Safety Assessment of Trimethylbenzoyl Diphenylphosphine Oxide as Used in Cosmetics

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All interested persons are provided 60 days from the above release date (i.e., January 20, 2025) to comment on this safety assessment, and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available for review by any interested party, and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.

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ABBREVIATIONS

CAS	Chemical Abstracts Service
CCK-8	cell counting kit-8
CFR	Code of Federal Regulations
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
CPSC	Consumer Product Safety Commission
Dictionary	web-based *International Cosmetic Ingredient Dictionary and Handbook*
EC_3	amount of chemical that is required to elicit a 3-fold increase in lymph node proliferative activity
ECHA	European Chemicals Agency
EU	European Union
FDA	Food and Drug Administration
HEK293T	human embryonic kidney 293 cells
HPLC	high-performance liquid chromatography
HRIPT	human repeated-insult patch test
HUVEC-12	human umbilical vein endothelial cells
K_{ow}	n-octanol/water partition coefficient
L02	human fetal hepatocyte line
LD_{50}	median lethal dose
LLNA	local lymph node assay
LOD	limit of detection
MoCRA	Modernization of Cosmetics Regulation Act
MCF-7	Michigan Cancer Foundation-7
MOE	margin of exposure
MOS	margin of safety
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide
NR	not reported
NOAEL	no-observed-adverse-effect-level
OECD	Organisation for Economic Co-operation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
PBS	phosphate-buffered saline
PND	post-natal day
RLD	Registration and Listing Data
SED	systemic exposure dose
SCCS	Scientific Committee on Consumer Safety
SIDS	screening information dataset
TG	test guideline
TI	tail intensity
US	United States
UV	ultraviolet
VCRP	Voluntary Cosmetic Registration Program

INTRODUCTION

This assessment reviews the safety of Trimethylbenzoyl Diphenylphosphine Oxide as used in cosmetic formulations. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*), this ingredient is reported to function in cosmetics as an artificial nail builder.[1]

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an extensive search of the world's literature; a search was last conducted November 2024. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Expert Panel for Cosmetic Ingredient Safety (Panel) typically evaluates, is provided on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Much of the data included in this safety assessment was found on the European Chemicals Agency (ECHA)[2] and the Scientific Committee on Consumer Safety (SCCS)[3] website. Please note that these websites provide summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when these sources are cited.

CHEMISTRY

Definition and Structure

Trimethylbenzoyl Diphenylphosphine Oxide (CAS No. 75980-60-8) is an aromatic monoacylphosphine oxide that conforms to the structure given in Figure 1:

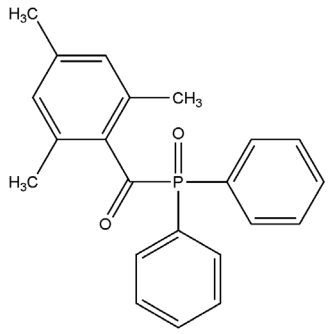

Figure 1. Trimethylbenzoyl Diphenylphosphine Oxide

This ingredient is an alpha-cleavage photo-initiator (Norrish type-1 photoinitator) with low energy bonds, which after homolytic cleavage yields active radicals.[4] Type-1 photoinitiators do not require co-initiators and involve absorption of high energy violet light and subsequent excitation to singlet state and photochemical cleavage of carbon-phosphorous bonds. Trimethylbenzoyl Diphenylphosphine Oxide undergoes rapid cleavage from a triplet excited state and yields two radicals: trimethylbenzoyl radical and diphenylphosphinoyl radical. The resulting radicals are able to initiate polymerization at different rate constants. It is assumed that Trimethylbenzoyl Diphenylphosphine Oxide is quickly consumed during the polymerization process when used in nail gel products, and therefore, very little residual amounts would remain.[3] Under the unlikely event that minimal residual amounts are present, they would be trapped in the hardened polymer matrix of the formed nail coating.

Chemical Properties

Trimethylbenzoyl Diphenylphosphine Oxide is a synthetic, yellow substance with a molecular weight of 348.4 g/mol, melting point of 93ºC, and log K_{ow} of 3.1 (@ 23ºC and pH of 6.4).[2,5] This ingredient absorbs ultraviolet light (UV) in UVA, UVB, and UVC bands with 3 primary peaks at 385, 290, and 235 nm, respectively.[4,6] Other chemical properties of this ingredient can be found in Table 1.

Method of Manufacture

The following methods of manufacturing are general to the production of Trimethylbenzoyl Diphenylphosphine Oxide, and it is unknown whether they are used in the manufacture of Trimethylbenzoyl Diphenylphosphine Oxide for use in cosmetics. Trimethylbenzoyl Diphenylphosphine Oxide is commonly synthesized by using the Arbuzov-type reaction of 2,4,6-trimethylbenzoyl chloride with alkoxylphosphine, that is synthesized from diphenylphosphine chloride and low-boiling point alcohol.[7] As this method is associated with several drawbacks (e.g., toxic pollutants), alternative methods of manufacture of this ingredient have been described in the literature. These methods are described below.

A Schleck tube was charged with diphenylphosphine oxide, 2,4,6-trimethylbenzaldehyde, and toluene and stirred at room temperature for 16 h.[7] Residue was washed with ethyl acetate and recrystallization resulted in α-hydroxy(2,4,6-trimethylbenzyl)diphenylphosphine oxide. A mixture of α-hydroxy(2,4,6-trimethylbenzyl)diphenylphosphine oxide,

dichloromethane, and manganese dioxide was stirred at room temperature for 1 h, followed by removal of manganese dioxide and the solvent. The crude product was diluted in deuterated chloroform, and Trimethylbenzoyl Diphenylphosphine Oxide was purified through a silica gel column with ethyl acetate and hexane.

A 500 ml, three-necked, round-bottomed flask was charged with triphenylphosphine oxide and dry tetrahydrofuran.[8] After ice bath cooling, sodium dispersion was added dropwise via a 50 ml syringe. The crude reaction mixture was filtered under nitrogen, the insoluble part was washed with tetrahydrofuran, and the organic layers were combined. Trimethylsilyl chloride was then dropwise added followed by removal of volatiles. Hexane was then added, and the sodium chloride precipitate was filtered under nitrogen. The solid was washed with hexane and methyl chlorothioformate and added to the hexane solution overnight (over continuous heating), and Trimethylbenzoyl Diphenylphosphine Oxide formed as a precipitate. Simple filtration yielded pure Trimethylbenzoyl Diphenylphosphine Oxide.

Impurities

Impurities data were not found in the published literature, and unpublished data were not submitted.

USE

Cosmetic

The safety of the cosmetic ingredient addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of Trimethylbenzoyl Diphenylphosphine Oxide in cosmetics. Data included herein were obtained from the FDA and in response to a survey of maximum use concentrations conducted by the Personal Care Products Council (Council), and it is these values that define the present practices of use and concentration. Frequencies of use obtained from the FDA include data from the Voluntary Cosmetic Registration Program (VCRP) database as well as Registration and Listing Data (RLD). As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was terminated in 2023, and as of 2024, manufacturers and processors have been mandated to register and list their products (and ingredients therein) with the FDA (i.e., RLD). Consequently, RLD are product-centric, whereas VCRP data were ingredient-centric. However, because there are numerous differences in the ways the data for the VCRP and the RLD were collected and processed, it is not appropriate to contrast data from the VCRP and RLD to determine a trend in frequency of use.

