JOURNAL OF THE AMERICAN COLLEGE OF TOXICOLOGY
Volume 11, Number 1, 1992
Mary Ann Liebert, Inc., Publishers

2

Final Report on the Safety Assessment of Dilauryl Thiodipropionate

Dilauryl Thiodipropionate (DLTDP) is the diester of lauryl alcohol and 3,3'-thiodipropionic acid which is used as an antioxidant and sequestering agent in cosmetics at concentrations up to 1%.

When administered orally to rats and mice, DLTDP was slightly toxic and was relatively nontoxic in subchronic oral studies with rats. No irritation was produced by a formulation containing 0.05% DLTDP when tested at 0.0025% on intact and abraded skin. DLTDP was nonmutagenic in four different assay systems. This cosmetic ingredient was not a teratogen or reproductive toxicant in oral studies in mice, rats, hamsters or rabbits. A formulation containing 0.05% DLTDP when tested at 0.05% was not a sensitizer in a guinea pig maximization test. DLTDP, at a concentration of 0.05% in a makeup foundation, was not an irritant, sensitizer, or phototoxin when tested on human volunteers.

The maximum reported safety test concentration used in dermal toxicity of DLTDP was 0.05%. The report limits its safety conclusion by concluding that DLTDP is safe for use in cosmetic products at the maximum dermal tested concentration of 0.05%.

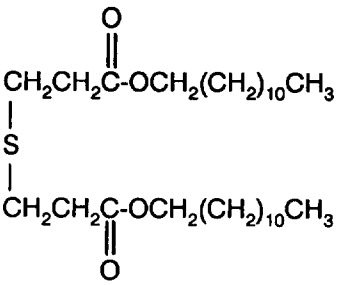
INTRODUCTION

The following is a literature review on the chemistry, use, and toxicology of Dilauryl Thiodipropionate. Dilauryl Thiodipropionate generally is recognized as safe (GRAS) as a food additive. The toxicologic data received under the Freedom of Information (FOI) Act from the Food and Drug Administration (FDA) were from studies on either dilauryl thiodipropionic acid, thiodipropionic acid, or thiodipropionic acid and its dilauryl ester (Dilauryl Thiodipropionate). All of these studies are included in this report.

CHEMISTRY

Definition and Structure

Dilauryl Thiodipropionate (CAS No. 123-28-4) is the diester of lauryl alcohol and 3,3'-thiodipropionic acid (TDPA). It conforms to the following structure:[1]



Dilauryl Thiodipropionate is also known as didodecyl 3,3'-thiodipropionate,[1-3] thiobis (dodecylpropionate), *bis*(dodecyloxycarbonylethyl) sulfide,[4] and thiodipropionic acid, dilauryl ester.[2,3]

PROPERTIES

Dilauryl Thiodipropionate (DLTDP) occurs as white, crystalline flakes and has a characteristic sweet ester odor. It is soluble in most organic solvents and insoluble in water.[2,3,5,6] Its melting/solidification point is 40°C,[2,6] and in solid form at 25°C, it has a specific gravity of 0.975.[2,3]

IMPURITIES

Cosmetic grade DLTDP may contain up to 0.2% free carboxylic acids (as thiodipropionic acid). It may have a maximum of 0.1% sulfated ash, 3 ppm arsenic, and 20 ppm lead.[6] The Food Chemicals Codex (FCC)[5] lists the same specifications for acidity, ash, and arsenic, but it specifies that DLTDP may not contain more than 10 ppm lead nor more than 0.002% heavy metals.

