These include the cosmetic ingredients dicetyl thiodipropionate, dimyristyl thiodipropionate, distearyl thiodipropionate, and ditridecyl thiodipropionate.

This safety assessment, therefore, presents the safety test data from the original safety assessment and updates those data with more recent findings on all of the listed ingredients.

Chemistry

Definition and Structure

The definitions of these ingredients as listed in the *International Cosmetic Ingredient Dictionary and Handbook*[2] are shown in Table 1,[3-6] along with chemical formulas and chemical classes.

Thiodipropionic acid. TDPA is also known as 3,3′-thiodipropionic acid; bis(2-carboxyethyl) sulfide; β,β-thiodipropionic acid; 3,3′-thiobis(propanoic acid); 4-thiaheptanedioic acid; diethyl sulfide 2,2′-dicarboxylic acid; and thiodihydracrylic acid.[2,7]

The chemical structure of TDPA is shown in Figure 1.

Dilauryl thiodipropionate. DLTDP is also known as didodecyl 3,3′-thiodipropionate; propanoic acid, 3,3′-thiobis-, didocecyl ester; 3,3′-thiodipropionic acid di-n-dodecyl ester; propionic acid, 3,3′-thiodi-, didoceyl ester; bis(dodecyloxycarbonylethyl) sulfide; thiobis (dodecylpropionate), bis(dodecyloxycarbonylethyl) sulfide; thiodipropionic acid, dilauryl ester; dilauryl β′,β′- thiodipropionate; and dilauryl β-thiodipropionate.[2,7-9]

Dicetyl thiodipropionate. Dicetyl thiodipropionate is also known as propanoic acid, 3,3′-thiobis-, dihexadecyl ester and 3,3′-thiobispropanoic acid, dihexadecyl ester.[2]

[1] Cosmetic Ingredient Review Scientific Analyst/Writer
[2] Cosmetic Ingredient Review Technical Editor
[3] Cosmetic Ingredient Review Expert Panel Member
[4] Cosmetic Ingredient Review Director

Corresponding Author:
Monice Zondlo Fiume, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036
Email: cirinfo@cir-safety.org

Table 1. Definitions, Chemical Classes, and Functions for TDPA and Its Dialkyl Esters From the *International Cosmetic Ingredient Dictionary and Handbook*[2]

Ingredient (CAS No.)	Definition	Chemical Class	Function	Dialkyl Moiety Safety Assessment
Dilauryl thiodipropionate (123-28-4)	Diester of lauryl alcohol and thiodipropionic acid	Ester; thio compound	Antioxidant	—
Thiodipropionic acid (111-17-1)	A carboxylic acid	Carboxylic acid	Skin-conditioning agent—miscellaneous	—
Dicetyl thiodipropionate (3287-12-5)	Diester of cetyl alcohol and thiodipropionic acid	Ester; thio compound	Antioxidant	Cetyl alcohol found safe and conclusion reaffirmed[3,4]
Dimyristyl thiodipropionate (16545-54-3)	Diester of myristyl alcohol and thiodipropionic acid	Ester; thio compound	Antioxidant	Myristyl alcohol found safe and conclusion reaffirmed[3,4]
Distearyl thiodipropionate (693-36-7)	Diester of stearyl alcohol and thiodipropionic acid	Ester; thio compound	Antioxidant	Stearyl alcohol found safe and conclusion reaffirmed[5,6]
Ditridecyl thiodipropionate (10595-72-9)	The diester of tridecyl alcohol (qv) and thiodipropionic acid (qv)	Ester; thio compound	Antioxidant	—

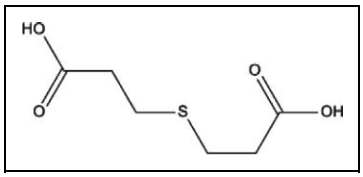

Figure 1. Thiodipropionic acid (TDPA).

Dimyristyl thiodipropionate. Dimyristyl thiodipropionate is also known as ditetradecyl 3,3′-thiobispropanoate; propanoic acid, 3,3′-thiobis-, ditetradecyl ester; ditetradecyl 3,3-thiodipropionate; ditetradecyl 3,3′-thiodipropionate; 3,3′-thiodipropionic acid di-n-tetradecyl ester; dimyristyl β′,β′-thiodipropionate; and dimyristyl β-thiodipropionate.[2,7]

Distearyl thiodipropionate. Distearyl thiodipropionate is also known as propanoic acid, 3,3′-thiobis-, dioctadecyl ester, and 3,3′-thiobispropanoic acid, dioctadecyl ester.[2]

Ditridecyl thiodipropionate. Ditridecyl thiodipropionate is also known as propanoic acid, 3,3′-thiobis-, ditridecyl ester.[2]

These dialkyl esters of TDPA differ only in the length of fatty alcohols esterified with TDPA. Their structures are shown in Figure 2.

Properties

Dilauryl thiodipropionate. DLTDP has a molecular weight of 514.85 and a characteristic sweet ester odor, and it occurs as white crystalline flakes. It is soluble in most organic solvents and insoluble in water.[7-11] Its melting/solidification point is 40°C, and in solid form at 25°C it has a specific gravity of 0.975.[8,9,11]

DLTDP is insoluble in water and alcohol and soluble in almost any organic solvent.[7] It is stable under ordinary conditions.

Thiodipropionic acid. TDPA has a molecular weight of 178.21 and occurs as a white crystalline powder.[7] It has a melting point of 131°C to 134°C and is soluble in hot water, acetone, and alcohol. TDPA is stable under ordinary conditions.

Dimyristyl thiodipropionate. Dimyristyl thiodipropionate has a molecular weight of 570.95 and occurs as white crystalline flakes.[7] It is insoluble in water and alcohol and soluble in almost any organic solvent. Dimyristyl thiodipropionate is stable under ordinary conditions.

Methods of Manufacture

According to the *International Cosmetic Ingredient Dictionary and Handbook*,[2] DLTDP and dimyristyl thiodipropionate have plant and synthetic sources. TDPA and ditridecyl thiodipropionate have a synthetic source. Dicetyl thiodipropionate has plant, animal, and synthetic sources. Distearyl thiodipropionate has animal and synthetic sources.

A patented method of manufacture of TDPA was reported by Gresham and Shaver.[12] Compounds that are reacted to produce TDPA include ethyl thiohydracrylate, sodium hydroxide, β-propiolactone, and hydrochloric acid.

Analytical Methods

DLTDP may be identified by its solidification point.[10] An infrared (IR) spectrum for DLTDP has been published.[11] TDPA has been determined via IR spectrophotometry, and in food products it was determined by isolation with 70% ethanol followed by conversion of trimethylsilyl derivatives and determination by gas–liquid chromatography.[13,14] DLTDP and distearyl thiodipropionate were determined by capillary (high-resolution) gas chromatography after polyethylene packages were Soxhlet-extracted.[15] DLTDP, dimyristyl thiodipropionate, and distearyl

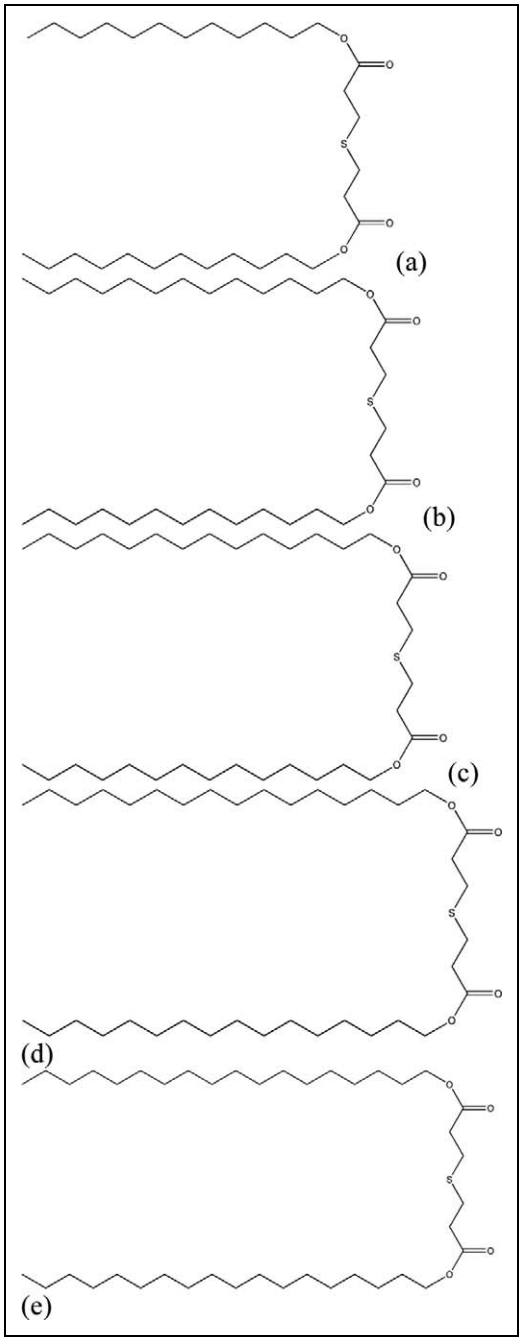

Figure 2. Dialkyl esters of thiodipropionic acid (TDPA) showing the long-chain fatty alcohol groups esterified to the basic dicarboxylic acid structure: (a) dilauryl thiodipropionate (DLTDP); (b) ditridecyl thiodipropionate; (c) dimyristyl thiodipropionate; (d) dicetyl thiodipropionate; and (e) distearyl thiodipropionate.