According to 2023 VCRP survey data, Trimethylbenzoyl Diphenylphosphine Oxide is used in 127 total formulations, all of which are manicuring preparations (Table 2).[9] RLD data (2024) indicate that Trimethylbenzoyl Diphenylphosphine Oxide is used in 1849 total formulations (this data indicate that Trimethylbenzoyl Diphenylphosphine Oxide is used in several product categories (manicuring preparations, makeup preparations, fragrance preparations, eye makeup preparations, and children's makeup preparations (not eye)).[10] The results of the concentration of use survey conducted by the Council in 2023 indicate that this ingredient is used at up to 4% in nail polish and enamel.[11]

RLD data indicate that Trimethylbenzoyl Diphenylphosphine Oxide is used in products that may be incidentally ingested (lipstick and lip glosses), used near the eyes (eyelash and eyebrow adhesives, glues, and sealants), or used by children (children's foundations) (concentrations for these uses not provided). In addition, this ingredient is reported to be used in formulations that may be inhaled (perfumes (concentration not provided)). In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.

Some products containing Trimethylbenzoyl Diphenylphosphine Oxide may be marketed for use with airbrush delivery systems; however, this information is not available from the VCRP, RLD, or the Council survey. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety. Without information regarding the frequency and concentrations of use of this ingredient, and without consumer habits and practices data or particle size data related to this use technology, the Panel is not able to determine safety for use in airbrush formulations. Accordingly, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

According to the European Union, Trimethylbenzoyl Diphenylphosphine Oxide has restricted use in cosmetics.[12] Regulations state that this ingredient may be safely used in artificial nail systems at a maximum concentration of 5%. In addition, products containing this ingredient should be for professional use only, skin contact should be avoided, and product directions should be carefully read.

Cosmetic use application

Two artificial nail systems (nail polishes and nail enhancement products) containing Trimethylbenzoyl Diphenylphosphine Oxide are commonly used for fingernails and toenails.[3] For polishes, nails are cleaned and prepared, a brush is wetted, dipped into the gel with initiator, applied to the nail, shaped, and cured under a UV lamp (the application

process consists of a base, middle, and top coat, with curing following each application). The polymerization is completed in approximately 2 – 3 min (procedure may be repeated up to 2 – 3 times). Applications of nail enhancement products are typically performed every 2 – 3 wk (with refills every 1 – 2 wk). Full application is in the range of between 2 – 4 g of gel and 1 g of gel for the refill (for artificial nail systems), corresponding to a maximum of 200 mg Trimethylbenzoyl Diphenylphosphine Oxide in total for all nail plates (which corresponds to an amount of 10 mg/nail ((considering the total fingernail and toenail area of 22 cm^2)).

Quantification of residual Trimethylbenzoyl Diphenylphosphine Oxide on artificial nail tips following gel application

The amount of Trimethylbenzoyl Diphenylphosphine Oxide per usage was evaluated via application on artificial nail tips.[3] A base coat gel was first applied to the artificial nail tip (nails made up of acrylonitrile-butadiene-styrene copolymer), followed by an intermediate color coat gel, and a topcoat gel (each gel contained 3% Trimethylbenzoyl Diphenylphosphine Oxide). Each step was followed by curing under a UV lamp. (Therefore, only the base coat was applied to the nail; other applications were to the polymerized base coat). The weight of gel samples applied to 2 nail tips was approximately 72 and 78 mg/nail (corresponding to approximately 2.16 – 2.34 mg Trimethylbenzoyl Diphenylphosphine Oxide in uncured gels). The cured polish was then immersed in an aqueous 0.1% sodium chloride solution for extraction. The extracted solution was analyzed using high-performance liquid chromatography (HPLC) with a UV detector. The extracted Trimethylbenzoyl Diphenylphosphine Oxide was nearly undetectable (0.0044 and 0.0047 mg at 22 and 50°C, respectively) due to the curing process, with the limit of detection (LOD) being 0.2 ppm. This result indicates that less than 0.14 – 0.16 mg of Trimethylbenzoyl Diphenylphosphine Oxide per nail, which is less than 0.2% of the total Trimethylbenzoyl Diphenylphosphine Oxide content in the uncured gel, could have been theoretically extracted.

Non-Cosmetic

Trimethylbenzoyl Diphenylphosphine Oxide is used in several industries/products including printing inks, paints/ coatings/lacquers/varnishes, adhesives/sealants, and fillers/putties/plasters.[13] This ingredient may also be used as a photoinitiator in the dental industry.[4]

TOXICOKINETIC STUDIES

No toxicokinetics studies were found in the published literature, and no unpublished data were submitted. However, according to an SCCS opinion on Trimethylbenzoyl Diphenylphosphine Oxide, this ingredient is a lipophilic substance and sparingly soluble in water and is therefore unlikely to penetrate the nail plate.[3]

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

Acute dermal toxicity was evaluated in Wistar rats (5/sex).[2] The test substance (40% Trimethylbenzoyl Diphenylphosphine Oxide (99.5% purity) suspended in olive oil) was applied to the clipped skin of rats under semi-occlusive conditions at a dose of 2000 mg/kg bw for 24 h (application area approximately 40 cm^2). Sites were observed 30 – 60 min after patch removal, and at regular intervals until the last day of observation (day 14). No mortality or signs of systemic toxicity were observed, and no abnormalities were noted at necropsy. The acute dermal median lethal dose (LD_{50}) was determined to be > 2000 mg/kg bw. Results regarding dermal irritation can be found in the Dermal Irritation section of this report.

Oral

An acute oral toxicity study was performed in fasted Sprague-Dawley rats (5/sex/group).[2] Animals were given Trimethylbenzoyl Diphenylphosphine Oxide (purity not stated) in 0.5% aqueous carboxymethylcellulose at levels of 1000 and 5000 mg/kg via gavage. No adverse effects were observed during the 14-d observation period. The acute oral LD_{50} was determined to be > 5000 mg/kg bw. A similar study was performed according to the Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 401 using fasted Sprague-Dawley rats (5/sex) given 5000 mg/kg bw Trimethylbenzoyl Diphenylphosphine Oxide (99% purity) in arachis oil via gavage. No mortalities were observed. One animal exhibited a decreased respiratory rate 1 h post-dosing, and all animals exhibited hunched posture, lethargy, and piloerection 4-h post-dosing. All animals appeared normal after day 1 of treatment. No abnormalities were noted at necropsy. The acute oral LD_{50} was determined to be > 5000 mg/kg.

Short-Term and Subchronic Toxicity Studies

Details on the repeated dose oral toxicity studies summarized below can be found in Table 3.

A 28-d oral toxicity study was performed using Sprague-Dawley rats (5/sex/group) given up to 750 mg/kg bw/d Trimethylbenzoyl Diphenylphosphine Oxide (purity 99%) in arachis oil via gavage.[3,2,14] The no-observed-adverse-effect-level (NOAEL) was determined to be 50 mg/kg bw/d due to abnormalities observed at higher concentrations (decreased body weight gain, increased liver and kidney weights, testicular atrophy, and blood/urine abnormalities indicative of hepatic and renal injury). Conversely, no adverse effects were observed in a 28-d toxicity study in which male Wistar rats (number of animals not stated) were given Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.3%; 1000 mg/kg bw/d) suspended in

0.5% aqueous carboxymethylcellulose via gavage.[3] An NOAEL of 100 mg/kg bw/d was determined in a 90-d toxicity study in which Wistar rats (10/sex/group) were given Trimethylbenzoyl Diphenylphosphine Oxide (purity 94.8%; 100, 300, or 1000 mg/kg bw/d) in 0.5% aqueous carboxymethylcellulose via gavage.[2,3] Some of the adverse effects observed in this study include body weight reduction, abnormalities in clinical chemistry, increased liver, kidney, brain, adrenal gland, and testes weight, and marked diffuse atrophy of the testicular parenchyma (compared to controls; these effects were observed in the mid- and high-dose groups). Testicular atrophy, decreased mean testes weight, and decreased mean body weights (compared to controls) were also observed in a different 90-d assay performed in male Wistar rats (10/group) given Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.3%; 1000 mg/kg bw/d) in a 0.5% carboxymethylcellulose aqueous solution via gavage.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Details on the oral developmental and reproductive toxicity studies summarized below can be found in Table 4.

