# Safety Assessment of Triphenyl Phosphate as Used in Cosmetics

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## ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of Triphenyl Phosphate, which is reported to function as a plasticizer in manicuring products. The Panel reviewed the available data to determine the safety of this ingredient. The Panel concluded that Triphenyl Phosphate is safe in cosmetics in the present practices of use and concentration described in this safety assessment.


## INTRODUCTION

Triphenyl Phosphate is reported to function as a plasticizer in cosmetics, as described by the web-based *International Cosmetic Dictionary and Handbook* (wINCI; *Dictionary*).[1] In cosmetic products, this ingredient is used exclusively in manicuring preparations, including nail polishes and enamels.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated.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 exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that CIR typically evaluates, is provided on the CIR website (respectively, http://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; http://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Some chemical and toxicological data on Triphenyl Phosphate included in this safety assessment were obtained from robust summaries of data submitted to the European Chemical Agency (ECHA) by companies as part of the REACH chemical registration process. Additionally, some data were obtained from an assessment by the Organisation for Economic Co-Operation and Development Screening Information Data Sets (OECD SIDS). These data summaries are available on the ECHA and OECD SIDS websites, respectively, and when appropriate, information from the summaries has been included in this report. .

## CHEMISTRY

### Definition

Triphenyl Phosphate is the organic compound that conforms to the structure in Figure 1.[1] It is reported to function as a plasticizer in cosmetic products.

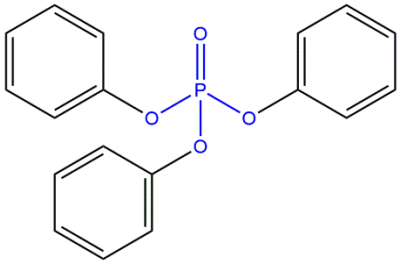


**Figure 1.** Triphenyl Phosphate

### Physical and Chemical Properties

Triphenyl Phosphate is a nonflammable, crystalline powder, with a melting point of 49 - 50 ºC.[2] Additional physical and chemical properties of Triphenyl Phosphate are provided in Table 1.

### Method of Manufacturing

According to one source, Triphenyl Phosphate can be prepared by reacting metaphosphoric anhydride and phenol or by reacting triethyl phosphite with sodium *p*-toluenesulfonchloramide.[2] Triphenyl Phosphate can also be derived by reacting phenol and phosphorus oxychloride.[3,4]

### Composition/Impurities

The purity of Triphenyl Phosphate is reported to be greater than or equal to 99.6% w/w.[4] Impurities may include water, phenol, and esters.

### Ultraviolet (UV) Absorption

In spectral analysis of Triphenyl Phosphate, no maximum UV absorption peaks were observed in the UVA and UVB ranges.[5]

## USE

### Cosmetic

The safety of the cosmetic ingredient included in this assessment is evaluated based on data received from the U.S. Food and Drug Administration (FDA) and the cosmetics industry on the expected use of this ingredient in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to 2018 VCRP data, Triphenyl Phosphate is used solely in 331 nail products, with the majority of the uses (286) being reported in nail polishes and enamels.[6] The results of the concentration of use survey conducted in 2017 by the Council indicate that Triphenyl Phosphate is used solely in leave-on manicuring preparations, at a maximum use concentration range of 1% to 14.5%, with the highest maximum concentration of use reported to be in polish strips.[7] Use concentrations were reported to be at up to 11.9% for nail enamels and at up to 1% in nail lotions.

Triphenyl Phosphate is not restricted from use in any way under the rules governing cosmetic products in the European Union.[8] OECD SIDS determined this chemical is low priority for further work regarding human health impact due to its low hazard potential.[4]

### Non-Cosmetic

Triphenyl Phosphate is a fire retarding agent and plasticizer for cellulose acetate and nitrocellulose.[3] Triphenyl Phosphate is a noncombustible substitute for camphor in celluloid; it is also used to render acetylcellulose, nitrocellulose, airplane "dope," etc., stable and fireproof; impregnating roofing paper; plasticizer in lacquers and varnishes.[2]

Triphenyl Phosphate is an approved indirect food additive in substances for use only as components of adhesives (21 CFR 175.105).

## TOXICOKINETICS

### Dermal Penetration

***In Vitro***

The dermal uptake and percutaneous penetration of Triphenyl Phosphate and other organophosphate esters was studied using human skin in Franz diffusion cells.[9] The exposed skin area in the mounted Franz diffusion cell was 2.64 $cm^2$ and 16.6 ml was the average volume of the receptor chamber. The receptor fluid was an aqueous solution of 0.9% sodium chloride, 5% bovine serum albumin, 40 mg/l hexamycin, and disodium phosphate buffer (to pH 7.4). The skin was dosed with 1000 ng Triphenyl Phosphate in 500 µl ethanol:toluene (4:1) solution to cover the entire skin surface. The diffusion cells were studied at 24, 48, and 72 h after dosing and the donor cell wash, epidermis, dermis and receptor fluid were analyzed for the ester content. When compared to the other esters, Triphenyl Phosphate tended to build up in the skin tissues, primarily in the upper layers. Only "smaller amounts" of Triphenyl Phosphate permeated the skin and reached the receptor fluid within 72 h.