ANALYTICAL METHODS

DLTDP may be identified by its solidification point.[5] An infrared (IR) spectrum for DLTDP has been published.[6]

CHEMICAL REACTIONS

Oils and fats, essential oils, perfumes, vitamins, and to a lesser degree, other organic compounds, are prone to oxidation, specifically auto-oxidation. Unsaturation tends to increase the incidence of oxidation, and even small amounts of unsaturated

compounds in a formulation are sufficient to start a chain reaction of oxidative deterioration. Antioxidants are added to cosmetic formulations to impede the oxidation reactions and to help preserve color and texture of the product.[7] The mechanism and rates of oxidation of fats and oils is not completely understood, but it is agreed that the first stage involves the production of an oxide or peroxide, initiated by a free radical. Antioxidants react as free radical scavengers.[8] Antioxidants may also supply the hydrogen atoms that are required to end the initiation or propagation of the oxidation chain reaction.[9] Thiodipropionates, in the antioxidant class of organic acids, alcohols, and esters,[7] also are widely used as sequestering agents.[8] As sequestering agents, the thiodipropionates are often used in conjunction with the phenol class of antioxidants.[8] The antioxidant combination of thiodipropionate and phenols is synergistic.[7,8] 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 may cause discoloration and odors when used in higher concentrations.[8]

USE

Cosmetic

United States

DLTDP is used in cosmetics as an antioxidant and sequestering agent.[7,8]

Data submitted to the Food and Drug Administration in 1988 indicate that DLTDP was used in a total of 53 cosmetic products (Table 1). Product types containing DLTDP include eye and face makeup products, skin care, and fragrance products, and skin cleansing preparations.[10] The greatest use of DLTDP was in the categories of eye and face makeup products (34 products) and skin care and fragrance products (13 products). All of the formulations contained DLTDP at concentrations of ≤1%.

A more detailed listing of cosmetic product formulations[11] indicates that DLTDP was used in eye makeup preparations, fragrance preparations; tonics, dressings, and other hair grooming aids; foundations, makeup bases, rouges, and other makeup preparations; skin cleansing products; face, body, and hand preparations (excluding shaving preparations); and in moisturizing products, night cream preparations, and other skin care preparations. In 1984, DLTDP was used in a total of 70 cosmetic formulations at concentrations of up to 1% (except for one makeup base in which DLTDP was reported to be in the concentration range 10–25%). The greatest use of DLTDP was in the category of makeup bases (41 products) and moisturizing products

TABLE 1. PRODUCT FORMULATION DATA FOR DILAURYL THIODIPROPIONATE[10]

Product category	*Total no. of formulations in category*	*Total no. containing ingredient*	*No. of product formulations within each concentration range (%)* ≤1
Eye and face makeup products	1131	34	34
Skin care and fragrance products	2303	13	13
Skin cleansing preparations	730	6	6
1988 TOTALS		53	53

Source: From Ref. 10.

(11 products). The FDA cosmetic product formulation computer printout[12] is compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations.[13] Ingredients are listed in preset concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product; the actual concentration would be a fraction of that reported to the FDA. Data submitted within the framework of preset concentration ranges provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration.

Cosmetic products containing DLTDP may come into contact with all parts of the body, including the eye area and mucous membranes. Products containing DLTDP may be applied repeatedly throughout the day or over an extended period of time, and may remain in contact with the skin for variable periods of time or be rinsed off.

International

DLTDP is approved for use in cosmetic formulations by the Japan Ministry of Health and Welfare as a traditional cosmetic ingredient.[14]

Noncosmetic

As previously mentioned, both DLTDP and thiodipropionic acid (TDPA) are GRAS food substances.[15–17] DLTDP and TDPA were accepted as direct food additives by the FAO/WHO Expert Committee on Food Additives.[18] Recommended daily unconditional intake allowances of 0–3 mg/kg and conditional allowances of 3–15 mg/kg for these two food additives were approved by the FAO/WHO Expert Committee on Food Additives.