The NOAEL for maternal and developmental toxicity was determined to be 150 mg/kg bw/d in a study in which female Wistar rats (22 females/group) were given Trimethylbenzoyl Diphenylphosphine Oxide in 1% aqueous carboxymethylcellulose at doses of up to 500 mg/kg bw/d via gavage on days 6 – 20 post-coitum.[2] Adverse effects in both dams (e.g., decreased body weight gain) and fetuses (e.g., increased incidence of fetuses with bent limb bones) were observed at 500 mg/kg bw/d. An overall reproductive toxicity NOAEL of 60 mg/kg bw/d was established in a one-generation reproductive toxicity assay performed in Wistar Han rats (5/sex/group) given up to 600 mg/kg bw/d Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.3%) in 1% aqueous carboxymethylcellulose (parental males treated prior to mating and during mating; parental females treated prior to mating up until at least 20 d after delivery). Fertility indices were 100, 90, 100 and 0% for the control, 60, 200, and 600 mg/kg groups, respectively. Testicular abnormalities were observed in mid- and high-dosed paternal males. No treatment-related clinical signs or adverse gross pathological findings were observed in pups. The maternal and developmental NOAEL was determined to be >100 mg/kg bw/d in a study performed using New Zealand White rabbits (22 females/group) given Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.3%) in 1% aqueous carboxymethylcellulose at doses of up to 100 mg/kg via gavage on days 6 – 28 post-coitum. No clinical signs of toxicity, treatment-related mortality, body weight changes, or gross pathological abnormalities were observed in dams. No dose-dependent adverse effects were observed in fetuses; however, a statistically significant increase in the incidence of misaligned vertebrae was observed in fetuses of the high dose group compared to controls (9.2% versus 3.8% in controls); however, the value remained within the maximum value of the available historical control data (10.2% per litter)

GENOTOXICITY STUDIES

Details regarding the genotoxicity studies summarized below can be found in Table 5.

No genotoxicity was observed in an Ames assay performed using Trimethylbenzoyl Diphenylphosphine Oxide (purity > 98%; up to 2500 µg/plate) in methanol using *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA 100 (performed with and without metabolic activation).[3,2] Similarly, no genotoxicity was observed in a 2-part Ames assay in which *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 were exposed to Trimethylbenzoyl Diphenylphosphine Oxide (purity 99%; in ethanol) at concentrations of up to 5000 µg/plate (performed with and without metabolic activation). Trimethylbenzoyl Diphenylphosphine Oxide (purity 99%; in dimethyl sulfoxide; up to 30 µg/ml with metabolic activation; up to 25 µg/ml without metabolic activation) was considered to be non-clastogenic in a chromosomal aberration assay performed using Chinese hamster lung cells. Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.5%; in ethanol) was considered to be non-mutagenic in a 2-part mammalian gene cell mutation test using Chinese hamster lung fibroblasts up to maximum concentrations of 30 µg/ml (without S9 mix) and 40.5 µg/ml (with S9 mix) (cytotoxicity observed at higher concentrations). Conversely, Trimethylbenzoyl Diphenylphosphine Oxide (purity > 99.8%; in ethanol; up to 1.0 µg/ml) resulted in statistically significantly increased tail intensity (parameter used to evaluate genotoxicity) when evaluated at concentrations of 0.04 µg/ml and higher compared to the solvent control (study performed using human fetal lung fibroblast cells).[15]

CARCINOGENICITY STUDIES

No relevant carcinogenicity studies on Trimethylbenzoyl Diphenylphosphine Oxide were found in the published literature, and unpublished data were not submitted.

ANTI-CARCINOGENICITY STUDIES

The potential anti-cancer effect of Trimethylbenzoyl Diphenylphosphine Oxide with and without irradiation was evaluated in breast cancer cells (human Michigan Cancer Foundation-7 (MCF-7) and mouse 4T1 cells).[16] Cells were plated and incubated overnight with Trimethylbenzoyl Diphenylphosphine Oxide at concentrations of 5, 10, 20, 40, and 80 µM. Cells were cultured in two different types of environments (dark for up to 24 h or exposed to irradiation (405 nm) for different irradiation times (0, 1, 5, 10, and 15 min)). 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assays were performed to evaluate cell viability after exposure to the test substance. A statistically significant decrease of cell viability in 4T1 and MCF-7 cells was observed in the dark group at concentrations of 40 µM and higher,

compared to the control group ($p < 0.05$). Irradiation use resulted in further decreased cell viability in both 4T1 cells and MCF-7 cells. Further testing of the apoptotic effect of Trimethylbenzoyl Diphenylphosphine Oxide (0, 5 or 20 μM) in MCF-7 and 4T1 cells was evaluated via fluorescence microscopy with and without 15 min of irradiation (405 nm). Apoptosis was not observed in non-irradiated cells in a statistically significant manner; however, significant cell death was observed in irradiated cells in a concentration-dependent manner (effect was statistically significant at both tested concentrations in 4T1 cells and at a concentration of 20 μM in MCF-7 cells).

OTHER RELEVANT STUDIES

Cytotoxicity

The cytotoxic potential of Trimethylbenzoyl Diphenylphosphine Oxide (1 – 50 μM; vehicle: 0.2% ethanol) was evaluated in various mammalian cell lines (human embryonic kidney cells (HEK293T), human umbilical vein endothelial cells (HUVEC-12), human fetal hepatocyte line (L02), and primary lymphocyte cells; 24 h incubation).[17] Cells were treated with 0.2% ethanol as the negative control. HEK293T cells were exposed to the test substance with and without irradiation (irradiation with 455 nm blue light for 5 min). Cytotoxicity was evaluated via an MTT assay and a cell counting kit-8 (CCK-8) assay (for lymphocyte cells only). Cell viability of HUVEC-12, L02, lymphocytes, and HEK293T cells (without irradiation) decreased in a dose-dependent manner. Cell viability was approximately 80% in HUVEC-12, L02, lymphocytes, and HEK293T cells (without irradiation) and 65% in HEK293T cells (with irradiation) when treated with 50 μM Trimethylbenzoyl Diphenylphosphine Oxide (controls yielded 100% cell viability in all assays).

The cytotoxicity of Trimethylbenzoyl Diphenylphosphine Oxide (1 – 50 μM; vehicle: 1% dimethyl sulfoxide) was also evaluated in a different assay using L-929 fibroblasts.[6] MTT assays were performed to evaluate cytotoxicity after a 24 h incubation period. Cell viability was approximately 93.35, 92.01, 85.14, 76.80, and 61.84% when tested at 1, 5, 10, 25, and 50 μM, respectively. Cell viability of the positive and negative controls was 7.58 and 95.8%, respectively (substances used for positive and negative controls not stated).

DERMAL IRRITATION AND SENSITIZATION STUDIES

Details on the dermal irritation and sensitization studies summarized below can be found in Table 6.

Dermal irritation was evaluated in Wistar rats (5/sex) following the application of 40% Trimethylbenzoyl Diphenylphosphine Oxide (99.5% purity; 2000 mg/kg bw; semi-occlusive application) suspended in olive oil for 24 h.[3,2] Local skin irritation was observed in 1 male and all females throughout the study. (Results regarding systemic toxicity endpoints evaluated in this study can be found in the Acute Toxicity section of this report.) A 50% aqueous formulation of Trimethylbenzoyl Diphenylphosphine Oxide (purity > 98%; 500 mg) was considered to be slightly irritating in an assay performed in Vienna White rabbits (2 males, 4 females) in which the test substance was applied to intact and abraded skin (use of occlusion and exposure duration not stated (however, it can be assumed to be 24 h as this was the first observation point).