### Absorption, Distribution, Metabolism, Distribution

***In Vitro***

In an in vitro metabolism study, Triphenyl Phosphate incubated with rat liver homogenate (without nicotinamide adenine dinucleotide phosphate (NADPH) and soluble fractions) was determined by gas chromatography to be metabolized to diphenyl phosphate via hydrolysis.[10] Triphenyl Phosphate was prepared in an ethanol solution at 0.0004 M.

In a qualitative in vitro metabolism study on phosphate flame retardants and plasticizers in human liver S9 fraction and microsomes, Triphenyl Phosphate was mainly transformed to a diester metabolite and to a hydroxylated metabolite.[11]

In a related study of phosphate flame retardants, the metabolite formation from Triphenyl Phosphate was characterized using primary human hepatocytes.[12] Cryopreserved human hepatocytes were thawed and suspended in media with 20 µM Triphenyl Phosphate for up to 2 h. Extracts of these materials were then analyzed by liquid chromatography-quadrupole-time-of-flight mass spectrometry. This analysis found that diphenyl phosphate corresponded to less than half of the depletion of Triphenyl Phosphate following the 2 hour exposure. Other metabolites, mainly sulfate and glucuronide conjugates, were produced at lower rates.

***Human***

The potential for Triphenyl Phosphate to be absorbed during cosmetic application was assessed in human volunteers.[13] Two cohorts (26 volunteers total) were recruited to assess the exposure of Triphenyl Phosphate by fingernail painting. The volunteers provided urine samples before and after applying a polish containing 0.97% Triphenyl Phosphate by weight. The metabolite, diphenyl phosphate, was then measured in urine samples ($n = 411$). Prior to application, the geometric mean of diphenyl phosphate for the control samples was 0.96 ng/ml. The concentration of diphenyl phosphate was found to increase nearly seven-fold approximately 10 – 14 hours after fingernail painting (13.02 ng/ml; $p < 0.001$). To determine relative contributions of inhalation and dermal exposure, 10 volunteers total also painted their own nails and synthetic nails adhered to gloves on two separate occasions. Urine was then collected for 24 hours following applications for metabolite analysis. Urinary diphenyl

phosphate was significantly diminished (near background concentration; geometric mean not reported) when the volunteers wore gloves, allowing the researchers to suggest that the primary route of exposure is dermal.

## TOXICOLOGICAL STUDIES

### Acute Toxicity Studies

Acute dermal, oral, and inhalation studies are summarized in Table 2. In rabbits, the dermal $LD_{50}$ for Triphenyl Phosphate (concentration not reported) was greater than 10,000 mg/kg.[4,14,15] The oral $LD_{50}$ values for Triphenyl Phosphate in guinea pigs, rats, and mice were greater than 4000 mg/kg (concentration not reported), greater than 20,000 mg/kg (25% aqueous solution), and greater than 5000 mg/kg (20% emulsion in gum Arabic), respectively.[4,14-16] Additional oral studies in mice at up to 500 mg/kg Triphenyl Phosphate found choline esterase activity was partially inhibited in the whole blood in a dose-dependent manner (87%-88% activity in 10-50 mg/kg to 30.4% in 500 mg/kg).[16] The $LC_{50}$ for inhalation exposure to Triphenyl Phosphate in rats was greater than 200 mg/L/h.[4,14] In inhalation studies in mice at up to 757 $mg/m^3$ for up to 4 h, mean cholinesterase activity was lower in treated groups than in controls; however, significance was only observed in the 2 h exposure in the 757 $mg/m^3$ dose group.[16]

### Short-Term and Subchronic Toxicity Studies

Short-term dermal and short-term and subchronic oral studies are summarized in Table 3. The no-observed-adverse-effect-level (NOAEL) for 50% (w/v) Triphenyl Phosphate in a 3-week dermal repeated dose study in rabbits was 1000 mg/kg/day, the maximum dose tested.[4,14] In oral studies of 5 to 10 days in duration in cats at doses up to 50 mg/kg/day 2% Triphenyl Phosphate, mortalities, dyspnea, weakness, and decreased body weight were observed.[4,14] Cholinesterase activity was 64% to 71% of normal values. In rat dietary studies of up to 90 days in duration, the NOAEL was 1500 ppm based on liver weight increases.[4,14,16] In a 4 month rat dietary study of the effects of Triphenyl Phosphate at up to 1.0% on neuromotor function (see Other Relevant Studies – Neurotoxicity) body weight gains were significantly reduced starting at 0.5%.[17] The no-observed-effect-level (NOEL) for non-immunotoxic effects in a 120 day rat dietary study on immunotoxic effects (see Other Relevant Studies – Immunotoxicity) was 0.75% Triphenyl Phosphate due to reduction of body weight gains.[14,18]

## DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

The effects of 300 to 7500 ppm Triphenyl Phosphate on the reproductive organs were also investigated in the 90-day dietary study (see Short-Term and Subchronic Toxicity Studies, summarized in Table 3).[14] No adverse effects were observed during microscopic examination or weight measurements of the gonads (males: testes and epididymes, seminal vesicles including coagulating glands; females ovaries, uterus including cervix, vagina) at dietary doses up to 7500 ppm.

The effects of Triphenyl Phosphate on prenatal development were studied in pregnant New Zealand rabbits in accordance with the OECD Test Guideline (TG) 414.[14] The dams received Triphenyl Phosphate in 1% aqueous carboxymethyl cellulose once daily via gavage from days 6 to 28 post-coitum at doses of 0, 32, 80 and 200 mg/kg bw/day. The dams were checked daily for clinical signs of toxicity, and feed consumption and body weights were measured periodically. Dams that survived to day 29 post-coitum were killed and underwent external, thoracic, and abdominal macroscopic examinations. The uteri, placentas, and ovaries were examined, and the numbers of fetuses, early and late resorptions, total implantations, and corpora lutea were recorded. Gravid uterine weights were recorded, and net body weights and net body weight changes were calculated. The fetuses were weighed, sexed, and examined for external, visceral, and skeletal malformations and developmental variations.

No adverse effects were observed in any of the maternal parameters investigated in this study, including mortality, clinical signs, body weights, food consumption, and macroscopic examination. No adverse effects were noted in any of the developmental parameters investigated in this study, including litter size, sex ratio, fetal body weights, external, visceral and skeletal developmental malformations or variations. The authors of this study concluded that the maternal and developmental NOAELs for Triphenyl Phosphate are at least 200 mg/kg bw/day each, based on the absence of adverse effects.[14]

The teratogenic potential of Triphenyl Phosphate was investigated in Sprague-Dawley rats.[19] Groups of 40 male and 40 female rats received 0%, 0.25%, 0.50%, 0.75%, or 1.0% Triphenyl Phosphate in their feed from 4 weeks post-weaning through mating and gestation (91 days). Daily intake of Triphenyl Phosphate during pregnancy was determined to be 0, 166, 341, 516, and 690 mg/kg bw, respectively (no further details on the males were provided). Body weights of the pregnant rats and feed consumption were measured on days 7 and 14 of gestation and before laparotomies were performed on day 20. The dams were observed daily for clinical signs of toxicity. The major organs were examined and the ovaries were removed and examined for numbers of corpora lutea. The gravid uterus was removed and weighed. Litter size and resorptions were recorded. The fetuses were examined for gross abnormalities, sexed, weighed, measured, and underwent skeletal or visceral examinations.

In general, feed consumption was slightly greater in the treated animals than in the controls, except during days 0-7 of gestation. Maternal body weights of the treated animals on gestation day 0 were similar to the controls, except for the high dose group, which were significantly lower. Body weight gains during pregnancy and adjusted body weight gain excluding the gravid uterus had dose-dependent decreases, but were not significant. No toxic effects to reproduction or development were observed in the dams or the offspring at any dose level. Slight increases in the number of soft tissue variations were observed, but these were not dose-related. Number and type of developmental anomalies in the treated groups were comparable to those in the controls. The authors of the study concluded that Triphenyl Phosphate was not teratogenic in this rat study.[19]

## GENOTOXICITY STUDIES

Genotoxicity studies are summarized in Table 4. Triphenyl Phosphate was not mutagenic in Ames tests at up to 10,000 µg/plate, nor was it mutagenic in a mouse lymphoma test at up to 75 µg/ml.[4,14,20] Triphenyl Phosphate (99.6% pure) was not clastogenic in a Chinese hamster V79 cell assay at up to 60 µg/ml.[14]

## CARCINOGENICITY STUDIES

No relevant published carcinogenicity studies on Triphenyl Phosphate were identified in a literature search for this ingredient, and no unpublished data were submitted.