The principal noncosmetic use of DLTDP is as an antioxidant in edible fats and oils and especially in food wraps and films.[2,15,17] In foods, DLTDP is restricted to a concentration of not more than 0.02% of the fat and oil content, including essential oil content, of the food.[15,17]

As an antioxidant, DLTDP is used as an additive for high pressure greases and lubricants. It is also used as a softening agent and as a plasticizer.[2] DLTDP may be a minor component of polyvinyl chloride (PVC) bottles.[19]

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, and Excretion

Carboxyl-[^{14}C]TDPA and Carboxyl-[^{14}C]DLTDP were administered to fasted male Sprague-Dawley rats (number of rats not stated) either in the feed or by intubation.[20] When the TDPA and DLTDP were administered in the diet, the lab chow was placed in the cages with the fasted rats and allowed to remain in place for 4–8 h. When the test materials were administered by stomach tube, the TDPA was dissolved in 1:1 ethanol-water, and the DLTDP was dissolved in corn oil. Sample collections were made at 24-h intervals. Doses were 3.1, 241, 551, 572, and 650 mg/kg for the rats

receiving TDPA, and 107, 166, and 208 mg/kg for those receiving DLTDP. Approximately 90% of each 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% for TDPA, and from 0.1 to 3.5% for DLTDP). 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 resulting from treatment with TDPA and DLTDP. TDPA was excreted in the urine either unchanged or as an acid labile conjugate which was not a glucuronide. DLTDP was also excreted as either free TDPA or an acid labile conjugate. Oral administration of radioactive TDPA or DLTDP 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. Radioactivity was near normal in all of the tissues tested except in the adipose tissue of the rats administered DLTDP. The radioactivity in the adipose tissue of the rats administered DLTDP 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.

Rats, fed 3.0% TDPA or DLTDP in a chronic feeding study, were placed in individual metabolism cages and their urine was collected for 24 hours.[21] TDPA was found in the urine of test animals. The rats of the TDPA test group (five rats) consumed an average of 741 mg/rat/day of TDPA; an average of 87.5 mg/rat/day was excreted in the urine during the first 24 hours. The rats of the DLTDP test group consumed an average of 714 mg/rat/day of DLTDP. These rats excreted an average of 38.5 mg/rat/day of TDPA in the urine.

In a second study, groups of six rats also were placed in metabolism cages and the urine and feces were collected over a 24-h period.[21] The rats received 3.0% of either TDPA or DLTDP in the diet. The rats which received 3.0% TDPA consumed an average of 741 mg/rat/day, and excreted an average of 104.3 mg TDPA/rat/day. No TDPA was recovered from the feces. The rats receiving 3.0% DLTDP consumed an average of 715 mg DLTDP/rat/day and excreted an average of 55.7 mg TDPA/rat/day in the urine. No DLTDP was recovered from the urine and neither TDPA nor DLTDP was recovered from the feces.

The author of the above two studies concluded that the amount of chemical recovered in either the urine or feces did not account for the entire amount ingested, and that the TDPA and DLTDP were almost entirely absorbed from the intestine and were excreted in part in the urine.[21] 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.

A 75 mg/kg dose of TDPA was administered intravenously to a rabbit.[21] 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-h period.

Urine samples from dogs that received 0.1% or 3.0% DLTDP in the diet were analyzed for the presence of TDPA 24 hours after introduction of the test compounds in the feed.[21] 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. These data suggested that DLTDP was absorbed by the intestine and excreted by the kidneys as either TDPA or a conjugate of TDPA.

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

In acute oral toxicity studies using mice, the LD_{50} exceeded 1000 mg/kg for TDPA dissolved in water and 2000 mg/kg for DLTDP dissolved in olive oil.[22] Of the mice which died, some died up to 2 days after administration of the test material; the immediate cause of death was not determined.[21]

The LD_{50} in rats for DLTDP exceeded 2500 mg/kg.[18,20,23]

TDPA, 5000 mg/kg, in a suspension of 0.85% saline was administered by intubation to two adult male rats.[24] 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.

When TDPA was administered to rats in single oral doses of 1000 and 2000 mg/kg in saline, one of six rats of the low-dose group died 7 days after dosing, and two of 15 rats of the high-dose group died, one after 4 days and one after 7 days.[21] In the rats which received doses of 2000 or 2500 mg/kg of DLTDP in olive oil (five and ten rats, respectively) there was no mortality. No lesions of the liver, spleen, stomach, and intestines were found at necropsy in the rats which died during the study or in those sacrificed at the termination of the study.