A local lymph node assay (LLNA) was performed using CBA/CaOlaHsd mice (5/group) given daily topical applications of Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.5%) in acetone and olive oil at concentrations of 0, 10, 25, and 50% on the dorsal surface of both ears for 3 consecutive days.[3,2] Stimulation index results for the test substance at 10, 25, and 50% were determined to be 2.22, 2.96, and 3.46 (values above 3 considered positive), indicating an EC_3 (amount of chemical that is required to elicit a 3-fold increase in lymph node proliferative activity) value of 27% (test substance was considered to be sensitizing). Human repeat insult patch tests (HRIPTs) were performed using a nail gel color containing a 2.6% Trimethylbenzoyl Diphenylphosphine Oxide (n = 51) and a nail gel sealer containing Trimethylbenzoyl Diphenylphosphine Oxide at an unknown concentration (n = 50).[3] The test substances were considered to be non-irritating and non-sensitizing.

OCULAR IRRITATION STUDIES

Animal

The potential ocular irritation of Trimethylbenzoyl Diphenylphosphine Oxide (purity > 98%; tested undiluted) was evaluated.[3,2] The test substance (56 mg) was placed in the left eye of Vienna White rabbits (2 males, 4 females), and animals were evaluated 24, 48, and 72 h and 5 d after instillation. Irritation parameters (corneal opacity, iris score, conjunctivae score, conjunctiva discharge, chemosis) were evaluated via the Draize system. This study was summarized in both an ECHA dossier[2] and in an SCCS opinion[3] results differed in both sources. According to ECHA, mean corneal opacity scores, iris scores, conjunctivae scores (in 4/6 animals), chemosis, and conjunctival discharge scores were 0/4, 0/2, 0.3/3, 0/4, and 0/3, respectively (results for time point 24/48/72 h). According to the SCCS opinion, no effects on the iris were noted; however, at 24 h, conjunctival redness was observed in all animals, and persisted up until the 48-h reading. In 2 animals, corneal opacity was observed by the 72-h reading.

RISK ASSESSMENT

Margin of exposure (MOE) is a quantitative factor calculated for cosmetic ingredients by dividing the NOAEL obtained for an ingredient in an animal experiment by the estimated systemic exposure dose (SED) for the ingredient in humans, generally according to US Environmental Protection Agency (EPA) and EU SCCS guidelines. An MOE value greater than 100 has traditionally been considered an indication of safety. The basis for this MOE value of 100 comes from two multiplication factors: a 10-fold factor accounts for the extrapolating data from test animals to human being (interspecies extrapolation), and an additional 10-fold for accommodating differences among the human population (intraspecies extrapolation). The MOE is sometimes referred to as the margin of safety (MOS) despite the parameters being definitionally different.

A margin of exposure (MOE) calculation for the use of Trimethylbenzoyl Diphenylphosphine Oxide in artificial nail gel systems was calculated by the SCCS and determined to be 1515, which is based off a maximum concentration of use at 5%.[3] CIR staff has updated the calculations following the same approach with the current maximum concentration of use at 4%, according to the 2023 concentration of use survey conducted by the Council.[11] The resulting MOE is 1851. Details regarding the parameters used to perform this calculation can be found in Table 7.

SUMMARY

The safety of Trimethylbenzoyl Diphenylphosphine Oxide as used in cosmetics is reviewed in this safety assessment. According to the *Dictionary*, this ingredient is reported to function in cosmetics as an artificial nail builder.

According to 2023 FDA VCRP survey data, Trimethylbenzoyl Diphenylphosphine Oxide is used in 127 total formulations, all of which are manicuring preparations. RLD data (2024) indicate that this ingredient is used in 1849 total formulations in several product categories (e.g., manicuring preparations, makeup preparations, eye makeup preparations, children's makeup (not eye)). The results of the 2023 concentration of use survey conducted by Council indicate that this ingredient is used at up to 4% in nail polish and enamel.

Trimethylbenzoyl Diphenylphosphine Oxide is used as a photoinitiator in nail products and is therefore used in gel products (nail enhancement products and gel nail polishes) requiring curing under a UV lamp. Full application of nail enhancement products typically results in a maximum exposure of 200 mg Trimethylbenzoyl Diphenylphosphine Oxide for all nail plates. The amount of Trimethylbenzoyl Diphenylphosphine Oxide extracted was lower than the limit of detection (0.2 ppm) after curing in an assay in which the amount of Trimethylbenzoyl Diphenylphosphine Oxide was quantified in artificial nails painted with gel polishes (base, intermediate, and topcoat) containing 3% Trimethylbenzoyl Diphenylphosphine Oxide.

The dermal LD_{50} was determined to be > 2000 mg/kg bw in a dermal toxicity assay in which 2000 mg/kg of 40% Trimethylbenzoyl Diphenylphosphine Oxide in olive oil was applied to the skin of rats for 24 h. Acute oral LD_{50}s of > 5000 mg/kg bw were determined in two acute oral toxicity assays performed in rats given Trimethylbenzoyl Diphenylphosphine Oxide (in 0.5% aqueous carboxymethylcellulose or arachis oil; up to 5000 mg/kg bw) via gavage.

An NOAEL of 50 mg/kg bw/d was determined in a 28-d toxicity study performed in rats given up to 750 mg/kg bw/d Trimethylbenzoyl Diphenylphosphine Oxide in arachis oil via gavage. Several adverse effects including decreased body weight gain, increased liver and kidney weights, and testicular atrophy were observed in this study. Conversely, no adverse effects were observed in a 28-d toxicity study performed in male rats given 1000 mg/kg bw/d Trimethylbenzoyl Diphenylphosphine Oxide in 0.5% aqueous carboxymethylcellulose via gavage. An NOAEL of 100 mg/kg bw/d was determined in a 90-d toxicity study in which rats were given Trimethylbenzoyl Diphenylphosphine Oxide in 0.5% aqueous carboxymethylcellulose via gavage at doses of up to 1000 mg/kg bw/d. Body weight reduction, clinical chemistry abnormalities, increased organ weights, and testicular abnormalities were observed in this study. Similarly, testicular atrophy, decreased mean testes weight, and decreased mean body weights were observed in a different 90-d assay performed in rats given the same test substance at a dose of 1000 mg/kg bw/d via gavage.

Decreased body weight gain in dams and increased incidences of fetuses with bent limb bones were observed in a developmental toxicity assay in which female rats were treated with Trimethylbenzoyl Diphenylphosphine Oxide in 1% aqueous carboxymethylcellulose at doses of up to 500 mg/kg bw/d via gavage on days 6 – 20 post-coitum. An overall reproductive toxicity NOAEL of 60 mg/kg bw/d was established in a one-generation reproductive toxicity assay performed in male and female rats given up to 600 mg/kg bw/d Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.3%) in 1% aqueous carboxymethylcellulose (parental males treated prior to mating and during mating; parental females treated prior to mating up until at least 20 d after delivery). Signs of parental toxicity include a 0% fertility index (in high-dosed animals) and testicular abnormalities (in mid- and high-dosed males). No signs of toxicity were observed in F1 pups. No signs of toxicity were observed in maternal rabbits given Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.3%) in 1% aqueous carboxymethylcellulose at doses of up to 100 mg/kg via gavage on days 6 – 28 post-coitum. No dose-dependent adverse effects were observed in fetuses; however, a statistically significant increase in the incidence of misaligned vertebrae was observed in fetuses of the high dose group compared to controls; however, the value remained within the maximum value of the available historical control data.