thiodipropionate, as polymer additives, were determined using gas chromatography/mass spectrometry.[16]

Impurities

Cosmetic-grade DLTDP may contain up to 0.2% free carboxylic acids (as TDPA). It may have a maximum of 0.1% sulfated ash, 3 ppm arsenic, and 20 ppm lead.[11] The Food Chemical Codex (FCC) lists the same specifications for acidity, ash, and arsenic, but it specifies that DLTDP may not contain more than 10 ppm lead or more than 0.002% heavy metals (as Pb).[10]

Chemical Reactions

According to Balsam and Sagarin,[17] oils and fats, essential oils, perfumes, vitamins, and to a lesser degree other organic compounds are prone to oxidation. Antioxidants (one of the functions for dialkyl esters of TDPA) are added to cosmetic formulations to impede the oxidation reactions and to help preserve color and texture of the product.

Wilkinson and Moore[18] stated that thiodipropionates also are widely used as sequestering agents in conjunction with the phenol class of antioxidants. The antioxidant combination of thiodipropionate and phenols is synergistic. DLTDP is the ester of a fatty alcohol, and, as such, it has a greater solubility in oils. Its synergistic effect with phenols allows for the use of smaller amounts of phenols, which in turn avoids the discoloration and odors when phenols are used in higher concentrations.

Use

Cosmetic

Table 2 gives the current uses and use concentration data on DLTDP and TDPA. Dicetyl thiodipropionate, dimyristyl thiodipropionate, distearyl thiodipropionate, and ditridecyl thiodipropionate are not reported as being used.

According to information supplied to the US Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Ingredient Reporting Program (VCRP), DLTDP was reported as being used in 11 cosmetic formulations.[19] In addition, the VCRP contains data on the total number of products in each category. For example, of the 635 makeup foundations (column 1), only 1 (column 2) contained DLTDP.

The industry trade association, the Cosmetic, Toiletry, and Fragrance Association (CTFA), which is now the Personal Care Products Council, conducts a survey of current use concentrations. That survey reported use of DLTDP at 0.001% to 4%.[20]

According to data reported to the FDA under the VCRP, TDPA was reported to be used in 15 cosmetic formulations. According to the industry survey, TDPA is used at concentrations of 1% to 2%.[21]

Noncosmetic

As given in the Code of Federal Regulations (CFR), DLTDP and TDPA are generally recognized as safe (GRAS) food substances when the total content of antioxidants is not more than 0.02% of fat or oil content, including essential (volatile) oil content of food, provided the substance is used in accordance with good manufacturing practice (21CFR parts 175.300, 181.24, 182.3109, and 182.3280).[22]

DLTDP and TDPA were accepted by the World Health Organization (WHO) as direct food additives.[23] Recommended

Table 2. Historical and Current Cosmetic Product Uses and Concentrations

Product Category (Total Products in Category)	2007 Uses[19]	2007 Concentrations (%)[20,21]
Dilauryl thiodipropionate (DLTP)		
Makeup		
Foundations (635)	1	—
Skin-care products		
Skin cleansing creams, lotions, liquids, pads (1368)	—	0.001
Face and neck creams, lotions, powders, sprays (1195)	1	4
Body and hand creams, lotions, powders, sprays (1513)	4	—
Moisturizers (2039)	5	2
Other (1244)	—	0.01
Total for DLTP	11	0.001-4
Thiodipropionic acid (TDPA)		
Bath products		
Other (239)	1	—
Eye makeup		
Eye lotion (177)	2	2
Skin-care products		
Skin cleansing creams, lotions, liquids, pads (1368)	—	1
Face and neck creams, lotions, powders, sprays (1195)	3	—
Body and hand creams, lotions, powders, sprays (1513)	5	1
Moisturizers (2039)	1	2
Night preparations (343)	1	—
Other (1244)	1	—
Suntan products		
Suntan gels, creams, liquids (156)	1	—
Total for TDPA	15	1-2

daily unconditional intake allowances are 0 to 3 mg/kg and conditional allowances are 3 to 15 mg/kg.

TDPA is used as a primary or secondary antioxidant and color stabilizer for polymers, including polyolefins, styrenics, and rubbers, and in the soap industry.[7] It is an esterifier in plasticizers and lubricants.[13]

As an antioxidant, DLTDP is added to high-pressure greases and lubricants. It is also used as a softening agent and as a plasticizer.[9] DLTDP may be a minor component of polyvinyl chloride bottles.[24]

Dimyristyl thiodipropionate is used as a secondary stabilizer and antioxidant in combination with phenolic antioxidants for polymers.[7] It is also used as a stabilizer in oils, lubricants, sealants, and adhesives.

Distearyl thiodipropionate is an antioxidant that is commonly used in polypropylene for food packaging.[25]

General Biology

Absorption, Distribution, Metabolism, and Excretion

Dilauryl thiodipropionate. Tullar[26] fed 3.0% DLTDP or TDPA to rats in a chronic feeding study. The rats were placed in individual metabolism cages, and their urine was collected for 24 hours. TDPA was found in the urine of test animals. The rats consumed an average of 714 mg of DLTDP per rat per day and excreted an average of 38.5 mg of TDPA per rat per day in the urine.

In a second study, groups of 6 rats were placed in metabolism cages, and the urine and feces were collected over a 24-hour period. The rats received 3.0% DLTDP in the diet. Average consumption was 715 mg of DLTDP per rat per day, and the rats excreted an average of 55.7 mg of TDPA per rat per day in the urine. No DLTDP was recovered from the urine, and neither TDPA nor DLTDP was recovered from the feces.

The author concluded that the amount of chemical recovered in either the urine or feces did not account for the entire amount ingested and that DLTDP was almost entirely absorbed from the intestine and excreted in part in the urine. Lack of total recovery of the chemicals ingested was due either to chemical changes that occurred during digestion or excretion or to the method of analysis.

Urine samples from 2 dogs that received either 0.1% or 3.0% DLTDP in the diet were collected. The samples were analyzed for the presence of TDPA 24 hours after introduction of the test compound in the feed. No TDPA was found in the urine of the dog receiving the low dose of DLTDP in the diet. In the urine of the high-dose dog, 394 mg TDPA was recovered, and this was considered equivalent to 1138 mg of DLTDP. The author suggested that DLTDP was absorbed by the intestine and excreted by the kidneys as either TDPA or a conjugate of TDPA.[26]

Reynolds et al[27] conducted a study in which carboxyl-[^{14}C] DLTDP was administered to fasted male Sprague-Dawley rats (number of rats not stated) either in feed or by intubation. When DLTDP was administered in the diet, the lab chow was placed in the cages with the fasted rats and allowed to remain in place for 4 to 8 hours. When the test material was administered by stomach tube, the DLTDP was dissolved in corn oil. Sample collections were made at 24-hour intervals. The doses were 107, 166, and 208 mg/kg.

Approximately 90% of the test material was excreted in the urine, and 5% of the dose was exhaled as radioactive carbon dioxide (CO_2). The feces were a minor pathway of excretion (0.1%-3.5%). Elimination of 90% of the total administered radioactivity occurred within 24 hours; no dose-related excretion trends were found. Reverse isotope dilution studies were performed to determine the urinary metabolites. DLTDP was excreted as either free TDPA or an acid labile conjugate.

Oral administration of radioactive DLTDP resulted in rapid uptake and elimination of the chemical as either TDPA or conjugates, with little or no retention of radioactivity in the tissues. Radioactivity was assayed in the liver, heart, kidneys, brain, lungs, gastrointestinal tract, and adipose tissue. Radioactivity was near normal in all of the tissues tested except in the adipose tissue. The radioactivity in the adipose tissue of the rats was elevated on day 4 and remained so through days 8 and 34. The radioactivity retained in the adipose tissue after a single 166-mg/kg dose of DLTDP was 12 ppm, but this was not

considered significant as the dose was considerably higher than the maximum allowable daily intake of either TDPA or DLTDP.[27]

Thiodipropionic acid. Tullar[26] fed 3.0% TDPA to rats in a chronic feeding study. Five rats were placed in individual metabolism cages, and their urine was collected for 24 hours. TDPA was found in the urine of test animals. The rats consumed an average of 741 mg of TDPA per rat per day; an average of 87.5 mg per rat per day was excreted in the urine during the first 24 hours.