Intraperitoneal

The i.p. LD_{50} of TDPA in mice was 250 mg/kg.[21] The LD_{50} for DLTDP exceeded 2000 mg/kg, with no dose-related increase in mortality noted over a dose range of 300–2000 mg/kg. No mortality was observed in 5 rats which received a single 200 mg/kg i.p. dose of TDPA in water. Within 5 days after a single i.p. dose of 500 mg/kg TDPA, nine of 15 rats had died. Necropsy was not performed on these rats.

Intravenous

The i.v. LD_{50} of TDPA in water was 175 mg/kg in mice.[21] Most deaths followed nonspecific convulsions and occurred within an hour. When an i.v. dose of 150 mg/kg was administered to a group of five rats, one rat died within 1 min of injection, while the remaining rats survived the study. When a dose of 300 mg/kg was administered to each of a group of 15 rats, one rat died within 2 min, and a second rat died within 1 day. It was not known whether the mortality of the rats which died within minutes was due to the TDPA or to blood dilution caused by rapid injection of the test material.

Subchronic Oral Toxicity

Groups of 10 male albino rats were fed diets containing either TDPA or DLTDP over a period of 6 months in order to establish doses for a subsequent chronic study.[21] Doses were 0.5% and 3.0% in the feed for both compounds tested. During the study, two of 10 control rats died, one rat of the low-dose TDPA group died, two rats of the high-dose TDPA group died, and three rats of the high-dose DLTDP group died. The deaths of the two rats of the high-dose TDPA group were attributed to paratyphoid infection, and all other deaths were attributed to feeding. The test materials were 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 a 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.[21] 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 when 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.

Chronic Oral Toxicity

The rats used in the previously mentioned subchronic study were continued on their dosage regimen (0.5 and 3.0% for both TDPA and DLTDP) for an additional 22 months.[21] Of 11 control rats, two survived to the end of the study. Of the rats receiving TDPA and DLTDP, low and high doses of each chemical, respectively, 7/11, 7/10, 1/10, and 0/10 rats survived the study. The percent mortalities for each group of rats were as follows: controls, 82%; 0.5% TDPA, 36%; 3.0% TDPA, 30%; 0.5% DLTDP, 90%; and 3.0% DLTDP, 100%. Two of the deaths in the high-dose DLTDP group were due to paratyphoid infections rather than to treatment with DLTDP. For the rats which 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 which 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 either TDPA or DLTDP at concentrations of 0.5, 1.0, or 3.0% in the diet for 2 years.[21] TDPA and DLTDP had no significant effects on the weight gains of the treated rats when compared with the controls. No deaths were observed for the first 9 months of the study. After 9 months, deaths were observed in the DLTDP groups and after 13 months, deaths were observed in the TDPA groups. There was a conspicuous number of deaths 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 as follows: controls, 3/20; 0.5% TDPA, 5/20; 1.0% TDPA, 6/20; 3.0% TDPA, 4/20; 0.5% DLTDP, 16/20; 1.0% DLTDP, 7/20; 3.0% DLTDP, 10/20.

A study to determine the effect of heating on the chronic toxicity of antioxidants in lard was performed using groups of 20 male albino rats.[25] The lard was preserved either with 0.1% TDPA and 1.0% DLTDP or with 1.0% TDPA and 10.0% DLTDP. All lard samples (including the control) were heated at 190° for 30 minutes. The lard was incorporated into the feed at a concentration of 10% of the diet. The low-dose group received 0.11% antioxidant in the diet and the high-dose group received 1.1% antioxidant in the diet. The rats had continuous access to water and to the appropriate test diet. The rats were weighed and feed consumption was determined weekly. After 1 year on these diets, 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 for these two groups during the same time period. Of the rats of the high-dose group, there was a lower, though not significant, weight gain when compared with the control group for the first 6 months of the study. There were no differences in feed consumption and mortality during this period. During the second 6 months of the study, the decreases in weight were more pronounced, though still not significant. Feed consumption was significantly less than that of the controls during this period. The decrease in average feed consumption was attributed to the refusal of the