No genotoxicity was observed in an Ames assay performed using Trimethylbenzoyl Diphenylphosphine Oxide (purity > 98%; up to 2500 µg/plate) in methanol (assay performed in *S. typhimurium* strains) or in a 2-part Ames assay using Trimethylbenzoyl Diphenylphosphine Oxide (purity 99%; in ethanol) at concentrations of up to 5000 µg/plate (assay performed in *S. typhimurium* strains and *E. coli* strain WP2). Ames assays were performed with and without metabolic activation. Trimethylbenzoyl Diphenylphosphine Oxide (purity 99%; in dimethyl sulfoxide; up to 30 µg/ml with metabolic activation; up to 25 µg/ml without metabolic activation) was considered to be non-clastogenic in a chromosomal aberration assay performed using Chinese hamster lung cells. Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.5%; in ethanol) was considered to be non-mutagenic in a 2-part mammalian gene cell mutation test using Chinese hamster lung fibroblasts up to maximum concentrations of 30 µg/ml (without S9 mix) and 40.5 µg/ml (with S9 mix). Conversely, Trimethylbenzoyl Diphenylphosphine Oxide (purity > 99.8%; in ethanol) resulted in statistically significantly increased tail intensity when evaluated at concentrations of 0.04 µg/ml and higher compared to the solvent control (study performed using human fetal lung fibroblast cells).

The potential anti-cancer effect of Trimethylbenzoyl Diphenylphosphine Oxide (5 – 80 µM) with and without irradiation was evaluated in breast cancer cells (MCF-7 and 4T1 cells). A statistically significant decrease of cell viability in 4T1 and MCF-7 cells was observed in the dark group at concentrations of 40 um and higher, compared to the control group ($p < 0.05$). Irradiation resulted in further decreased cell viability in both 4T1 cells and MCF-7 cells.

The cytotoxic potential of Trimethylbenzoyl Diphenylphosphine Oxide (1 – 50 µM; vehicle: 0.2% ethanol) was evaluated in various mammalian cell lines (HEK293T, HUVEC-12, L02, and primary lymphocytes) with and without irradiation. Cell viability of HUVEC-12, L02, lymphocytes, and HEK293T cells (without irradiation) decreased in a dose-dependent manner. The cytotoxicity of Trimethylbenzoyl Diphenylphosphine Oxide (1 – 50 µM; vehicle: 1% dimethyl sulfoxide) was also evaluated in a different assay using L-929 fibroblasts. Cell viability was approximately 93.35, 92.01, 85.14, 76.80, and 61.84 % when tested at 1, 5, 10, 25, and 50 µM, respectively.

Local skin irritation was observed in rats in a dermal irritation assay using rats exposed to a dermal application of 40% Trimethylbenzoyl Diphenylphosphine Oxide (99.5% purity; 2000 mg/kg bw; semi-occlusive application) suspended in olive oil for 24 h. Slight irritation was observed in a study using rabbits exposed to a 50% aqueous formulation Trimethylbenzoyl Diphenylphosphine Oxide (purity > 98%; 500 g; use of occlusion and duration not stated). Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.5%; concentrations up to 50%) in acetone and olive oil was considered to be sensitizing in an LLNA performed in mice. No irritation or sensitization were observed in HRIPTs performed using a nail gel color containing a 2.6% Trimethylbenzoyl Diphenylphosphine Oxide (n = 51) and a nail gel sealer containing Trimethylbenzoyl Diphenylphosphine Oxide at an unknown concentration (n = 50).

The potential ocular irritation of Trimethylbenzoyl Diphenylphosphine Oxide (purity > 98%; tested undiluted) was evaluated in rabbits. This study was summarized in both an ECHA dossier and in an SCCS opinion. Results differed in both sources. According to ECHA, mean corneal opacity scores, iris scores, conjunctivae scores (in 4/6 animals), chemosis, and conjunctival discharge scores were 0/4, 0/2, 0.3/3, 0/4, and 0/3, respectively (results for time point 24/48/72 h). According to the SCCS opinion, no effects on the iris were noted; however, at 24 h, conjunctival redness was observed in all animals, and persisted up until the 48-h reading. In 2 animals, corneal opacity was observed by the 72-h reading.

An MOE calculation for the use of Trimethylbenzoyl Diphenylphosphine Oxide in artificial nail gel systems was calculated by the SCCS and determined to be 1515. It should be noted that this calculation was based off of a maximum concentration of 5%. An MOE of 1851 was obtained when calculated using the same approach, but a maximum concentration of use of 4% (the 2023 concentration of use survey conducted by Council indicates that the current maximum concentration of use of Trimethylbenzoyl Diphenylphosphine Oxide in nail products is 4%).

INFORMATION SOUGHT

The following data on Trimethylbenzoyl Diphenylphosphine Oxide is being requested:

- Method of manufacturing data for cosmetic ingredient manufacturing
- Impurities data
- Dermal DART data
- HRIPT at maximum concentration of use
- Phototoxicity/photosensitization assays
- Application instructions and details regarding nail products containing Trimethylbenzoyl Diphenylphosphine Oxide

TABLES

Table 1. Chemical properties

Property	Value	Reference
Physical Form	liquid, pellets, large crystals, or dry powder	5,2
Color	yellow	2
Molecular Weight (g/mol)	348.4	5
Specific Gravity (@ 20 ºC)	1.218	2
Vapor pressure (Pa @ 25ºC)	0.00000305	3
Melting Point (ºC)	93	2
Boiling Point (ºC)	> 300	3
Water Solubility (mg/L @ 20 ºC & pH of 6.9)	3.4	2
log K_{ow} (@ 23 ºC & pH of 6.4)	3.1	2
UV Absorption (λ_{max}) (nm)	235, 290, 385	3

Table 2. Frequency (RLD/VCRP) and concentration of use of Inositol according to likely duration and exposure and by product category

	# of Uses		Max Conc of Use
	RLD (2024)[10]	VCRP (2023)[9]	% (2023)[11]
Totals*	**1849**	**127**	**2.7 – 4**
summarized by likely duration and exposure**			
Duration of Use			
Leave-On	***	*123*	*2.7 - 4*
Rinse-Off	***	*4*	*NR*
Diluted for (Bath) Use	***	*NR*	*NR*
Exposure Type			
Eye Area	***	NR	NR
Incidental Ingestion	***	NR	NR
Incidental Inhalation-Spray	***	NR	NR
Incidental Inhalation-Powder	***	NR	NR
Dermal Contact	***	NR	NR
Deodorant (underarm)	***	NR	NR
Hair - Non-Coloring	***	NR	NR
Hair-Coloring	***	NR	NR
Nail	***	127	2.7 – 4
Mucous Membrane	***	NR	NR
Baby Products	***	NR	NR
as reported by product category			
Eye Makeup Preparations (other than children's eye makeup preparations)	***3***		
Eyelash and Eyebrow Adhesives, Glues, and Sealants	3	NA	NR
Fragrance Preparations	***7***		
Perfumes	7	NR	NR
Makeup Preparations (not eye; not children's)	***8***		
Lipsticks and Lip Glosses	8	NR	NR
Makeup Preparations for Children (not eye)	***1***		
Children's Foundations	1	NA	NR
Manicuring Preparations	***1837***		
Basecoats and Undercoats	67	9	NR
Cuticle Softeners	7	NR	NR
Nail Creams and Lotions	8	NR	NR
Nail Extenders	336	1	NR
Nail Polishes and Enamels	1343	106	2.7 – 4
Nail Polish and Enamel Removers	14	4	NR
Other Manicuring Preparations	555	7	NR
Other Preparations (i.e., those preparations that do not fit another category)	***27***	NA	NR

NR – not reported; NA – not applicable (this category was not part of the VCRP)

*The total FOU provided for RLD refers to the ingredient count supplied by FDA, and is not a summation of the number of uses per category because each product may be categorized under multiple ***product*** categories. For data supplied via the VCRP or by the Council survey, the sum of all exposure types may not equal the sum of total uses because each ingredient may be used in cosmetics with multiple ***exposure*** types.