In a second study, 6 rats were placed in metabolism cages, and the urine and feces were collected over a 24-hour period. The rats received 3.0% TDPA in the diet. An average of 741 mg per rat per day was consumed, and an average of 104.3 mg TDPA per rat per day was excreted. TDPA was not recovered from the feces.

The author concluded that the amount of chemical recovered in either the urine or feces did not account for the entire amount ingested and that TDPA was almost entirely absorbed from the intestine and was excreted in part in the urine. Lack of total recovery of the chemical ingested was due either to chemical changes that occurred during digestion or excretion or to the method of analysis.

Tullar[26] administered a 75-mg/kg dose of TDPA intravenously to a rabbit. After 2 hours, the urinary bladder was catheterized and the urine was analyzed for the presence of TDPA. Of the administered dose of TDPA, 80% was recovered in the urine after a 2-hour period.

Reynolds et al[27] conducted a study in which carboxyl-[^{14}C]TDPA was administered to fasted male Sprague-Dawley rats (number of rats not stated) either in feed or by intubation using the procedures described earlier, except that TDPA was dissolved in 1:1 ethanol/water for intubation. Rats received doses of 3.1, 241, 551, 572, or 650 mg/kg. Approximately 90% of the test material was excreted in the urine, and 5% of the dose was exhaled as radioactive CO_2. The feces were a minor pathway of excretion (<1%). Elimination of 90% of the total administered radioactivity occurred within 24 hours; no dose-related excretion trends were found. Reverse isotope dilution studies were performed to determine the urinary metabolites. TDPA was excreted in the urine either unchanged or as an acid labile conjugate that was not a glucuronide.

Oral administration of radioactive TDPA resulted in rapid uptake and elimination of the chemicals as either TDPA or conjugates, with little or no retention of radioactivity in the tissues. Radioactivity was assayed in the liver, heart, kidneys, brain, lungs, gastrointestinal tract, and adipose tissue and was near normal in all of the tissues tested.[27]

Effect on Recombinant Tumor Necrosis Factor-α–Induced Cytotoxicity

Brekke et al[28] reported that TDPA had minimal effects on recombinant tumor necrosis factor-α–induced cytotoxicity.

Animal Toxicology

Acute Oral Toxicity

Dilauryl thiodipropionate. Tullar et al,[29] in studies using mice, reported that the median lethal dose (LD_{50}) was 2000 mg/kg for DLTDP dissolved in olive oil.[29] Of the mice that died, some died up to 2 days after administration of the test material. The immediate cause of death was not determined.

Rats received a single dose of 2000 or 2500 mg/kg DLTDP in olive oil (5 and 10 rats, respectively). There was no mortality. No lesions of the liver, spleen, stomach, or intestines were found at necropsy in the rats that died during the study or in those killed at the termination of the study.[26]

The oral LD_{50} of DLTDP was greater than 2000 mg/kg for mice and greater than 2500 mg/kg for rats.[27,30-32]

Thiodipropionic acid. Tullar et al[29] reported that in acute oral toxicity studies using mice, the LD_{50} exceeded 1000 mg/kg for TDPA dissolved in water. Of the mice that died, some died up to 2 days after administration of the test material. The immediate cause of death was not determined.

When TDPA was administered to rats in single oral doses of 1000 and 2000 mg/kg in saline, 1 of 6 rats of the low-dose group died 7 days after dosing and 2 of 15 rats of the high-dose group died, 1 after 4 days and 1 after 7 days. No lesions of the liver, spleen, stomach, or intestines were found at necropsy in the rats that died during the study or in those killed at the termination of the study.[26]

The oral LD_{50} of TDPA was 2000 mg/kg or more for mice and greater than 2500 mg/kg for rats.[30]

TDPA, 5000 mg/kg in a suspension of 0.85% saline, was administered by intubation to 2 adult male rats. The rats were observed for 5 days post treatment; both appeared normal during the observation period. No abnormalities were found at necropsy. The study was repeated with 10 male rats and the same results were observed.[33]

Distearyl thiodipropionate. The oral LD_{50} of distearyl thiodipropionate was more than 2000 mg/kg for mice and more than 2500 mg/kg for rats.[30]

Acute Parenteral Toxicity

Dilauryl thiodipropionate. The intraperitoneal (IP) LD_{50} of DLTDP exceeded 2000 mg/kg, with no dose-related increase in mortality noted over a dose range of 300 to 2000 mg/kg.[26]

Thiodipropionic acid. The IP LD_{50} of TDPA in mice was 250 mg/kg. No mortality was observed in 5 rats that received a single 200-mg/kg IP dose of TDPA in water. Within 5 days after a single IP dose of 500 mg/kg TDPA, 9 of 15 rats had died. Necropsy was not performed on these rats.[26]

The IP LD_{50} of TDPA was 250 mg/kg for mice and 500 mg/kg for rats.[30]

The intravenous (IV) LD_{50} of TDPA in water was 175 mg/kg in mice. Most deaths followed nonspecific convulsions and occurred within an hour.[26]

The IV LD_{50} of TDPA was 175 mg/kg for mice and more than 300 mg/kg for rats.[30]

Distearyl thiodipropionate. The IP LD_{50} of distearyl thiodipropionate was more than 2000 mg/kg for mice.[30]

Subchronic Oral Toxicity

Dilauryl thiodipropionate. Tullar[26] reported a study in which groups of 10 male albino rats were fed diets containing 0.5% or 3.0% DLTDP over a period of 6 months to establish doses for a subsequent chronic study. During the study, 2 of 10 control rats died and 3 rats of the high-dose DLTDP group died. The test material was considered to be relatively nontoxic at the dosages used, and the rats were maintained on the diets for more than 2 years for the completion of the chronic toxicity study.

Thiodipropionic acid. Tullar[26] reported a study in which groups of 10 male albino rats were fed diets containing 0.5% or 3.0% TDPA over a period of 6 months to establish doses for a subsequent chronic study as described previously. During the study, 2 of 10 control rats died, 1 rat of the low-dose group died, and 2 rats of the high-dose group died. The deaths of the 2 rats of the high-dose TDPA group were attributed to paratyphoid infection, and all other deaths were attributed to feeding. TDPA was considered to be relatively nontoxic at the doses used, and the rats were maintained on the diets for more than 2 years for the completion of the chronic toxicity study.

TDPA was administered for 4 months at a dose of 0.5% in the drinking water to a group of 12 guinea pigs. A second group of 12 guinea pigs served as controls. Two guinea pigs of the control group died on days 40 and 93, respectively. Four guinea pigs of the TDPA group died during the study between days 21 and 49. The animals of the TDPA group had reduced body weights compared with the control group during the first 8 weeks of the study. During the last 10 weeks of the study, the animals of the TDPA group gained weight at a faster rate than those of the control group.[26]

Chronic Oral Toxicity

Dilauryl thiodipropionate. The rats used in the previously mentioned subchronic study by Tullar[26] were continued on their dosage regimen (0.5% or 3.0% DLTDP) for a total of 28 months. Of 11 control rats, 2 survived to the end of the study. Of the low- and high-dose rats, 1 of 10 and 0 of 10 rats, respectively, survived the study with mortality rates for the control, low-dose, and high-dose groups of 82%, 90%, and 100%, respectively. Two of the deaths in the high-dose group were due to paratyphoid infections rather than treatment with DLTDP. For the rats that survived the study, there was an average weight gain. The deaths in the control group occurred 6 months to a year later than the deaths that occurred in the treated groups. No significant differences in weight gain and general appearance were found between any of the test groups or the control group.

In a second chronic feeding study, groups of 20 rats were fed DLTDP at concentrations of 0.5%, 1.0%, or 3.0% in the diet for 2 years. DLTDP had no significant effects on the weight gains of the treated rats compared with the controls. No deaths were observed for the first 9 months of the study. After 9 months, deaths were observed in the test groups. A conspicuous number of deaths occurred in the DLTDP test groups, but no attempt was made to explain this observation. Total numbers of deaths at the end of 2 years were 3 of 20 for controls and 16 of 20 for 0.5%, 7 of 20 for 1.0%, and 10 of 20 for 3.0% DLTDP.[26]

In a study in which groups of 20 rats were fed 0.5%, 1.0%, or 3.0% DLTDP in the diet, the number of animals surviving after 2 years was 10, 13, and 4, respectively.[30] No pathological changes were observed.

Thiodipropionic acid. The rats used in the previously mentioned subchronic study by Tullar[26] were continued on their dosage regimen (0.5% or 3.0% TDPA) for an additional 22 months. Of 11 control rats, 2 survived to the end of the study. In the low- and high-dose groups, 7 of 11 and 7 of 10 rats survived the study, and the mortality rate was 82% for the controls, 36% for the low-dose group, and 30% for the high-dose group. For the rats that survived the study, there was an average weight gain as compared to controls. The deaths in the control group occurred 6 months to a year later than the deaths that occurred in the treated groups. No significant differences in weight gain or general appearance were found between the test groups or the control group.