rats to eat in the weeks before death rather than to healthy rats not eating. By the end of one year, 17 of 20 rats of the high-dose group had died. There was a decline in feed consumption, loss of weight, unkempt appearance, nasal secretion, and labored breathing prior to death, with feed consumption declining 2 or more weeks prior to death. Pleural fluid and mottled consolidated areas of the lungs were found at necropsy. Further study was done on the rats of the high-dose group to determine the cause of the high incidence of mortality.[26] Because certain thio compounds may cause pleural effusion (it was noted that no probable mechanism existed by which either TDPA or DLTDP would break down to form this type of compound), a study was performed in which the heated lard–antioxidant mixture was administered orally at a dose equivalent to 50 mg/kg of the acid to seven male rats. The rats were sacrificed and necropsied 30 hours after administration of the test material and no pleural fluid was found, indicating that the test compounds were not the cause of the pleural fluid evident in the rats of the chronic study. It was also determined that this was not a condition common to the particular strain of rat used (Carworth Farms). After collaboration with various researchers, it was determined that the deaths were most likely caused by *Yersinia pseudotuberculosis*. The author concluded that the mortality noted in the high-dose group was not related to treatment with the lard-antioxidant mixture.

DERMAL IRRITATION AND SENSITIZATION

A makeup foundation containing 0.05% DLTDP was tested for dermal irritation using six New Zealand white rabbits.[27] The foundation, 0.5 ml, was applied to the clipped, intact, and abraded skin of the rabbits. The test sites were covered with gauze pads, and were taped and wrapped, with the test material remaining in contact with the skin for 24 h. After the 24 h test period, the patches were removed and the skin was washed. Test sites were evaluated 24 and 72 h after exposure to the test material. 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.

A makeup foundation containing 0.05% DLTDP was assessed for sensitization potential in a guinea pig maximization test.[28] Prior to the definitive test, a preliminary test to determine maximum tolerated dermal and intradermal doses of the test material was performed on one Hartley guinea pig. The guinea pig was injected with three concentrations of the test material, 1, 3, and 5%, in Freund's complete adjuvant. Two intradermal injections of each concentration of test material were administered to the guinea pig. A dermal patch of undiluted test material was also applied. After 24 h, all test sites were evaluated. The concentration of test material used in the definitive test was determined by the preliminary test site which received the highest test concentration of DLTDP without necrosis. It was determined that the 5% dilution of the test material 0.0025% in Freund's adjuvant 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; two of these animals were negative controls and two were positive controls, with the remaining ten as the test animals. Each of the test guinea pigs received two 0.1 ml injections of Freund's complete adjuvant, test material diluted in Freund's adjuvant, and undiluted test material. Negative controls received distilled water and positive controls received 5% formalin. One week later, a 5% dilution of the

test material was applied under a patch to a naive site on each of the test animals. Control animals received patches containing the respective control materials. Patches remained in place for 48 h. Two weeks after the second induction, a patch containing test material was applied to the same site as the previous site, where it remained for 24 h. Control animals received corresponding control patches. The challenge sites were evaluated on a scale of 0 to 3 twenty-four (24) hours after patch removal. There were no reactions in any of the 10 test guinea pigs. The two positive control animals received scores of 3 and the negative control animals that had no erythema 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.

TDPA, 30 mg/ml in water, or 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.[21] 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 water or olive oil. No signs of redness, swelling, or other signs of irritation were observed upon patch removal or at 48 and 72 hours.

Because it was the only compound of those tested which was soluble in water, TDPA was tested for dermal sensitization in guinea pigs (number of guinea pigs not stated).[21] 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 injections were repeated every other day for a total of 10 injections. After 10 days during which no injections were given, a single injection was administered. The test site was observed for signs of irritation or sensitization immediately after the injection and 24 hours later. 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.