**Likely duration and exposure are derived from VCRP and survey data based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)

***Because RLD are product-centric and not ingredient-centric, each ingredient may be reported under several product categories, making a summation of RLD misleading in comparison to VCRP data. Accordingly, RLD are presented below by product category (as supplied by FDA), but are not summarized by likely duration and exposure.

Table 3. Repeated dose oral toxicity studies

Test Article	Vehicle	Animals/ Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
Trimethylbenzoyl Diphenylphosphine Oxide (purity 99%)	arachis oil	Sprague-Dawley rats (5/sex/group)	28 d	0, 50, 250, or 750 mg/kg bw/d	Animals given test substance via gavage; control animals were given the vehicle only; recovery groups were treated with the same test substance at 750 mg/kg bw/d or the vehicle alone for 28 consecutive days, and then were maintained without treatment for a further 14-d period; hematological analyses, urinalysis, organ weight assessment, and histopathological assessments were performed.	One female from the recovery high-dose group and one female from the recovery control group died during the study period (study authors claimed this was not treatment-related). Hunched posture, increased salivation, lethargy, and piloerection were observed in animals treated with 250 and 750 mg/kg bw/d. Decreased body weight gain, decreased food efficiency, increased liver and kidney weights, and small testes were also observed in these groups. Blood chemistry (increased bilirubin, triglycerides, cholesterol, gamma glutamyl transpeptidase, alkaline phosphatase, creatinine, and urea in plasma) and urine abnormalities (ketones in urine) indicative of hepatic and renal injury were observed in mid- and high-dosed groups. These abnormalities (aside from slight increase in cholesterol in females and calcium in males) were considered to be reversible as they were not seen in the treated recovery animals. Periportal hepatocyte vacuolization and basophilia were observed in the high-dose group, but were not observed in the recovery groups (treated and untreated). Testicular atrophy was observed in the high-dose group as well as in the treated recovery group. The no-observed-adverse-effect-level (NOAEL) was determined to be 50 mg/kg bw/d.	[2,3]
Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.3%)	0.5% aqueous carboxymethyl-cellulose	Male Wistar rats (number of animals in test group not stated; 3 animals in control group)	28 d	0 or 1000 mg/kg bw/d	Animals given test substance via gavage; control animals given vehicle only; analyses on mortality, clinical parameters, body weight, and organ weights were performed	No signs of toxicity observed.	[3]

Table 3. Repeated dose oral toxicity studies

Test Article	Vehicle	Animals/ Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
Trimethylbenzoyl Diphenylphosphine Oxide (purity 94.8%)	0.5% aqueous carboxymethyl-cellulose	Wistar rats (10/sex/group)	90 d	0, 100, 300, or 1000 mg/kg bw/d	OECD TG 408; Animals given test substance via gavage; control animals given vehicle only; clinical signs, body weight, food consumption, blood chemistry, neurotoxicity, and histopathological parameters were evaluated	Two females of the high dose group died during the study. Increased food consumption was observed in female rats of the high dose group. A significant reduction in body weight in male rats of the 300 (12% reduction) and 1000 mg/kg bw/d (26% reduction) groups was observed compared to controls. High-dose animals displayed hairless extremities and reddening/scale formation on the ears. Abnormalities in clinical chemistry were observed in high-dose females (decreased erythrocytes, hemoglobin, hematocrit, thromboplastin time, alkaline phosphatase, gamma-glutamyltransferase, total protein, globulins, and cholesterol; increased leucocytes, platelets, eosinophilic granulocytes, neutrophilic polymorphonuclears, and triglycerides). Abnormalities (increased alkaline phosphatase, gamma-glutamyltransferase, alanine aminotransferase; decreased triglycerides) were also observed in high-dose males. Hematocrit and hemoglobin values were decreased, and leucocytes, eosinophilic granulocytes, neutrophilic polymorphonuclears, and calcium values were increased in females treated with 300 mg/kg bw/d. Relative kidney and liver weights (40 - 60% above control values) were observed in high-dose females, and similar effects were noted in mid- and high-dose males. Relative brain weights and adrenal gland weights were also significantly increased in mid- and high-dosed males compared to controls (this effect was not observed in females). Absolute testes weights in animals treated with 0, 100, 300, and 1000 mg/kg bw/d were reported to be 3.56, 3.68, 1.69, and 1.69 g, respectively. Marked diffuse atrophy of the testicular parenchyma and slight moderate interstitial edema was observed all males of the mid- and high-dose groups. No signs of neurotoxicity were observed. The NOAEL was determined to be 100 mg/kg bw/d.	[3,2,14]
Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.3%)	0.5% carboxy-methylcellulose	Male Wistar rats (10/group)	90 d	0 or 1000 mg/kg bw/d	Animals given test substance via gavage; control animals received vehicle only; Body weight and histopathological assessments were performed	Absolute mean body weights were decreased in the treated group compared to controls (10% decrease). Absolute mean testes weights were determined to be 3.29 and 2.1 g in the control and treated groups, respectively. Treated animals also revealed a slight to severe diffuse atrophy of the seminiferous tubules of the testes. In 4 treated animals, edemas and minimal to slight hyperplasia of the Leydig cells were observed. Reduced testes size was correlated with an oligozoospermia up to grade 5.	[3,2]

OECD = Organisation for Economic Co-operation and Development; TG = test guidelines

Table 4. Oral developmental and reproductive toxicity studies[2]

Test Article	Vehicle	Animals/Group	Dose/Concentration	Procedure	Results
Trimethylbenzoyl Diphenylphosphine Oxide (purity not stated)	1% aqueous carboxymethylcellulose	22 female Wistar rats/group	0, 50, 150, and 500 mg/kg bw/d	OECD TG 414; animals treated via gavage from days 6 – 20 post-coitum, inclusive; control animals given vehicle only; animals killed for examination on day 21 post-coitum (or within 24 h of abortion or early delivery); maternal and fetal evaluations performed	Six total animals delivered early (1 control animal, 1 low-dose animal, 2 mid-dose animals, and 2 high-dose animals); increased salivation was observed in dams in a dose-dependent manner (since no correlated findings were noted, researchers attributed this to the taste of the test substance); piloerection (in 7/22 dams) and hunched posture (in 4/22 dams) was observed in animals treated with the highest dose; mean body weight gain was significantly reduced in the highest dose group compared to controls from day 9 post-coitum onwards (mean body weight on day 21 post-coitum was 285 g in 500 mg/kg bw/d treated group compared to 305 g in controls); no effects were observed on the number of pregnant females, corpora lutea, implantations sites, or pre- or post-implantation loss; 4 animals were found not pregnant (effect was not dose-dependent) At 500 mg/kg bw/d, female fetal weights were slightly but significantly lower compared to the control group (4.8 g versus 5.1 g in controls); a similar effect was observed in fetal males of the high-dose group, however, this was not statistically significant; the male:female ratio was unaffected by treatment; litter size was unaffected by treatment; no treatment-related external malformations were observed (tail malformations were observed in 2 pups of the high-dose group; however, this was not considered to be related to treatment); a statistically significant increase in the number of fetuses with bent limb bones were observed in the high-dose group compared to controls; this group also had a statistically increased incidence of reduced ossification of the skull and unossified metatarsals and metacarpals compared to controls; no visceral malformations were observed The NOAEL for maternal and developmental toxicity was determined to be 150 mg/kg bw/d

Table 4. Oral developmental and reproductive toxicity studies[2]