## OTHER RELEVANT STUDIES

### Endocrine Activity

***In Vitro***

The effects of Triphenyl Phosphate (> 99% pure, dissolved in 0.1% dimethyl sulfoxide [DMSO]) on induction of oxidative stress and gene expression were investigated in the murine Leydig cell line, TM3.[21] The TM3 cells were cultured in 0, 20, or 60 µg/ml Triphenyl Phosphate for up to 24 h. After 24 h exposure, cell growth declined and morphology changed in the high dose groups. Significant increases were observed in superoxide dismutase, catalase, glutathione peroxidase, and glutathione *S*-transferase activities and their respective gene expressions in a dose-dependent and/or time-dependent manner in Triphenyl Phosphate treated groups. Triphenyl Phosphate significantly reduced the expression of main genes related to testosterone synthesis, especially in the high dose group at 24 h. Triphenyl Phosphate treatments for 24 h caused significant decreases in T levels in the medium. Co-treatments of human chorionic gonadotropin (hCG) with Triphenyl Phosphate could inhibit hCG-induced changes in the expression of testosterone and testosterone synthesizing genes. The authors of the study concluded that Triphenyl Phosphate could induce oxidative stress and endocrine activation in TM3Leydig cells.

In vitro reporter gene assays indicated Triphenyl Phosphate had potential endocrine-disrupting properties: as agonist, Triphenyl Phosphate could stimulate estrogen receptor α/β (ER α / ERβ), and pregnane X receptor (PXR) activity; as antagonist, Triphenyl Phosphate could inhibit androgen receptor (AR) and glucocorticoid receptor (GR) activity. In comparison, Triphenyl Phosphate showed no effects on the activity of thyroid hormone receptor α (TRα), TRβ, retinoic acid receptor α (RARα), retinoid X receptor α (RXR α), peroxisome proliferator-activated receptor (PPARα), orPPARγ.[22] In rat pituitary cells (GH3), significant up-regulation of thyroid hormone receptor α/β (*trα/trβ*) genes was observed following exposure to 10 or 100 µg/L Triphenyl Phosphate, and the expression of thyroid-stimulating hormone β (*tshβ*) gene was significantly up-regulated by exposure to 100 µg/L Triphenyl Phosphate.[23] In rat thyroid follicular cells (FRTL-5), the expression of the sodium/iodide symporter (*nis*) and thyroid peroxidase (*tpo*) genes was significantly up-regulated after exposure to after exposure to 3 or 10 mg/L Triphenyl Phosphate. The authors of the study pointed out these results suggested Triphenyl Phosphate could stimulate thyroid hormone synthesis in the thyroid gland.

Triphenyl Phosphate showed statistically significant estrogenic activity, with an $EC_{20}$ value of 88 µM, measured by flow-cytometric proliferation assay, in MCF-7 human breast adenocarcinoma cells.[24] While in MVLN cells, a bioluminescent MCF-7-derived cell line, Triphenyl Phosphate acted as estrogen receptor antagonists by inhibiting binding of 17β-estradiol (E2) to estrogen receptor.[25]

***In Vivo***

The same researchers evaluated the effects of Triphenyl Phosphate (> 99% pure) on the induction of oxidative stress and endocrine activation in groups of 7 ICR male mice.[26] The mice received 0, 100, or 300 mg/kg/bw Triphenyl Phosphate in feed daily for 35 days. At the end of the exposure period, the mice were killed, and livers and testes were removed and weighed. The livers were then homogenized and underwent enzyme analysis, while the testes underwent histopathological examination. Gene expression analysis was performed on the total RNA in the livers and testes.

Compared to the control group, statistically significant decreases in body and testes weights were observed in the 300 mg/kg Triphenyl Phosphate-treated mice. Hepatic malondialdehyde content increased significantly in a dose-dependent manner, while the contents of glutathione decreased significantly in the 300 mg/kg dose group. Triphenyl Phosphate exposure affected hepatic activities of antioxidant enzymes including glutathione peroxidase (increased activity), catalase (increased activity), and glutathione *S*-transferase (decreased activity) as well as related gene expression. In the testes, exposure to 300 mg/kg Triphenyl Phosphate resulted in histopathological damage and a decrease of testicular testosterone levels, whereas no morphologic changes, except a slight reduction of Sertoli cells, were observed in the 100 mg/kg dose group. The expression of the main genes related to testosterone synthesis, including steroidogenic acute regulatory protein, low-density lipoprotein receptor, cytochrome P450 cholesterol side-chain cleavage enzyme, and cytochrome P450 17α-hydroxysteroid dehydrogenase in the testes also was decreased after the exposure to 300 mg/kg Triphenyl Phosphate. The authors of the study concluded that Triphenyl Phosphate induced oxidative stress and endocrine activation in mice.[26]

In zebrafish (*Danio rerio*) larvae at 7 days post-fertilization, exposure to Triphenyl Phosphate from 40 to 500 µg/L led to significant increases in both triiodothyronine (T3) and thyroxine (T4) concentrations and influenced the expression of several genes associated with the thyroid system, including corticotrophin-releasing hormone (crh), tshβ, trα, trβ, nis and tg genes.[23]

Exposure to Triphenyl Phosphate also significantly upregulated the expression of the genes related to the metabolism (dio1), transport (ttr), and elimination (ugt1ab) of thyroid hormones.