Phototoxicity

A makeup foundation containing 0.05% DLTDP was tested for phototoxicity using six New Zealand white rabbits.[29] 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 quartz lamp. The test material, 0.5 ml, was applied to three 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 injection of 1% sulfanilamide was used as the positive control. One of the treated sites received 0.5 MED, one site received 1 MED, and the third site received 3 MED using the Hanovia Ultraviolet Hot Quartz Lamp; the negative and positive control sites also received irradiation at the three different MEDs. After exposure to ultraviolet light, the test sites were washed free of test material and were evaluated 1 min, 1 h, and 24 h after irradiation using a scale of 0 (no erythema) to 3 (erythema and trauma). Of the test sites receiving 0.5 MED, positive reactions were noted at the 24 h examination at the positive control sites of two 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 six rabbits received a score of 1 at the 24 h reading. Of the test sites receiving 3 MED, no responses were observed at the 1 min and 1 h examinations. At the 24 h examination, four of the six rabbits had scores of 1 at the DLTDP test site and the remaining two 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 h 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.

Ocular Irritation

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 nine New Zealand albino rabbits. The eyes were held shut for 1 s, and the eyes of three of the rabbits were rinsed with 50 ml of water 10 s after instillation of the test substance.[30] The eyes were graded at 24, 48, and 72 h post-instillation. 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.

One drop of a solution containing 0.8 mg/ml TDPA was placed into the right conjunctival sacs of two rabbits; the contralateral eyes received drops of saline and served as controls.[21] No signs of irritation were observed at 24 or 48 hours.

Teratogenicity/Reproduction Studies

Female albino CD-1 mice were used in a teratogenicity study of TDPA.[31] Groups (average of 21 pregnant mice/group) of the mice were intubated with 16.0, 74.0, 350.0, or 1600.0 mg/kg TDPA on days 6–15 of gestation (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. Weights were obtained 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 6–15 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.

A teratogenicity study of TDPA was also performed using female albino Wistar rats.[31] Groups averaging 21 rats (average number of pregnant rats/group) were intubated with 16.0, 74.0, 350.0, or 1600.0 mg/kg TDPA on days 6–15 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 6–15 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 two previous studies was performed using female golden hamsters.[31] Groups of 21 hamsters (average number of pregnant hamsters/group) were intubated with 16.0, 74.0, 350.0, or 1600.0 mg/kg TDPA on days 6–10 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 two 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 resorptions, and live and dead fetuses were recorded. The urogenital tracts of the dams, and the fetuses were examined as in the previous two 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 6–10 of gestation. No significant differences in the number of soft or skeletal tissue abnormalities were found between treated and sham control fetuses.

Adult Dutch-belted female rabbits were used in a teratogenicity study of TDPA.[32] On day 0, the rabbits were administered an intravenous 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 10.0, 45.0, 216.0, or 1000.0 mg/kg TDPA on days 6–18 (average 10 rabbits/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. 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 were 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 6–18 of gestation. There were no significant differences between the treated and sham control fetuses in the numbers of soft or skeletal tissue abnormalities.

MUTAGENICITY

TDPA was tested for mutagenic effects in a host-mediated assay, *in vivo* and *in vitro* cytogenetics studies, and in a dominant lethal assay.[24] 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 dimethylnitrosamine (DMN) (*Salmonella* study) or 350 mg/kg ethylmethanesulfonate (EMS) (yeast study). The indicator organisms used were the his G-46 and TA1530 strains of *Salmonella typhimurium* and the D-3 strain of *Saccharomyces 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 TA 1530 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 also was performed using the same protocol except that the mice received five oral doses of the test material at 24-h intervals, and the indicator organism was injected within 30 min 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.

TDPA was also applied directly to cultures of *S. typhimurium* G-46 and TA1530. Ten-fold serial dilutions, 5.0, 50.0, and 500.0 μg/ml, respectively, of the cultures were plated and mutant colonies were noted and scored. Dilutions of *S. cerevisiae* were shaken with the test material, diluted, and plated. Test results for *S. cerevisiae* were recorded as % 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.