Test Article	Vehicle	Animals/Group	Dose/Concentration	Procedure	Results
Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.3%)	1% aqueous carboxymethylcellulose	Wistar Han rats (5/sex/group)	0, 60, 200, and 600 mg/kg bw/d	OECD TG 421; one-generation reproductive toxicity study; test item was administered via gavage 7 d/wk for a minimum of 12 wk; males treated for 85-92 d up to and including the day before scheduled necropsy (including a minimum of 10 wk prior to mating) and during mating; females that delivered were treated for 10 wk prior to mating, during the variable time to conception, during pregnancy, and at least 20 d after delivery; females that failed to deliver or had total litter loss were treated for 99-117 d; control animals treated with vehicle only; evaluated parameters include clinical and reproductive performance of P0, clinical evaluation of F1 pups, live birth indices, mortality, pup body weight, pup gross pathological evaluation	One female of the control group and one female of the 600 mg/kg died during the premating period. Extended diestrus cycles during the mating period was observed was observed in 1 female treated with 60 mg/kg and 3 females treated with 600 mg/kg. Mating indices were 67% at 600 mg/kg and 100% for all other groups. Precoital time was considered not to be affected by treatment up to 600 mg/kg for all mated females. At 600 mg/kg, all mated females presented with 0 implantation sites (and 0 corpora lutea). At 60 and 200 mg/kg, the mean number of implantation sites remained in the same range of controls. Fertility indices were 100%, 90%, 100% and 0% for the control, 60, 200, and 600 mg/kg groups, respectively. Gestation indices were 100%, 100%, and 90% for the control, 60 and 200 mg/kg groups, respectively. Average live litter sizes were 10.6, 10.8, and 10.4 living fetuses/litter for the control, 60 and 200 mg/kg groups, respectively. One female at 200 mg/kg had only 1 living pup. Tubular atrophy was present in all males treated with the highest dose (correlating with decreased testes weight/reduced testes size). Atypical residual bodies and multinucleated giant cells were present in all males treated at 200 mg/kg at a slight to moderate degree. Atypical residual bodies were present in all males treated at 200 mg/kg at a slight to moderate degree. Multinucleated giant cells were present in a single male treated at 200 mg/kg and in a single male treated at 600 mg/kg at a moderate degree. Degeneration and depletion of germ cells were present in a single male treated at 200 mg/kg at moderate degree. Cell debris was present in the epididymis of a single male treated at 200 mg/kg to a moderate degree and in most males treated at 600 mg/kg up to moderate degree. Reduced sperm was present in a single male treated at 200 mg/kg to a slight degree and in all males treated at 600 mg/kg at a high degree. A minimal increase in hypertrophy of the follicular epithelium of the thyroid glands was noted in males at 200 and 600 mg/kg and in females at 600 mg/kg (considered non-adverse at current severity and in absence of any other pathological finding). No treatment-related clinical signs or adverse gross pathological findings were observed in pups. Live birth indices (number of live offspring on PND 1 as percentage of total number of offspring born) were 97% for the control and 99% for the 60 and 200 mg/kg groups. Parental toxicity NOAEL: 200 mg/kg bw/d. Developmental toxicity NOAEL: 200 mg/kg bw/d. Overall reproductive toxicity NOAEL: 60 mg/kg bw/d.

Table 4. Oral developmental and reproductive toxicity studies[2]

Test Article	Vehicle	Animals/Group	Dose/Concentration	Procedure	Results
Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.3%)	1% aqueous carboxymethylcellulose	New Zealand White rabbits (22 females/group)	0, 10, 30, or 100 mg/kg bw/d	OECD TG 414; animals treated with test substance via gavage on day 6-28 post-coitum, inclusive; control animals were treated with the vehicle only; maternal and fetal evaluations performed	No clinical signs of toxicity, treatment-related mortality, body weight changes, or gross pathological abnormalities were observed in dams. The number of pregnant females, corpora lutea, implantation sites, and pre- and post-implantation loss were similar in control and treated groups. Slightly decreased fetal weight was observed in the 100 mg/kg dose group compared to controls. No abnormalities regarding the female:male ratio or litter size/weight were observed. External malformations were observed in 2, 3, and 1 fetus(es) of the control, 10, and 30 mg/kg groups, respectively (effect not seen in the high-dose group). A statistically significant increase in the incidence of misaligned vertebrae was observed in fetuses of the high-dose group compared to controls (9.2% versus 3.8% in controls; however, the value remained within the maximum value of the available historical control data (10.2% per litter). Visceral malformations occurred in 2, 3, 2, and 1 fetus(es) I the control, 10, 30, and 100 mg/kg groups, respectively. The maternal and developmental NOAEL was determined to be >100 mg/kg bw/d

NOAEL = no-observed-adverse-effect-level; OECD = Organisation for Economic Co-operation and Development; PND = post-natal day; TG = test guideline

Table 5. In vitro genotoxicity studies

Test Article	Vehicle	Concentration/Dose	Test System	Procedure	Results	References
Trimethylbenzoyl Diphenylphosphine Oxide (purity > 98%)	methanol	0, 500, and 2500 µg/plate	*S. typhimurium* strains TA1535, TA1537, TA98, and TA 100	Ames assay; OECD TG 471; performed with and without metabolic activation; negative controls: untreated and vehicle; positive controls: cyclophosphamide, methyl-N-nitro-N-nitrosoguanidine, 2-aminoanthracene	Non-genotoxic; cytotoxicity was observed at 2500 µg/plate in the presence of metabolic activation in all strains, and without S9 in TA1535, but no increase in the number of his-positive revertants could be detected under all conditions tested; controls gave expected results.	[3,2]
Trimethylbenzoyl Diphenylphosphine Oxide (purity 99%)	ethanol	Experiment 1: 0, 8, 40, 200, 1000, and 5000 µg/plate Experiment 2: 0, 312.5, 625, 1250, 2500 and 5000 µg/plate	*S. typhimurium* strains TA1535, TA 1537, TA98, TA100 and *E. coli* strains WP2	2-part Ames assay; OECD TG 471; performed with and without metabolic activation; negative controls: untreated and vehicle; positive controls: methyl-N-nitro-N-nitrosoguanidine, 4-nitro-*o*-phenylenediamine, 9-aminoacridine, 4-nitroquinolone N-oxide, 2-aminoanthracene	Non-genotoxic; controls gave expected results	[3,2]
Trimethylbenzoyl Diphenylphosphine Oxide (purity 99%)	dimethyl sulfoxide	6-h treatment without S9 mix: 0, 15, 20, 23.3, and 25 µg/ml 6-h treatment with S9 mix: 0, 20, 23.3, 26.6, and 30 µg/ml 24-h treatment without S9 mix: 0, 5, 10, 15, and 20 µg/ml 48-h treatment without S9 mix: 0, 2.5, 5, 10, and 20 µg/ml	Chinese hamster lung cells	Chromosomal aberration assay; OECD TG 473; cells incubated without S9 mix for either 6, 24, or 48 h or with S9 mix for 6 h; negative control: vehicle; positive controls: mitomycin c, cyclophosphamide A preliminary test was performed to determine levels at which precipitation would occur. Maximum levels of 20 µg/ml (without S9 mix) and 30 µg/ml (with S9 mix) were determined for this assay.	Non-clastogenic; controls gave expected results	[3,2]
Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.5%)	ethanol	Experiment 1: 4-h treatment without S9 mix: 1.3, 2.5, 5.0, 10, 20, 30,* 40*µg/ml 4-h treatment with S9 mix: 3.4, 6.8, 13.5, 27, 40.5, 54 µg/ml Experiment 2: 24-h treatment without S9 mix: 5, 10, 15, 20, 25, 30, 35, 40* µg/ml 4-h treatment with S9 mix: 0, 20, 30, 40,* 45,* 50,* 55,* 60* µg/ml	Chinese hamster lung fibroblasts (V79)	2-part mammalian cell gene mutation test (*hprt* locus); OECD TG 476; in experiment 1, test substance was added to cultures for 4 h, with and without S9 mix; in experiment 2, test substance was added to cultures for 24 h without S9 mix and 4 h with S9 mix; negative control: ethanol; positive controls: ethyl methanesulfonate, 7,12-dimethylbenz(a)an-thracene	Non-mutagenic; cytotoxicity observed in all experiment parts at concentrations ≥ 10 µg/ml (without S9 mix) and ≥40 µg/ml (with S9 mix); no reproducible increase in mutant frequency observed up to maximum concentrations of 30 µg/ml (without S9 mix) and 40.5 µg/ml (with S9 mix); controls gave expected results	[3,2]
Trimethylbenzoyl Diphenylphosphine Oxide (purity ≥ 99.8%)	ethanol	0.008, 0.04, 0.20 and 1.0 µg/ml	Human fetal lung fibroblasts (MRC-5)	Comet assay; cells exposed to test substance for 24 h; positive control: 4-nitroquinolone-1-oxide: negative control: ethanol; TIs scored as reflection of DNA damage	Genotoxic; TIs were statistically significantly higher in cells treated with the solvent control when tested at 0.04 µg/ml and higher ($p < 0.05$); positive control gave expected results	[15]