After 14-day of zebrafish exposure, Triphenyl Phosphate significantly increased plasma E2 concentration and decreased testosterone (T) and 11-ketotestosterone (11-KT) among male fish.[25] Among females, both plasma T and E2 concentrations increased but there was no change of 11-KT. Transcription of *cytochrome P450 (CYP)17* and *CYP19a* genes in gonad was significantly up-regulated in both sexes, while the *vitellogenin (VTG) 1* gene in the liver was down- and up-regulated in female and male fish, respectively. In another study, after 21-day of zebrafish exposure to Triphenyl Phosphate, there was a significant decrease in fecundity along with significant increases of plasma E2 concentrations, VTG levels, and E2/ T and E2/11-KT ratios were observed.[27] Several genes of the hypothalamus–pituitary–gonad (HPG) axis changed after the exposure in a sex-dependent manner. Overall, the zebrafish study authors concluded Triphenyl Phosphate could alter sex hormone balance through several mechanisms including alterations of steroidogenesis or estrogen metabolism.

### Neurotoxicity

The effects of dietary exposure of Triphenyl Phosphate on neuromotor function were studied in a 4 month study in rats.[17] Groups of 10 male Sprague-Dawley rats received 0, 0.25%, 0.50%, 0.75%, or 1.0% Triphenyl Phosphate in their feed *ad libitum*. Daily doses were determined to be 0, 161, 345, 517, and 711 mg/kg/day, respectively. Behavioral tests including measures for motility, exploratory behavior, balance and general motor coordination, and muscular strength were performed on a monthly basis. No treatment-related effects were noted in the behavioral assessments at any of the monthly test sessions. The study authors concluded that Triphenyl Phosphate at up to 1.0% in a 4 month dietary study in rats did not cause neurotoxicity.

### Immunotoxicity

The potential immunotoxic effects of Triphenyl Phosphate were examined in a dietary study in rats.[14,18] Groups of 10 male and 10 female Spartan Sprague-Dawley rats received feed containing 0, 0.25%, 0.5%, 0.75%, and 1% Triphenyl Phosphate for 120 days. Total protein analysis and electrophoretic analyses of serum proteins were performed. Immunotoxicity was assessed by measurements of the weights of lymphoid organs, immuno-histochemical evaluation of spleen, thymus, and lymph nodes using immunoperoxidase staining, and the humoral response to antigens in sheep red blood cells.

A trend towards an increase in thymus weights was observed in male rats in the 0.75% dose group, but little to no differences were observed in the 1% dose group. No significant changes in spleen weights were observed. No significant changes were found in these organs and lymph nodes during histopathologic examinations. No significant alterations of serum protein were detected. Electrophoresis revealed increased levels of alpha- and beta-globulin in male and female rats but effects were similar at all dose levels, relative to the control group. There were no significant differences between animals immunized with sheep red blood cells and non-immunized animals. Only non-dose-dependent variation was found in the humoral immune response to sheep red blood cells in female rats. The authors of this dietary rat study concluded that the NOEL for immunotoxicity was 1% Triphenyl Phosphate.[14,18]

### Cytotoxicity

The cytotoxic potential of Triphenyl Phosphate was studied is several different cultured cell lines.[28] The test material was dissolved in DMSO (0.5%) and diluted in minimum essential medium and cultured with human (KB and HEL-R66), monkey (Vero) or dog (MDCK) cells for 72 h. After the incubation period, the number of viable cells was determined and compared to the DMSO control. Inhibition of growth by Triphenyl Phosphate was observed in a dose dependent manner in all cell lines. The dose that inhibited cell multiplication by 50% ($ID_{50}$) was 0.6 mM and 0.5 mM for the KB and HEL-R66 cell lines, respectively, 0.4 mM for the Vero cell line, and 0.5 mM for the MDCK cell line. The authors concluded Triphenyl Phosphate is toxic to the human, monkey and dog cell lines described in this study.

## DERMAL IRRITATION AND SENSITIZATION STUDIES

Dermal irritation and sensitization studies are summarized in Table 5. Triphenyl Phosphate was not a dermal irritant in rabbits at up to 50% or mice at 70% in alcohol.[4,14,16] No dermal sensitization was observed to Triphenyl Phosphate in guinea pig maximization tests up to 75%; however significant and dose-dependent allergic responses were observed in a non-validated mouse ear swelling test at concentrations of 3.0% or 10%.[4,14,29] In human repeated insult patch tests (HRIPTs) with nail products, concentrations of up to 7% Triphenyl Phosphate did not induce irritation or sensitization in human subjects.[30-34] No adverse events were reported in an in-use safety evaluation of a nail polish containing 1.0041% Triphenyl Phosphate.[35]

## OCULAR IRRITATION STUDIES

Ocular irritation studies are summarized in Table 6. Minimal ocular irritation effects were observed in rabbits tested with Triphenyl Phosphate, neat.[4,14]

## CLINICAL STUDIES

### Provocative Studies

In occlusive patch testing with 5% Triphenyl Phosphate in petrolatum in accordance with the International Contact Dermatitis Research Group (ICDRG) recommendations with a variety of plastic and glue allergens, no sensitization was observed in 174 patients with suspected occupational dermatoses.[36] One patient was observed with an irritation response. No further details were provided.