Male albino rats were used in the *in vivo* cytogenetics study.[24] 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, nine rats, received saline, and the positive control group, five rats, received 0.3 mg/kg triethylene melamine (TEM). The bone marrow cells were arrested in C-mitosis by the administration of colcemid, 4 mg/kg, by i.p. injection 4 hours after the last dose and 2 hours before sacrifice. At 6, 25, and 48 hours, five rats from each TDPA dosage group, and three rats of the negative control group, were sacrificed. The positive control rats were all sacrificed at 48 hours. The protocol for the short-term phase of the study was essentially the same as that for the acute phase except that the rats received five doses of the test material at 24-hour intervals, test material groups consisted of five rats each, the negative control group consisted of three rats, and there was no positive control group (other than those rats used in the acute study). All of the rats were sacrificed 6 hours after the last dose. The diploid bone marrow cells from the rats in both phases of the study were examined for chromatid or chromosome gaps or breaks, reunions, cells with more than ten aberrations, polyploidy, pulverization, or other chromosomal aberrations. A total of 50 metaphase spreads per rat was scored. 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.

Human embryonic lung cells (WI-38) were incubated with 5.0, 50.0, or 500.0 μg/ml TDPA, with saline (negative control), or with 0.1 μg/ml TEM (positive control) until an adequate number of mitoses were available for the examination of anaphase preparations. There was a significantly higher percentage of chromosomal aberrations in the positive control cells than in the negative control or test compound cells. No adverse effects were noted due to exposure of human embryonic lung cells to concentrations of up to 500 μg/ml TDPA.

The dominant lethal assay of TDPA in rats consisted of an acute phase and a short-term phase.[24] Groups of 10 male rats were intubated with 50.0, 500.0, or 5000.0 mg/kg TDPA, or with saline (negative control). Positive control rats received an i.p. injection of 0.3 mg/kg TEM. The rats of the acute study received a single dose, while the rats of the short-term study received one dose per day for 5 days. Following dosing, the male rats were sequentially mated to two female rats per week for 8 weeks in the acute study and for 7 weeks in the short-term study. The female rats were sacrificed 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 one 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.

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation and Sensitization

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 (Afro-American, Asian or Pacific Islander, Hispanic, or Caucasian).[33] 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 test subjects' upper backs. Patches remained in place for 24 h, 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 h followed the initial patch application. The test sites were re-evaluated before the application of the next patch. This procedure was followed every Monday, Wednesday, and Friday (there was a 48 h 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 challenge patch was applied to the same site as the induction patches, and it remained in place for 48 h. Test sites were scored immediately upon patch removal. A second challenge patch was applied one week later; this patch also remained in place for 48 h, and was scored immediately upon patch removal, and again at 72 h. 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, one 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.

A makeup foundation containing 0.05% DLTDP was evaluated in a supervised usage test with 30 subjects, aged 20 to 58.[34] The study participants used the product as they would any other product purchased over the counter daily for 4 weeks. At the end of the fourth week of usage period, the subjects were checked for any reactions and were asked for their subjective comments. Two subjects did not complete the study; one subject discontinued use after 2 weeks, commenting that the product caused acneiform lesions, and the other subject discontinued use after 3 days due to erythema, though erythema was not noted upon objective evaluation. None of the remaining subjects had reactions to the makeup foundation containing 0.05% DLTDP.

Phototoxicity and Photoallergenicity

A test for the phototoxic and photoallergenic potential of a makeup foundation containing 0.05% was conducted on 27 adult volunteers of both genders and of mixed