*precipitation observed

NOAEL = no-observed-adverse-effect-level; OECD = Organisation for Economic Co-operation and Development; TG = test guideline; TI = tail intensity (% of DNA in comet tail)

Table 6. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
IRRITATION						
ANIMAL						
Trimethylbenzoyl Diphenylphosphine Oxide (99.5% purity)	olive oil	40%; 2000 mg/kg bw	Wistar rats (5/sex)	Test substance applied to clipped skin of rats under semi-occlusive conditions for 24 h; 14-d observation; application area approximately 40 cm^2; sites were observed 30 – 60 min after patch removal, and at regular intervals until the last day of observation	Local skin irritation (erythema, incrustation, scaling) was observed in 1 male and all females throughout the study.	[2,3]
Trimethylbenzoyl Diphenylphosphine Oxide (purity > 98%)	water	50%; 500 mg	Vienna white rabbits (2 males, 4 females)	Test substance applied to intact and abraded skin; application area of 2.5 cm^2; use of occlusion and exposure duration not stated (however, it can be assumed to be 24 h as this was the first observation point); animals were evaluated for skin irritation 24, 48, and 72 h and 8 d after application	The mean primary irritation index for was determined to be 1.33 (fully reversible within 8 d; unknown if this average includes both abraded and intact skin; mean of results observed at 24, 48, and 72 h; potential maximum value not provided). Mean erythema and edema scores for intact skin were 0.6/4 and 0.3/4, respectively. Mean erythema and edema scores for abraded skin were 0.9/4 and 0.4/4. The test substance was considered to be slightly irritating.	[2,3]
SENSITIZATION						
ANIMAL						
Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.5%)	acetone and olive oil	0, 10, 25, and 50%	Female CBA/CaOlaHsd mice (5/group)	LLNA; OECD TG 429; test substance applied to the dorsal surface of both ears for 3 consecutive days; controls treated with vehicle alone (negative control) or alpha hexyl cinnamaldehyde (positive control); on day 6 animals were injected with 20.1 µCi of radiolabeled [3H]-thymidine in phosphate-buffered saline and killed 5 h later; lymph nodes were obtained and used for stimulation index calculations (values of 3 or more are considered positive) and EC_3 values required to elicit a stimulation index value of 3	Stimulation index results for the test substance at 10, 25, and 50% were determined to be 2.22, 2.96, and 3.46, indicating an EC_3 value of 27%. The stimulation index value was determined to be 1.00 for the negative control group (results not reported for positive control group). The test substance was considered to be sensitizing.	[2,3]

Table 6. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
			HUMAN			
Nail gel color containing 2.6% Trimethylbenzoyl Diphenylphosphine Oxide	none	100%	51 female subjects	HRIPT; nail gel was applied to the fingernails 3x/wk for a total of 9 induction applications; challenge application 2 wk after final induction application; each application consisted of a single coat applied using a brush, left on for 10 min, and wiped off; reactions scored on a scale of 0 – 4 It should be noted that this product would be used prior to polymerization (polymerization was not performed in this study)	Non-irritating and non-sensitizing; reaction score of 0 (no visible nail and cuticle reaction)	[3]
Nail gel sealer containing Trimethylbenzoyl Diphenylphosphine Oxide (concentration of Trimethylbenzoyl Diphenylphosphine Oxide in product not stated)	none	100%	50 female subjects	Same procedure as above	Non-irritating and non-sensitizing; reaction score of 0 (no visible nail and cuticle reaction) It should be noted that this product would be used prior to polymerization (polymerization was not performed in this study)	[3]

EC_3 = amount of chemical that is required to elicit a 3-fold increase in lymph node proliferative activity; LLNA = local lymph node assay; OECD = Organisation for Economic Co-operation and Development; TG = test guideline

Table 7. Margin of safety calculation[3]

Parameter	Value	Details
Amount of gel applied	4 g	Full artificial nail systems are typically applied every 2 – 3 wk, with a refill application after 1 - 2 wk; full application of artificial nail systems range between 2 – 4 g of gel; refills consist of approximately 1 g of gel
Concentration of Trimethylbenzoyl Diphenylphosphine Oxide in gel product	4%	Maximum concentration of use according to PCPC survey*
Total amount of Trimethylbenzoyl Diphenylphosphine Oxide applied	160 mg	The use of 4 g of gel containing 5% Trimethylbenzoyl Diphenylphosphine Oxide will result in a total application of 200 mg Trimethylbenzoyl Diphenylphosphine Oxide/human (corresponds to 10 mg/nail; considering total fingernail and toenail area of 22 cm^2)
Human body weight	60 kg	Default human body weight
Amount of Trimethylbenzoyl Diphenylphosphine Oxide applied/kg human bw	3.33 mg/kg bw	160 mg Trimethylbenzoyl Diphenylphosphine Oxide/60 kg = 2.67 mg/kg bw
Assumed residue	1% **	Worst-case assumption
Assumed absorption through the nail plate	100%	Worst-case assumption
SED	0.027 mg/kg bw/d	2.67 mg/kg bw * 0.01 = 0.027 mg/kg bw/d
NOAEL	100 mg kg/bw/d***	Based on a 90-d oral toxicity study performed in rats (can be found in the Short-Term and Subchronic Toxicity Studies section of this report)
Corrected NOAEL for 50% bioavailability	50 mg/kg bw/d	Standard procedure according to SCCS's Notes of Guidance for the testing of cosmetic ingredients and their safety evaluation
MOE	1851	50 mg/kg bw/d / 0.027 mg/kg bw/d = 1851

NOAEL = no-observed-adverse-effect-level; SCCS = Scientific Committee on Consumer Safety; SED = systemic exposure dose

*the maximum concentration of use of Trimethylbenzoyl Diphenylphosphine Oxide is 4% according to the 2023 concentration of use survey conducted by Council[11]

** Trimethylbenzoyl Diphenylphosphine Oxide is used as a chemical photo-initiator in UV-curable gel systems for artificial nails, where it rapidly splits into free radicals that integrate into the polymer chain ends and is mostly consumed during polymerization. Any residual Trimethylbenzoyl Diphenylphosphine Oxide, under a worst-case scenario assuming 1%, gets trapped in the hardened polymer matrix of the nail coating.[3]

*** The NOAEL in the 28-d toxicity study was 50 mg/kg bw/day, while in the 90-d study was 100 mg/kg bw/day. The lower NOAEL might be due to the respective dose selection. Since there was no significant escalation in the severity of observed effects over time, an overall NOAEL of 100 mg/kg bw/d for repeated dose oral toxicity has been established for calculating the MOE.[3]

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