### Case Reports

A 71-year-old female hospital patient with no prior history of allergies to plastics was treated with oxygen with an EN46001 System 22 clear facemask.[37] Erythema developed around her nose and mouth on the second day of admission that corresponded with the areas where the facemask had been in contact with her skin. By day 5, she had an acute facial eczema, which was diagnosed as allergic contact dermatitis. The patient was treated with mometasone cream, and the reaction cleared within 2 weeks. Patch tests were performed using the British Contact Dermatitis Society standard series, the plastics/glue series, the rubber chemicals series, a piece of the EN46001 System 22 oxygen facemask, a piece of the elastane strap, Triphenyl Phosphate, and tricresyl phosphate. Positive patch test results were observed to Triphenyl Phosphate (5% pet., + on day 2 and ++ on day 4), the facemask (as-is; ++ on day 2 and ++ on day 4), wool alcohols (30% pet.; ?+ on day 4 - likely an irritant reaction), and Amerchol L101 (100%; ?+ on day 4 – likely an irritant reaction). Prick tests to latex were negative. The facemask manufacturer reported that the facemask did not contain Triphenyl Phosphate, but it did contain triphenyl phosphite, which may have produced a cross-reaction.

A 29-year-old man with no previous allergic or atopic history reported a 6-month history of itchy fissured psoriasiform dermatitis on both palms.[38] The patient has a hobby that involves working with plastic glues. Positive patch test results of a standard series, balsams, plastics, and lacquers were observed for paraben-mix (15% pet.; ++), cobalt chloride (1% pet.; +), potassium dichromate (0.5% pet.; ++), formaldehyde (1% aq.; +), and Triphenyl Phosphate (5% pet.; ++).

In another case report, a 67-year-old woman reported an itchy eczematous eruption on the bridge of her nose and temples that were believed to be caused by her eyeglasses.[39] Patch tests were performed with the ICDRG standard series on Finn chambers. Additional tests were performed with the patient's facial products and acetone-moistened scrapings from her eyeglass frames. Patch test results were negative for the standard series (including benzocaine), but were positive for benzocaine liniment with phenyl salicylate and the scrapings from the frames. Further patch tests results were negative for tris(2,3-dibromopropyl)-phosphate (5% pet.), dibutylphthalate (5% pet.), methyl salicylate (2% pet.), and positive (++) for phenyl salicylate (1% pet.) and tricresyl phosphate (5% pet.). Tests with pure triphenyl phosphate (>98%) and tri-*m*-cresyl- and tri-*p*-cresyl phosphate at 0.05%, 0.5%, and 5% pet. were positive to triphenyl phosphate down to 0.05% (++ to +) and tri-*m*-cresyl phosphate down to 0.5% (++ to +), but no reactions were observed to tri-*p*-cresyl phosphate.

### Occupational Exposure

The National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit (REL) and the Occupational Safety Health Administration (OSHA) permissible exposure limit (PEL) are both 3 mg/m$^3$ time weighted average (TWA).[40] NIOSH established the immediately dangerous to life or health concentration (IDLH) as 1000 mg/m$^3$.

## SUMMARY

Triphenyl Phosphate is an organic compound reported to function as a plasticizer in cosmetics. According to 2018 VCRP data, Triphenyl Phosphate is used solely in 331 nail products, with the majority of the uses being reported in nail polishes and enamels. The results of the concentration of use survey conducted in 2017 by the Council indicate that Triphenyl Phosphate is used solely in leave-on manicuring preparations at 1% to 14.5%, with the highest maximum concentration of use reported to be in polish strips.

Triphenyl Phosphate is a fire retarding agent and plasticizer for cellulose acetate and nitrocellulose. It is a noncombustible substitute for camphor in celluloid; it is also used to render acetylcellulose, nitrocellulose, airplane "dope," etc., stable and fireproof; impregnating roofing paper; plasticizer in lacquers and varnishes. Triphenyl Phosphate is an approved indirect food additive in substances for use only as components of adhesives.

In a dermal penetration study of organophosphate esters performed in vitro, Triphenyl Phosphate tended to build up in the skin tissues, primarily in the upper layers. Only "smaller amounts" of Triphenyl Phosphate permeated the skin and reached the receptor fluid within 72 h.

Triphenyl Phosphate has been reported to metabolize to diphenyl phosphate and sulfate and glucuronide conjugates in metabolism studies performed in vitro. An absorption study of 0.97% Triphenyl Phosphate in nail polishes in 26 human volunteers found that the primary route of exposure was dermal exposure.