In a second chronic feeding study, groups of 20 rats were fed TDPA at concentrations of 0.5%, 1.0%, or 3.0% in the diet for 2 years. TDPA had no significant effect on the weight gains of the treated rats compared with the controls. No deaths were observed until after 13 months of study. The total numbers of deaths at the end of 2 years were 3 of 20, 5 of 20, 6 of 20, and 4 of 20 for the control, 0.5%, 1.0%, and 3.0% groups, respectively.[26]

In a study in which groups of 20 rats were fed 0%, 0.5%, 1.0%, and 3.0% TDPA in the diet, the number of animals surviving after 2 years was 17, 16, 13, and 15, respectively.[30] No pathological changes were observed.

Distearyl thiodipropionate. In a study in which groups of 20 rats were fed 0.5%, 1.0%, or 3.0% distearyl thiodipropionate in the diet, the number of animals surviving after 2 years was 18, 14, and 16, respectively.[30] No pathological changes were observed.

Dermal Irritation and Sensitization

Dilauryl thiodipropionate. DLTDP, 40 mg/mL in olive oil, was applied to the clipped skin of "several rabbits" where the material remained in place under a patch for 24 hours. The patch

sites were observed for signs of irritation upon removal of the patches and at 48 and 72 hours. Control rabbits received patches containing olive oil. No redness, swelling, or other signs of irritation were observed upon patch removal or at 48 and 72 hours.[26]

A makeup foundation containing 0.05% DLTDP was tested for dermal irritation using 6 New Zealand white rabbits. The foundation, 0.5 mL, was applied to the clipped intact and abraded skin of the rabbits. There was no evidence of irritation reactions in any of the rabbits at either of the scoring periods, and the makeup foundation received a primary irritation index (PII) score of 0. Under the conditions of the study, the makeup foundation containing 0.05% DLTDP was nonirritating to intact and abraded rabbit skin.[34]

Bio-Technics Laboratories assessed a makeup foundation containing 0.05% DLTDP for sensitization potential in a guinea pig maximization test.[35] Prior to the definitive test, a preliminary test to determine maximum tolerated dermal and intradermal doses of the test material was performed. The 5% dilution of the test material, 0.0025%, in Freund's complete adjuvant (FCA) was suitable for the maximization test.

In the definitive test, 14 albino Hartley guinea pigs were clipped free of hair on the anterior dorsal region of the body; 2 of these animals were negative controls and 2 were positive controls, with the remaining 10 as the test animals. Each of the test guinea pigs received two 0.1-mL injections of FCA, test material diluted in FCA, and undiluted test material. Negative controls received distilled water and positive controls received 5% formalin. There were no reactions in any of the 10 test guinea pigs. The 2 positive control animals received scores of 3 and the negative control animals had no erythema and received scores of 0. Under the conditions of the study, the makeup foundation containing 0.05% DLTDP and tested at 0.0025% was not a sensitizer.[35]

Thiodipropionic acid. TDPA, 30 mg/mL in water, was applied to the clipped skin of "several rabbits," where the material remained in place under a patch for 24 hours. Control rabbits received patches containing water. No redness, swelling, or other signs of irritation were observed upon patch removal or at 48 and 72 hours.[26]

TDPA was then tested for dermal sensitization in guinea pigs (number of guinea pigs not stated). The test solution, 0.1 mL, containing 0.8 mg/mL TDPA was injected intradermally into one side of the back of the guinea pigs; a saline injection on the opposite side served as a control. The TDPA solution caused slight erythema and edema following the injections, but these reactions did not increase in intensity or duration throughout the experiment and thus were considered local irritation rather than sensitization.[26]

Phototoxicity

Dilauryl thiodipropionate. Bio-Technics Laboratories tested a makeup foundation containing 0.05% DLTDP for phototoxicity using 6 New Zealand white rabbits.[36] The upper area of the back of each rabbit was shaved, and the minimal erythemal dose (MED) for each rabbit was determined using a Hanovia ultraviolet (UV) quartz lamp. The test material, 0.5 mL, was applied to 3 sites on the shaved area and allowed to dry. A site to which no test material was applied served as the negative control, and a subcutaneous (SC) injection of 1% sulfanilamide was used as the positive control.

Of the test sites receiving 0.5 MED, positive reactions were noted at the 24-hour examination at the positive control sites of 2 of the rabbits; all other sites received scores of 0 at all evaluation times. Of the test sites receiving 1 MED, none of the DLTDP test sites had any reaction. Both the positive and negative control sites of each of the 6 rabbits received a score of 1 at the 24-hour reading. Of the test sites receiving 3 MEDs, no responses were observed at the 1-minute and 1-hour examinations. At the 24-hour examination, 4 of the 6 rabbits had scores of 1 at the DLTDP test site, and the remaining 2 rabbits had scores of 0. All of the negative control sites had scores of 1, and the positive control sites had scores of either 1 or 2. Average scores at the 24-hour examination were 0.3 for the DLTDP sites, 0.5 for the negative control sites, and 1.0 for the positive control sites. The makeup foundation containing 0.05% DLTDP was nonphototoxic under the conditions of the study.[36]

Ocular Irritation—In Vivo

Dilauryl thiodipropionate. In a modified Draize eye irritation test, an unspecified amount of a makeup foundation containing 0.05% DLTDP was instilled into the conjunctival sac of the eyes of 9 New Zealand albino rabbits. None of the rabbits had ocular reactions to the test material at any of the observation times, and the makeup foundation containing 0.05% DLTDP was considered nonirritating to rabbit eyes under the conditions of the study.[37]

One drop of a solution containing 0.8 mg/mL TDPA was placed into the right conjunctival sacs of 2 rabbits; the contralateral eyes received drops of saline and served as controls. No signs of irritation were observed at 24 or 48 hours.[26]

Ocular Irritation—In Vitro

Dilauryl thiodipropionate. EpiOcular tissues (lot 8726) were incubated in MatTek assay media for 1 hour, which was then replaced with fresh media. An amount of 100 μL of a facial product containing 4% DLTDP was applied to the top of each tissue. The tissues were exposed for 64, 256, or 1200 minutes. A negative control was performed using sterile deionized tissue culture water for 16 minutes, and a positive control was performed using 0.3% Triton X-100 for 15 and 45 minutes. The facial product was found to be nonirritating.[38]

Reproductive and Developmental Toxicity

Thiodipropionic Acid

Groups of female albino CD-1 mice (average of 21 pregnant mice per group) were intubated with 16, 74, 350, or 1600 mg/kg TDPA on days 6 to 15 of gestation.[39] (Day 0 of gestation

was confirmed by the presence of a vaginal plug.) Control mice were sham treated, and positive controls were administered 150 mg/kg aspirin. Feed and water were available ad libitum. The mice were observed daily for general appearance and behavior, with emphasis on feed consumption. Body weights were determined on days 0, 6, 11, 15, and 17 of gestation. On day 17 of gestation, Cesarean sections were performed, and the numbers of implantation and resorption sites as well as the numbers of live and dead fetuses were recorded. The urogenital tract of each dam was examined for any abnormality, all fetuses were examined for any gross external abnormalities, and all live pups were weighed. Visceral examinations were performed on one third of the fetuses of each litter, and the remaining two thirds were examined for skeletal defects. No adverse effects were found with respect to implantations and maternal or fetal survival after oral administration to mice of up to 1600 mg/kg TDPA on days 6 to 15 of gestation. The number of abnormalities seen in the soft or skeletal tissues of the treated fetuses was comparable to that seen in the sham control fetuses.

This laboratory also performed a teratogenicity study of TDPA using female albino Wistar rats. Groups of pregnant rats (average of 21 pregnant rats per group) were intubated with 16, 74, 350, or 1600 mg/kg TDPA on days 6 to 15 of gestation. (Day 0 of gestation was confirmed by the presence of a vaginal plug.) Control rats were sham treated, and positive controls were administered aspirin at a dose of 250 mg/kg. The remaining study protocol followed that of the mouse study, with the exception that final dam weights were recorded and Cesarean sections were performed on day 20 of gestation. No adverse effects with respect to number of implantations and maternal or fetal death were noted after oral administration to rats of up to 1600 mg/kg TDPA on days 6 to 15 of gestation. There were no significant differences in numbers of abnormalities of the soft or skeletal tissues between the treated and sham control fetuses.