ethnicity (Afro-American, Asian or Pacific Islander, Hispanic, or Caucasian).[35] In the phototoxicity phase of the study, a minimal erythemal dose (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 $\mu l/cm^2$ was applied to two sites on the back of each test subject. One site was covered and the second site, as well as an untreated site, were exposed to 1 MED of ultraviolet light. The test sites were graded immediately after exposure to the UV light, and again 24 and 48 h later. Reactions were graded on a scale of 0 (no reaction) to 4 (erythema with edema and blistering). For the second phase of the study (photoallergenicity), approximately 5 $\mu l/cm^2$ of the test substance was applied to two sites on the back of each subject and the test sites were covered with patches. The patches were removed after 24 h, and one treated site, as well as one 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 ultraviolet light exposure. After a minimum of 24 h, the above procedure was repeated. This procedure of two applications per week was continued for a total of eight induction applications. After a 12 day nontreatment period, the test substance was applied to two additional sites on the back of each subject. After 24 h, the challenge patches were removed and one patch site and an untreated site were exposed to window glass filtered ultraviolet light for 30 seconds. The challenge sites were graded 24 and 48 h after irradiation using a sale of 0 (no reaction) to 4 (erythema with edema and blistering). The treated sites which were not irradiated and the untreated sites which 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.

SUMMARY

Dilauryl Thiodipropionate (DLTDP) is the diester of lauryl alcohol and 3,3'-thiodipropionic acid. The white crystalline flakes have a characteristic ester odor. DLTDP may contain the following impurities: thiodipropionic acid, sulfated ash, arsenic, lead, or heavy metals. DLTDP may be identified by its solidification point or by infrared spectrum.

DLTDP is used as an antioxidant and sequestering agent in cosmetics and in foods. DLTDP is used in eye and face makeup products, in skin care and fragrance products, and in skin cleansing preparations at concentrations of up to 1%. DLTDP is approved as a traditional cosmetic ingredient in Japan. Both DLTDP and thiodipropionic acid (TDPA) are considered GRAS food substances by the FDA. Both are approved as direct food additives. Both are used in food wraps and films. DLTDP is used as an antioxidant in high-pressure greases and lubricants; it is used also as a softening agent and plasticizer.

TDPA and DLTDP, when administered to rats, were largely excreted in the urine within the first 24 h. Urinary excretion accounted for the major amount of the radioactivity eliminated, while 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 which 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.

According to the classification scheme of Hodge and Sterner,[36] TDPA and DLTDP were slightly toxic when administered to mice and rats by the oral route. TDPA, when administered intraperitoneally, was moderately toxic to rats, while DLTDP was slightly toxic. TDPA was moderately toxic when administered intravenously to mice.

TDPA and DLTDP were considered relatively nontoxic in subchronic oral toxicity studies with rats. No specific treatment-related effects were noted when 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 DLTPD had no significant effects on weight gains. 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 two groups for the study period. Most of the rats of the high-dose group died during the last 6 months of the study. These deaths were considered due to infection with *Yersinia pseudotuberculosis* and were not considered treatment related.

No irritation was produced by a make-up foundation containing 0.05% DLTDP when tested at 0.0025% 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 was not a sensitizer in a guinea pig maximization test. TDPA was tested for sensitization potential in guinea pigs and though 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 solution containing 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 was negative for reversions in *S. typhimurium* strain TA1530 and in *S. cerevisiae* strain D-3 after a single oral dose and after five 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 was tested *in vitro* using *S. typhimurium* strains TA1530 and G-46 and using *S. cerevisiae* strain D-3. TDPA, when 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 TDPA. TDPA was considered nonmutagenic in dominant lethal assays in rats in which TDPA was administered either as a single oral dose or as five consecutive doses over 5 days.

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. The makeup foundation containing DLTDP was not a phototoxin or a photoallergen when tested in 27 healthy human volunteers.

DISCUSSION

The overall safety test data from oral feeding studies indicated that DLTDP is relatively nontoxic at concentrations up to 3.0%. Dermal studies, which are needed to evaluate the safety of ingredients used in cosmetic products, were limited to test concentrations up to 0.05%. Therefore, for cosmetic dermal use, the available data limits the Expert Panel's conclusion to the concentration tested.

CONCLUSION

Based upon the available data included in this report, the Expert Panel concludes that Dilauryl Thiodipropionate is safe for use in cosmetic products at concentrations not to exceed 0.05%.

ACKNOWLEDGEMENT

Julie Poudrier Skinner, Scientific Analyst and Writer, prepared the literature review and technical analysis of this report.

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