In rabbits, the dermal $LD_{50}$ for Triphenyl Phosphate (concentration not reported) was greater than 10,000 mg/kg. The oral $LD_{50}$ values for Triphenyl Phosphate in guinea pigs, rats, and mice were greater than 4000 mg/kg (concentration not reported), greater than 20,000 mg/kg (25% aqueous solution), and greater than 5000 mg/kg (20% emulsion in gum Arabic), respectively. Additional oral studies in mice at up to 500 mg/kg Triphenyl Phosphate found choline esterase activity was partially inhibited in the whole blood in a dose-dependent manner (87% - 88% activity in 10 - 50 mg/kg to 30.4% in 500 mg/kg). The $LC_{50}$ for

inhalation exposure to Triphenyl Phosphate in rats was greater than 200 mg/L/hr (concentration not reported). Inhalation studies in mice at up to 757 mg/m$^3$ for up to 4 h observed mean cholinesterase activity lower in treated groups than in controls; however, significance was only observed in the 2 h exposure in the 757 mg/m$^3$ dose group.

The NOAEL for 50% (w/v) Triphenyl Phosphate in a 3-week dermal repeated dose study in rabbits was 1000 mg/kg/day, the maximum dose tested. In oral studies in cats at doses up to 50 mg/kg/day 2% Triphenyl Phosphate, mortalities, dyspnea, weakness, and decrease body weight were observed. Cholinesterase activity was 64% to 71% of normal values. In rat dietary studies up to 90 days in duration, the NOAEL was 1500 ppm based on liver weight increases. No adverse effects were observed during microscopic examination or weight measurements of the gonads (males: testes and epididymes, seminal vesicles including coagulating glands; females ovaries, uterus including cervix, vagina) at dietary doses up to 7500 ppm in this 90 day study. In a 4 month rat dietary study of the effects of Triphenyl Phosphate at up to 1.0% on neuromotor function, body weight gains were significantly reduced starting at 0.5%. The NOEL for non-immunotoxic effects in a 120 day rat dietary study on immunotoxic effects was 0.75% Triphenyl Phosphate due to reduction of body weight gains.

The maternal and developmental NOAELs in female rabbits was 200 mg/kg/day Triphenyl Phosphate (maximum dose tested) due to the lack of observed adverse effects. Triphenyl Phosphate was not teratogenic in a rat study at doses up to 1.0% (690 mg/kg).

Triphenyl Phosphate was not mutagenic in Ames tests at up to 10 mg/plate nor was it mutagenic in a mouse lymphoma test at up to 75 µg/ml. Triphenyl Phosphate (99.6% pure) was not clastogenic in a Chinese hamster assay at up to 60 µg/ml.

In studies researching effects on the endocrine system, Triphenyl Phosphate (> 99% pure) was found to induce oxidative stress and reduce the expression of main genes related to testosterone synthesis in TM3 Leydig cells and in male mice at 300 mg/kg/day, but not at 100 mg/kg/day. In studies using animal and human cell lines and a zebrafish model, investigators found that Triphenyl Phosphate produced effects on sex hormone balance through various mechanisms including alterations of steroidogenesis and/or estrogen metabolism.

No neurotoxicity was observed in a subchronic dietary rat study of Triphenyl Phosphate at up to 1.0%. In another dietary rat study of Triphenyl Phosphate, the NOEL for immunotoxicity was 1% (maximum dose tested). Triphenyl Phosphate was toxic to human, monkey, and dog cell lines at 0.5 mM or 0.6 mM, 0.4 mM, and 0.5 mM, respectively.

Triphenyl Phosphate was not a dermal irritant in rabbits at up to 50% or mice at 70% in alcohol. No dermal sensitization was observed to Triphenyl Phosphate in guinea pig maximization tests up to 75%; however, significant and dose-dependent allergic responses were observed in a non-validated mouse ear swelling test at 3.0% or 10%. In HRIPTs with nail products, concentrations of up to 7% Triphenyl Phosphate did not induce irritation or sensitization in human subjects. No adverse events were reported in an in-use safety evaluation of a nail polish containing 1.0041% Triphenyl Phosphate.

Minimal ocular irritation effects were observed in rabbits tested with Triphenyl Phosphate, neat.

Sensitization was not observed in patch testing of dermatitic patients with 5% Triphenyl Phosphate in petrolatum. Case reports of allergic contact dermatitis were reported in patients that had been exposed to various plastic products containing Triphenyl Phosphate or triphenyl phosphite.

No relevant published carcinogenicity studies on Triphenyl Phosphate were identified in a literature search for this ingredient, and no unpublished data were submitted.