A teratogenicity study similar to the 2 previous studies was performed using female golden hamsters. Groups of 21 hamsters (average number of pregnant hamsters per group) were intubated with 16, 74, 350, or 1600 mg/kg TDPA on days 6 to 10 of gestation. (Day 0 of gestation was confirmed by the presence of motile sperm in a vaginal smear.) The hamsters were observed daily, as in the previous 2 studies, and weights were recorded on days 0, 8, 10, and 14 of gestation. Cesarean sections were performed on day 14, and numbers of implantations and resorption and live and dead fetuses were recorded. The urogenital tracts of the dams and the fetuses were examined as in the previous 2 studies. The numbers of implantations and maternal and fetal survival were not adversely affected by oral administration to hamsters of up to 1600 mg/kg TDPA on days 6 to 10 of gestation. No significant differences in the number of soft or skeletal tissue abnormalities were found between treated and sham control fetuses.[39]

Food and Drug Research Laboratories used adult female Dutch-belted rabbits in a teratogenicity study of TDPA.[40] On day 0, the rabbits were administered an IV injection of 0.4 mL of human chorionic gonadotropin, followed 3 hours later by artificial insemination with 0.3 mL of diluted semen. Groups of the rabbits were intubated with 10, 45, 216, or 1000 mg/kg TDPA on days 6 to 18 (average 10 rabbits per group at the end of the study). The control group rabbits were sham treated and the positive control group rabbits received a 2.5-mg/kg dose of 6-aminonicotinamide on day 9 of gestation. The rabbits had free access to feed and water and were observed daily for behavior, appearance, and feed consumption. Body weights were recorded on days 0, 6, 12, 18, and 29 of gestation. Cesarean sections were performed on day 29, and numbers of corpora lutea, implantation and resorption sites and live and dead fetuses were recorded. The urogenital tracts of the dams were examined for abnormalities, and all fetuses were examined for gross external abnormalities. Evaluation of neonatal survival was performed by placing all of the live fetuses in an incubator for 24 hours. After this time, surviving fetuses were examined by dissection for visceral abnormalities and then examined for skeletal defects. No adverse effects were found with respect to number of implantations or maternal or fetal survival after the oral administration to rabbits of up to 1000 mg/kg TDPA on days 6 to 18 of gestation. There were no significant differences between the treated and sham control fetuses in the numbers of soft or skeletal tissue abnormalities.

TDPA Genotoxicity

Bacterial Studies

Litton Bionetics tested TDPA for mutagenic effects in a plate test and an in vitro cytogenetics study.[33] TDPA was applied directly to cultures of *Salmonella typhimurium* G-46 and TA1530. Ten-fold serial dilutions, 5, 50, and 500 μg/mL TDPA, of the cultures were plated, and mutant colonies were noted and scored. Dilutions of *Saccharomyces cerevisiae* were shaken with the test material, diluted, and plated. Test results for *S cerevisiae* were recorded as percentage survival. No mutagenic effects were noted when TDPA was tested in vitro with *S typhimurium* G-46 and TA1530 or with *S cerevisiae* D-3 under the conditions of the study.

The mutagenic potential of TDPA was evaluated in a plate assay and a suspension assay using *S typhimurium* strains TA1535, TA1537, and TA1538 and *S cerevisiae* strain D4.[41] The tests were run with and without metabolic activation. For *S typhimurium*, concentrations of 0.00095%, 0.00190%, and 0.00380% were used; and for *S cerevisiae*, concentrations of 0.215%, 0.430%, and 0.860% were used. The positive controls without activation were ethylmethanesulfonate (EMS), 2-nitrofluorene, and quinacrine mustard. The positive controls with activation were dimethylnitrosamine (DMN), 2-acetylaminofluorene (2-AAF), 8-aminoquinoline, and 2-aminoanthracene. TDPA was not mutagenic in either the plate or the suspension assay.

Mammalian Cell Studies

Human embryonic lung cells (WI-38) were incubated with 5, 50, or 500 μg/mL TDPA; saline (negative control); or 0.1 μg/

mL triethylene melamine (TEM) (positive control) until an adequate number of mitoses were available for the examination of anaphase preparations. The investigators found a significantly higher percentage of chromosomal aberrations in the positive control cells than in the negative control or test compound cells.[33] No adverse effects were noted in human embryonic lung cells exposed to concentrations of up to 500 μg/mL TDPA.

In Vivo Studies

Litton Bionetics tested TDPA for mutagenic effects in a host-mediated assay, in in vivo cytogenetics studies, and in a dominant lethal assay.[33] In the host-mediated assay, groups of 10 male ICR mice were administered TDPA by intubation at doses of 50, 500, or 5000 mg/kg. The negative control group mice received saline, and the positive control group mice received either 100 mg/kg DMN (*Salmonella* study) or 350 mg/kg EMS (yeast study). The indicator organisms used were the G-46 and TA1530 strains of *S typhimurium* and the D-3 strain of *S cerevisiae*. The indicator organism, 2 mL, was administered intraperitoneally after intubation of the mice with the test material. The peritoneal fluid was removed 3 hours later under sterile conditions, and the indicator organisms were examined for mutants. There were no significant increases in reversion or recombination in *S typhimurium* strain TA1530 or in *S cerevisiae* strain D-3 after the administration of up to 5000 mg/kg TDPA. Reversions were induced in *S typhimurium* strain G-46. A short-term study was performed using the same protocol except that the mice received 5 oral doses of the test material at 24-hour intervals, and the indicator organism was injected within 30 minutes of the last dose of test material. Results of the short-term test were similar to those of the acute study, but the reversions seen in *S typhimurium* strain G-46 were not dose dependent. A repeat of the short-term test was performed with the same results.

Male albino rats were used in the in vivo cytogenetics study. In the acute phase of this study, groups of 15 rats were intubated with 50, 500, or 5000 mg/kg TDPA. The negative control group, 9 rats, received saline, and the positive control group, 5 rats, received 0.3 mg/kg TEM. No significant aberrations were noted in rat bone marrow metaphase cells after acute or short-term (5-day) oral administration of up to 5000 mg/kg TDPA.

The dominant lethal assay of TDPA in rats consisted of an acute phase and a short-term phase. Groups of 10 male rats were intubated with 50, 500, or 5000 mg/kg TDPA or with saline (negative control). Positive control rats received an IP injection of 0.3 mg/kg TEM. The rats of the acute study received a single dose, whereas the rats of the short-term study received 1 dose per day for 5 days. Following dosing, the male rats were sequentially mated to 2 female rats per week for 8 weeks in the acute study and for 7 weeks in the short-term study. The female rats were killed 14 days after separation from the male rat and were examined for the number of early and late fetal deaths and for the number of total implantations. There were instances of significant differences in fertility indices, number of implantations per pregnant female, average corpora lutea, average preimplantation losses, average resorptions, and proportion of females with 1 or more dead implantations in both phases of the study. Significant differences were usually dose related, but there was no clear pattern of either increases or decreases between the control and test groups in any of the parameters studied. TDPA was considered nonmutagenic under the conditions of the study.[33]

Inhibition of Mutagenesis

The ability of TDPA to inhibit *N*-methyl-*N′*-nitro-*N*-nitrosoguanidine (MNNG)–induced mutagenic activity was evaluated. TDPA, 1 or 10 mM, did not have a detectable effect on the spontaneous mutation frequency of MNNG-treated *S typhimurium* strain TA1535.[42] TDPA, 10^{-2} and 10^{-3} M, inhibited MNNG-induced mutagenesis in TA1535 by 22% and 17%, respectively.[43]

Clinical Assessment of Safety

Dermal Irritation

Dilauryl thiodipropionate. A makeup foundation containing 0.05% DLTDP was evaluated in a supervised usage test with 30 subjects aged 20 to 58 years. The study participants used the product as they would any other product purchased over the counter; the foundation was used daily for 4 weeks. At the end of the fourth week of use, the subjects were checked for any reactions and were asked for their subjective comments. Two subjects did not complete the study; 1 subject discontinued use after 2 weeks, commenting that the product caused acneiform lesions, and the other subject discontinued use after 3 days because of erythema, although erythema was not noted upon objective evaluation. None of the remaining subjects had reactions to the makeup foundation containing 0.05% DLTDP.[44]

Seventeen male and female subjects applied 0.2 mL of a facial product containing 4% DLTDP twice daily to the face for 4 days. The subjects did not use makeup or additional moisturizers during this time. Each afternoon, the subjects underwent a visual examination, facial wash, and reapplication of product. A discomfort questionnaire was filled out each day in addition to a gentleness questionnaire at the end of the study. One subject experienced an increase in erythema and a papule above the lip on day 2, which both returned to baseline on day 4. Four of the 17 subjects reported discomfort after using the product, ranging from somewhat irritating to very irritating. None of these effects lasted more than 5 minutes.[45]

Fifty-five female subjects applied a facial product with 4% DLTDP twice a day for 28 days. The subjects were instructed not to alter their normal cosmetological or grooming routines during this time, and no new products were to be used. Dermatological examinations were performed on day 14 and day 28. Sixteen subjects exhibited persistent mild or very slight erythema throughout. Eleven exhibited transient mild or very

slight erythema, of which 4 exhibited this on day 28. All others had no reaction.[46]

Thiodipropionic acid. A 24-hour single-insult occlusive patch test (SIOPT) was performed to determine the irritation potential of a product containing 2% TDPA.[47] Twenty subjects (gender not specified) were used, and the product was applied undiluted. A hydrating cream was used as a control material. Staining of the skin was observed. The product containing 2% TDPA did not produce any irritation reactions in any of the subjects in the SIOPT.

A 14-day cumulative irritation assay was performed to determine the irritation potential of a facial serum and a face cream containing 2% TDPA.[48] Twenty-seven female subjects were used in the repeat insult patch test (RIPT) in which 0.05 mL of each test material was applied under an occlusive patch to an area of the upper back daily 5 days per week for a total of 14 days; the patches were left in place over the weekend. Each test site was graded on a scale of 0 to 5 upon patch removal. A negative control (a plain Webril patch) and a positive control (0.25% sodium lauryl sulfate [SLS]) were also applied following the same protocol. The facial serum containing 2% TDPA had a sum of cumulative scores of 1 (1 subject had an irritation score of 1 on day 11), and a cumulative irritation index (CII) of 0. The face cream containing 2% TDPA and the negative control did not produce any irritation responses. All 3 were considered to have negligible irritation potential. The positive control, 0.25% SLS, had a CII of 0.6 and was considered to have severe irritation potential.

Dermal Sensitization

Dilauryl thiodipropionate. A makeup foundation containing 0.05% DLTDP was tested for irritation and sensitization potential using a modified Draize-Shelanski-Jordan patch test on 224 volunteers of both genders and of mixed ethnicity (African American, Asian or Pacific Islander, Hispanic, or white). Potential test subjects were excluded from the study if they had skin disease that could affect the interpretation of test results, if they were undergoing treatment for skin diseases other than dandruff or athlete's foot, or if they were taking anti-inflammatory medication. The test material, 0.2 mL, was applied to an occlusive patch and allowed to dry before being placed on the upper back of each subject. Patches remained in place for 24 hours, and upon removal, the patch test sites were evaluated and reactions were rated on a scale of 0 (no reaction) to 4 (intense erythema with edema and vesicles). A nontreatment period of 24 hours followed the initial patch application. The test sites were reevaluated before the application of the next patch. This procedure was followed every Monday, Wednesday, and Friday (there was a 48-hour nontreatment period over the weekends) for a total of 10 patch applications. A 13-day nontreatment period followed the tenth induction patch. At the end of this period, a 48-hour challenge patch was applied to the same site as the induction patches. Test sites were scored immediately upon patch removal. A second 48-hour challenge patch was applied 1 week later. This site was scored immediately upon patch removal and again at 72 hours.

Thirteen of the test subjects did not complete the entire study. No signs of irritation were observed in any of these subjects at the time they left the study. Of the remaining 211 test subjects, 1 had a nonspecific irritation reaction during the induction phase of the study; this reaction had subsided prior to the next patch application and did not recur. No reactions were observed in any of the other test subjects. Under the conditions of the study, the makeup foundation containing 0.05% DLTDP was neither an irritant nor a sensitizer to human skin.[49]

A maximization test was performed with a facial lotion containing 4% DLTDP using 26 subjects (21 female, 5 male; 18-64 years old). During the induction phase, 0.5 mL of 0.25% SLS was applied to a site on the upper outer arm, volar forearm, or back of each subject under an occlusive patch for 24 hours. Upon removal of the SLS patch, an occlusive patch containing 0.05 mL of the facial lotion was applied to the same site for 48 hours (or 72 hours on the weekends). The site was examined upon patch removal. If no irritation were present, the same SLS patch/test patch sequence was repeated. This continued for a total of 5 induction exposures. (If irritation developed at any point of the induction phase, the SLS patch was omitted.) After a 10-day nontreatment period, the challenge was performed in which a previously untreated site was pretreated with an occlusive patch of 0.5 mL of 5% SLS for 1 hour followed by an occlusive 48-hour patch containing 0.05 mL of the test material. The challenge site was graded on a scale of 0 to 3 at 15 to 30 minutes and 24 hours after patch removal. No incidences of adverse or unexpected reactions were observed during the induction phase, during the challenge phase, or after the challenge phase.[50]

Thiodipropionic acid. A maximization test was performed according to the procedure described previously using 26 subjects, 17 females and 9 males, to determine the sensitization potential of a face cream containing 2% TDPA.[51] One subject did not complete the study for non-test article–related reasons. Of the remaining 25 subjects, no adverse or unexpected reactions were observed during the induction phase, and no evidence of sensitization was seen at challenge. The researchers concluded that a face cream containing 2% TDPA did "not possess a detectable contact-sensitizing potential."

Phototoxicity/Photoallergenicity

Dilauryl thiodipropionate. A test for the phototoxic and photoallergenic potential of a makeup foundation containing 0.05% DLTDP was conducted on 27 adult volunteers of both genders and of mixed ethnicity (African American, Asian or Pacific Islander, Hispanic, or white). In the phototoxicity phase of the study, an MED was established for each subject using a Kromayer hot quartz spot lamp prior to application of the test substance. The test substance, approximately 5 mL/cm^2, was applied to 2 sites on the back of each test subject. One site was covered, and the second site as well as an untreated site was exposed to 1 MED of UV light. The test sites were graded immediately after exposure to the UV light and again 24 and 48 hours later.

For the second phase of the study (photoallergenicity), approximately 5 μL/cm^2 of the test substance was applied to 2 sites on the back of each subject, and the test sites were covered with patches. The patches were removed after 24 hours, and 1 treated site, as well as 1 untreated site, were exposed to 30 seconds of window glass–filtered light from a Kromayer hot quartz spot lamp. Test sites were evaluated for signs of irritation immediately after UV light exposure. After a minimum of 24 hours, the above procedure was repeated. This procedure of 2 applications per week was continued for a total of 8 induction applications. After a 12-day nontreatment period, the test substance was applied to 2 additional sites on the back of each subject. After 24 hours, the challenge patches were removed and 1 patch site and an untreated site were exposed to window glass–filtered UV light for 30 seconds. The challenge sites were graded 24 and 48 hours after irradiation using a scale of 0 (no reaction) to 4 (erythema with edema and blistering). The treated sites that were not irradiated and the untreated sites that were irradiated served as controls.

In the phototoxicity phase of the study, no erythema was observed at any of the test sites during any of the observation periods. No signs of erythema or edema were noted in any of the test subjects during either the induction or challenge phases of the photoallergenicity phase of the study. The makeup foundation containing 0.05% DLTDP was considered neither a phototoxin nor a photoallergen to human skin under the conditions of the study.[52]

Thiodipropionic acid. A test was performed to determine the phototoxic potential of a face cream containing 2% TDPA using 29 female subjects with fair skin (type I, II, or III).[53] The MED of each subject was determined prior to dosing using a 150-W compact xenon arc solar simulator; total irradiance at skin level was 210 mW/cm^2 and UVA irradiance was 142.5 mW/cm^2. Two occlusive patches containing 40 mg of the test product were applied to the lower back at a site that was normal in appearance and free of irritation and blemishes. One patch was removed 24 hours after application and the site was exposed to 10 J/cm^2 UVA and 0.5 MED of full-spectrum solar-simulated radiation (SSR). The second test site served as an unirradiated control. A third site was patched with vehicle and irradiated in the same manner as the test site and served as an irradiated control. Reactions were scored on a scale of 0 to 4 immediately and at 24 and 48 hours after irradiation. No reactions of phototoxicity were observed in any of the subjects, and the researchers concluded that a face cream containing 2% TDPA did "not possess a detectable phototoxic potential in human skin."

The photoallergenicity potential of a face cream containing 2% TDPA was determined.[54] The MED of each of the 29 fair-skinned female subjects was first determined using a 150-W compact xenon arc source; total irradiance at skin level was 202.5 mW/cm^2 and UVA intensity was 142.5 mW/cm^2. Induction consisted of an RIPT in which 40 mg of the test material was applied to the lower back of each subject for 24 hours. Upon patch removal, the test site was exposed to 3 MEDs and then left uncovered for 48 hours. A patch was then applied to the same test site following the same procedure; this was repeated twice weekly for 3 weeks for a total of 6 exposures. Eleven days after the last induction dose, the subjects received a single challenge exposure. Duplicate occlusive patches were applied to a previously untreated area of the lower back for 24 hours. One patch was removed, and the site was irradiated with 0.5 MED of SSR and 4 J/cm^2 UVA. The duplicate patch site served as an unirradiated control site. All test sites were scored on a scale of 0 to 3 at 48 and 72 hours after UV exposure. One subject was dropped from the study for unrelated reasons. No adverse effects were observed in any of the 28 remaining subjects, and the researchers concluded that a face cream containing 5% TDPA did "not possess a detectable photocontact-sensitizing potential in human skin."

Summary

DLTDP, dicetyl thiodipropionate, dimyristyl thiodipropionate, distearyl thiodipropionate, and ditridecyl thiodipropionate are the diesters of their respective alcohols and TDPA. DLTDP may contain the following impurities: TDPA, sulfated ash, arsenic, lead, or heavy metals. DLTDP may be identified by its solidification point or by infrared spectrum.

DLTDP, dicetyl thiodipropionate, dimyristyl thiodipropionate, distearyl thiodipropionate, and ditridecyl thiodipropionate function as antioxidants, whereas TDPA functions as a miscellaneous skin-conditioning agent. DLTDP is used in a total of 11 cosmetic formulations at concentrations up to 4%. TDPA is used in 15 cosmetic formulations at concentrations of 1% to 2%. Dicetyl, dimyristyl, distearyl, and ditridecyl thiodipropionate are not reported to be used. Both DLTDP and TDPA are considered GRAS food substances by the FDA. Both are approved as direct food additives.

TDPA and DLTDP, when administered to rats, were largely excreted in the urine within the first 24 hours. Urinary excretion accounted for the major amount of the radioactivity eliminated, whereas radioactive CO_2 accounted for most of the remaining amount. A minor pathway of elimination of radioactivity was the feces. TDPA, when administered to rats or rabbits, was excreted in the urine either unchanged or as a conjugate of TDPA that was not a glucuronide. DLTDP was excreted in the urine of rats and dogs as TDPA or an acid labile conjugate of TDPA. After administration of radioactive DLTDP, radioactivity was retained in fatty tissue.

TDPA, DLTDP, and distearyl thiodipropionate were slightly toxic when administered orally to mice (LD_{50} $\geq$2000 mg/kg) and rats (LD_{50} >2500 mg/kg). TDPA, when administered intraperitoneally, was moderately toxic to mice (LD_{50} 250 mg/kg) and rats (LD_{50} >200 mg/kg), whereas DLTDP and distearyl thiodipropionate were slightly toxic (LD_{50} >2000 mg/kg). TDPA was moderately toxic when administered intravenously to mice (LD_{50} 175 mg/kg) and rats (LD_{50} >300 mg/kg).

TDPA and DLTDP were considered relatively nontoxic in subchronic oral toxicity studies with rats. No specific

treatment-related effects were noted when 0.5% TDPA was administered in the drinking water to guinea pigs for 4 months.

In a chronic oral toxicity study using rats, DLTDP was more toxic over a period of time than was TDPA, but no significant differences in weight gain and general appearance were found between the control or test groups. In a second chronic oral toxicity study using rats, TDPA and DLTDP had no significant effects on weight gain. By the end of the 2-year study, mortality was higher in the DLTDP test groups. When a mixture of DLTDP and TDPA in lard was administered to rats in their diet for 1 year, there were no significant differences in average weight, average feed consumption, and mortality between the control and low-dose groups. No other signs of toxicity were noted in these 2 groups for the study period. Most of the rats of the high-dose group died during the last 6 months of the study, but these deaths were not considered treatment related.

No irritation was produced by a makeup foundation containing 0.05% DLTDP on intact and abraded skin of New Zealand white rabbits. Neither TDPA nor DLTDP produced signs of irritation when applied to the shaved skin of rabbits for 24 hours. A makeup foundation containing 0.05% DLTDP, when tested at 0.0025%, was not a sensitizer in a guinea pig maximization test. TDPA was tested for sensitization potential in guinea pigs, and although there were signs of local irritation at the injection sites, the TDPA was not considered a sensitizer. DLTDP, at a concentration of 0.05% in a makeup foundation, was not phototoxic to New Zealand white rabbits.

No signs of irritation were observed when a makeup formulation containing 0.05% DLTDP or a solution containing 0.8 mg/mL TDPA was placed into the conjunctival sacs of rabbits.

TDPA was neither a teratogen nor a reproductive toxicant when administered orally during gestation to mice, rats, hamsters, or rabbits.

In a host-mediated assay, TDPA 5000 mg/kg or less was negative for reversions in *S typhimurium* strain TA1530 and in *S cerevisiae* strain D-3 after a single oral dose and after 5 consecutive oral doses administered at 24-hour intervals. Reversions were noted in *S typhimurium* strain G-46; the reversions appeared to be dose dependent in the single-dose study but not in the 5-day study. The 5-day study was repeated with the same results. No mutagenic effects were noted when TDPA 500 μg/mL or less was tested in vitro using *S typhimurium* and *S cerevisiae*. TDPA, 5000 mg/mL or less administered orally, was negative for chromosomal aberrations in rat bone marrow metaphase cells. No adverse effects were noted after exposure of human embryonic cells to TDPA500 μg/mL or less. TDPA was considered nonmutagenic in dominant lethal assays in rats in which TDPA 5000 mg/kg or less was administered either as a single oral dose or as 5 consecutive doses over 5 days.

TDPA did not have an effect on MNNG-induced mutagenesis.

DLTDP, at a concentration of 0.05% in a makeup foundation, was not an irritant or a sensitizer when tested on 224 healthy human volunteers using a modified Draize-Shelanski-Jordan patch test or in a supervised usage test with 30 subjects. A makeup foundation containing 0.05% DLTDP was not a phototoxin or a photoallergen when tested in 27 healthy human volunteers. A facial product containing 4% DLTDP tested using 55 adult females caused 16 cases of persistent mild/very slight erythema and 11 cases of transient mild/very slight erythema after 28 days. Of 17 male and female subjects using a 4% DLTDP facial lotion, 1 experienced erythema that eventually returned to baseline, and 4 experienced discomfort that ranged from somewhat to very irritating; these effects did not persist for more than 5 minutes. A face cream containing 2% TDPA did not produce any irritation in an SIOPT. In a 14-day cumulative irritation study, a face serum and a face cream containing 2% TDPA were not irritants.

A maximization study of a facial lotion containing 4% DLTDP with 26 subjects yielded no adverse or unexpected reactions, and a maximization study of a face cream containing 2% TDPA was also negative for sensitization. In clinical phototoxicity and photoallergenicity studies, products containing 0.05% DLTDP and 2% TDPA were not phototoxic or photoallergenic.

Discussion

The CIR Expert Panel noted that the available data for dialkyl esters of TDPA address primarily DLTDP. It is the experience of the Expert Panel that if shorter side chain esters exhibit little significant toxicity, then it is likely that the same will be true for longer side chain fatty esters. Therefore, the Expert Panel considered that safety test data on DLTDP were relevant to the safety of dicetyl thiodipropionate, dimyristyl thiodipropionate, distearyl thiodipropionate, and ditridecyl thiodipropionate.

The acute, subchronic, and chronic safety test data, mostly from oral feeding studies, supported that the ingredients included in this report are relatively nontoxic at dietary concentrations up to the 3.0% tested. Likewise, there was no indication of reproductive or developmental toxicity in oral studies using TDPA at levels up to 1.6 g/kg per day. TDPA was not genotoxic in bacterial, mammalian, and in vivo assays.

Although many of the available dermal exposure studies used DLTDP at only 0.05%, clinical studies have been performed using products containing DLTDP at a concentration of 4% and TDPA at a concentration of 2% with no adverse reactions reported. The Expert Panel noted that some irritation was reported at 4%, and cosmetic products should be formulated to be nonirritating.

Conclusion

The CIR Expert Panel concludes that dilauryl thiodipropionate, thiodipropionic acid, dicetyl thiodipropionate, dimyristyl thiodipropionate, distearyl thiodipropionate, and ditridecyl thiodipropionate are safe as cosmetic ingredients in the practices of use and concentration given in this safety assessment when formulated to be nonirritating. Were the dialkyl esters of TDPA that are not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to DLTDP.

Authors' Note

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 1101 17th Street, Suite 412, Washington, DC 20036.

Declaration of Conflicting Interests

No potential conflict of interest relevant to this article was reported. F. Alan Andersen, PhD, Catherine Diamante, and Monice Zondlo Fiume are or were employed by Cosmetic Ingredient Review.

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References

1. Elder RL. Final report on the safety assessment of dilauryl thiodipropionate. *J Am Coll Toxicol*. 1992;11:25-41.
2. Gottschalck TE, Bailey J, eds. *International Cosmetic Ingredient Dictionary and Handbook.* Vols 1 and 3. 12th ed. Washington, DC: Cosmetic, Toiletry and Fragrance Association; 2008.
3. Elder RL. Final report on the safety assessment of cetearyl alcohol, cetyl alcohol, isostearyl alcohol, myristyl alcohol, and behenyl alcohol. *J Am Coll Toxicol*. 1988;7:359-413.
4. Cosmetic Ingredient Review. Reconfirmed safety assessment of cetearyl alcohol, cetyl alcohol, isostearyl alcohol, myristyl alcohol, and behenyl alcohol; 2005.
5. Elder RL. Final report on the safety assessment of stearyl alcohol, oleyl alcohol, and octyl dodecanol. *J Am Coll Toxicol*. 1985;4: 1-29.
6. Andersen FA. Final amended report on the safety assessment of stearyl alcohol, oleyl alcohol, and octyl dodecanol. *Int J Toxicol*. 2006;25(suppl 2):73-78.
7. Chemical Land 21. Dilauryl thiodipropionate, thiodipropionic acid, and dimyristyl thiodipropionate; 2008. http://www.chemicalland21.com/specialychem/finechem. Accessed November 2, 2008.
8. Sax NI. *Dangerous Properties of Industrial Materials*. 5th ed. New York, NY: Van Nostrand Reinhold; 1979.
9. Hawley GG, ed. *The Condensed Chemical Dictionary.* 8th ed. New York, NY: Van Nostrand Reinhold; 1971.
10. *Food Chemicals Codex*. Washington, DC: National Academy Press; 1996.
11. Estrin NF, Haynes CR, Whelan JW, eds. *CTFA Compendium of Cosmetic Ingredient Composition. Specifications/Spectra.* Washington, DC: CTFA; 1982.
12. Gresham TL, Shaver FW. United States Patent Office. Patent 2,449,992. Preparation of beta-thio carboxylic acid compounds; 1948.
13. Food and Drug Research Laboratories. *Scientific Literature Reviews on Generally Recognized as Safe (GRAS) Food Ingredients—Propionates and Thiodipropionates*. Springfield, Va: US Department of Commerce; 1974. Publication PB228538.
14. Kline DA, Joe FL Jr, Fazio T. A rapid gas-liquid chromatographic method for the multidetermination of antioxidants in fats, oils, and dried food products. *J Assoc Anal Chem*. 1978;61:513-519.
15. Tan S, Tadenuma S, Hojo M, et al. Determination of additives in polyethylene for food packaging (studies on plastic additives, III.) *J Food Hyg Soc Jpn*. 1986;27:229-237.
16. Kawamura Y, Watanabe K, Sayama K, Takeda Y, Yamada T. Simultaneous determination of polymer additives in polyethylene by GC/MS. *J Food Hyg Sci Jpn*. 1997;38:307-318.
17. Balsam MS, Sagarin E, eds. *Cosmetics Science and Technology.* Vol 3. 2nd ed. New York, NY: John Wiley; 1974:449-457.
18. Wilkinson JB, Moore RJ, eds. *Harry's Cosmeticology.* New York: Chemical Publishing; 1982:707-725.
19. US Food and Drug Administration. Voluntary Cosmetic Registration Program; 2008.
20. Cosmetic, Toiletry, and Fragrance Association (CTFA). Concentration of use information. Unpublished data submitted by CTFA; 2007.
21. Personal Care Products Council. Concentration of use of thiodipropionic acid. Unpublished data submitted by the Council; 2008.
22. Furia TE, ed. *CRC Handbook of Food Additives.* Vol 1. 2nd ed. Cleveland, OH: CRC Press; 1977.
23. World Health Organization. Seventeenth Report of the Joint FAO/WHO Expert Committee on Food Additives. *World Health Org Tech Rep Ser*. 1974, No. 539; FAO Nutrition Meetings Report Series, 1974, No. 53.
24. Gilbert J, Startin JR, McGuinness JD. Compositional analysis of commercial PVC bottles and studies of aspects of specific and overall migration into foods and stimulants. *Food Addit Contam*. 1986;3:133-143.
25. Garde JA, Catalá R, Gavara R. Global and specific migration of antioxidants from polypropylene films into food stimulants. *J Food Prot*. 1998;61:1000-1006.
26. Tullar PE. Final report on the pharmacology and toxicology of thiodipropionic acid and its dilauryl and distearyl esters. Unpublished data; 1947. FDA FOI request F88-8055. Document 001974-002031.
27. Reynolds RC, Astill BD, Fassett DW. The fate of 14C-thiodipropionate in rats. *Toxiol Appl Pharmacol*. 1974;28: 133-141.
28. Brekke O-L, Shalaby MR, Sundad A, Espevik T, Bjerve KS. Butylated hydroxyanisole specifically inhibits tumor necrosis factor-induced cytotoxicity and growth enhancement. *Cytokine*. 1992;4:269-286.
29. Tullar PE, Hazelton LW, Hellerman R. Pharmacological properties of thiodipropionic acid, dilauryl thiodipropionate, and distearyl thiodipropionate: a progress report. Unpublished data; November 1, 1946. FDA FOI request F88-8055. Document 001927-001973.
30. Lehman AJ, Fitzhugh OG, Nelson AA, Woodard G. The pharmacological evaluation of antioxidants. *Adv Food Res*. 1951;3: 197-208.
31. World Health Organization (WHO). Evaluation of the toxicity of a number of antimicrobials and antioxidants. Sixth Report of the Joint FAO/WHO Expert Committee on Food Additives. *World Health Org Tech Rep Ser*. 1962;228:99-101.
32. Radeva M, Dinoeva S. Toxicological study of the stabilizers Santonox and Advastab PS 800 used in the production of polyethylene for the food industry. *Khig Zdraveopazvane*.

1970;13:217-221. *Cited in Chem Abstr*. 1970;73:75771t (from reference 20).

33. Litton Bionetics. *Mutagenic Evaluation of Compound FDA 71-40: Dilauryl Thiodipropionic Acid*. Springfield, Va: U.S. Dept of Commerce, National Technical Information Service; 1973. Publication PB-245 452.
34. Bio-Technics Laboratories. Primary dental irritants. Test report 1-2-20673-4. Submission of unpublished data by CTFA; 1979.
35. Bio-Technics Laboratories. Guinea pig maximization test. Test report 1-2-22830-4. Submission of unpublished data by CTFA; 1979.
36. Bio-Technics Laboratories. Phototoxicity. Test report 1-2-22830-5. Submission of unpublished data by CTFA; 1979.
37. Bio-Technics Laboratories. Modified Draize eye irritation. Test report 1-2-22830-2. Submission of unpublished data by CTFA; 1979.
38. MB Research Laboratories. EpiOcular MTT Viability Assay. Unpublished data submitted by MB Research Laboratories; 2007.
39. Food and Drug Research Laboratories. *Teratologic Evaluation of FDA 71-40 (Dilauryl Thiodipropionic Acid) in Mice, Rats, and Hamsters*. Springfield, Va: US Dept. of Commerce, National Technical Information Service; 1972. Publication PB 221 77.
40. Food and Drug Research Laboratories. *Teratologic Evaluation of FDA 71-40 (Dilauryl Thio-Dipropionic Acid) in Rabbits*. Springfield, Va: US Department of Commerce; 1973. Publication PB 223 824.
41. Litton Bionetics. *Mutagenic Evaluation of Compound FDA 75-35, 000111-17-1, Thiodipropionic Acid 99.7%*. Springfield, Va: US Dept of Commerce, National Technical Information Service; 1976. Publication PB257874.
42. Rosin MP, Stich HF. Assessment of the use of the *Salmonella* mutagenesis assay to determine the influence of antioxidants on carcinogen-induced mutagenesis. *Int J Cancer*. 1979;23: 722-727.
43. Rosin MP. The use of a bacterial assay to identify which agents modify carcinogen-induced mutagenesis. *Short-Term Tests Chem Carcinog*. 1981:449-456.
44. UCLA. Supervised usage test of a makeup foundation containing 0.05% DLTDP. UCLA M-85-U.087. Study 018282 114E1-272. Submission of unpublished data by CTFA; 1985.
45. CTFA. Clinical safety memorandum: spot removal—step 1 (lotion), facial use test. Unpublished data submitted by CTFA; 2007.
46. Harrison Research Laboratories. Facial treatment use test: final report. Unpublished data submitted by Harrison Research Laboratories; 2007.
47. Research and Development. Clinical evaluation report: human patch test of a test material containing 2% thiodipropionic acid. Unpublished data submitted by the Council; 2004.
48. KGL. A 14-day cumulative irritation assay of face products containing 2% thiodipropionic acid. Unpublished data submitted by the Council; 2008.
49. Bio-Technics Laboratories. Modified Draize-Shelanski-Jordan human patch test. Test report 1-2-21130-8. Submission of unpublished data by CTFA; 1979.
50. KGL. An evaluation of the contact-sensitization potential of a topical coded product in human skin by means of the maximization assay. Unpublished data submitted by KGL; 2007.
51. KGL. An evaluation of the contact-sensitization potential of a topical coded product containing 2% thiodipropionic acid in human skin by means of the maximization assay. Unpublished data submitted by the Council; 2004.
52. Bio-Technics Laboratories. Human phototoxicity and photoallergenicity. Test report 1-2-21131-8. Submission of unpublished data by CTFA; 1979.
53. KGL. Human phototoxicity test of one coded topical product containing 5% Thiodipropionic Acid. Unpublished data submitted by the Council; 2005.
54. KGL. An assessment of the photocontact allergenicity potential of a topical coded product containing 5 thiodipropionic acid in human skin using an assay for phototcontact allergenicity. Unpublished data submitted by the Council; 2005.