## DISCUSSION

The Panel found that the systemic toxicity data, including developmental and reproductive toxicity and short-term toxicity studies, and dermal irritation and sensitization studies, in this report were sufficient. The Panel noted that Triphenyl Phosphate can be absorbed at a very low rate through the skin, but the safety profile and use solely in nail products suggests that no adverse effects are likely to occur. The Panel also noted the lack of carcinogenicity data, but this gap was mitigated by multiple genotoxicity studies that were negative.

The Panel discussed the endocrine disruption potential of Triphenyl Phosphate in available in vitro and in vivo studies, and determined that the results were not sufficient to characterize this ingredient as an endocrine disrupting chemical. For further explanation of what qualifies as endocrine activity or disruption, please refer to the CIR resource document: https://www.cir-safety.org/supplementaldoc/cir-precedents-endocrine-activity.

## CONCLUSION

The CIR Expert Panel concluded that Triphenyl Phosphate is safe in cosmetics in the present practices of use and concentration described in this safety assessment.

# TABLES

**Table 1.** Physical and chemical properties of Triphenyl Phosphate

| Property | Value | Reference |
|---|---|---|
| | | |
| Physical Form | Nonflammable needles; colorless, odorless crystalline powder | [2,3] |
| Molecular Weight (Da) | 326.28 | [2] |
| Density ($g/cm^3$ @ 60º C) | 1.27 | [3] |
| Vapor Pressure (mmHg @ 25º C) | $7.50 \times 10^{-6}$ | [14] |
| Melting Point (º C) | 49-50 | [2] |
| Boiling Point (º C at 11 mm Hg) | 245 | [2] |
| Water Solubility (mg/L @ 25º C) | 1.9 | [41] |
| Log P (@ 20º C) | 4.63 | [14] |

**Table 2.** Acute toxicity studies of Triphenyl Phosphate

| Concentration/Vehicle | Dose/Study Protocol | Results | $LD_{50}$ or $LC_{50}$ | Reference |
|---|---|---|---|---|
| | | ***Dermal*** | | |
| Vehicle not reported | 10,000 mg/kg body weight (bw) in 2 groups of 5 albino rabbits; 1 group had intact skin and the other had abraded skin; sex of animals not reported; no further details | No premature deaths or adverse effects observed | > 10,000 mg/kg bw | [4,14] |
| Undiluted | 7900 mg/kg in male and female New Zealand albino rabbits on intact, clipped dorsal skin; occlusive patch for 24 h; skin washed after exposure period; number of animals not reported | No premature deaths or adverse effects observed | > 7900 mg/kg bw | [14] |
| | | ***Oral*** | | |
| 20% emulsion with gum Arabic | 2500 or 5000 mg/kg administered to groups of 5 male and 5 female mice via gavage; strain not reported | Slight stupor observed; no premature deaths reported | > 5000 mg/kg bw | [4,14] |
| Concentration and vehicle not reported | 3000 mg/kg administered to 10 male CF-1 mice; method of administration not reported | No premature deaths and no clinical symptoms observed | > 3000 mg/kg | [16] |
| Concentration and vehicle not reported | Up to 500 mg/kg in 10 male CF-1 mice; method of administration not reported | Choline esterase activity was partially inhibited in the whole blood in a dose-dependent manner (87% - 88% activity in 10-50 mg/kg to 30.4% in 500 mg/kg); no cholinergic or other symptoms were reported | Performed in conjunction with the above acute oral toxicity study with $LD_{50}$ > 3000 mg/kg | [16] |
| Concentration and vehicle not reported | 3000 mg/kg administered to 11 male Holtzman rats; method of administration not reported | 1 death recorded within a month of exposure, no clinical symptoms observed | > 3000 mg/kg | [16] |
| 25% aqueous solution | 20,000 mg/kg bw administered to 5 male and 5 female Wistar albino rats via intragastric intubation | No premature deaths observed; gross examined revealed sporadic visceral hemorrhage | > 20,000 mg/kg bw | [4,14] |
| Concentration not reported; administered in corn oil | Maximum dose = 15,800 mg/kg administered to male and female Sprague Dawley rats via gastric intubation; number of animals not reported | Mortality and systemic toxicity data not provided | 10,800 mg/kg bw | [15] |
| 20% emulsion with gum Arabic | 2500 or 5000 mg/kg administered to groups of 5 male and 5 female rats via gavage; strain not reported | No premature deaths and no clinical symptoms observed | > 5000 mg/kg bw | [4,14] |
| Concentration and vehicle not reported | Up to 6400 mg/kg in rats, no further details provided | No details provided | > 6400 mg/kg bw | [4] |
| Concentration and vehicle not reported | 3000 and 4000 mg/kg administered to groups of 5 male albino guinea pigs; method of administration not reported | No premature deaths and no clinical symptoms observed | > 4000 mg/kg | [16] |
| | | ***Inhalation*** | | |
| 363 $mg/m^3$ and 757 $mg/m^3$; administered as a vapor | 363 $mg/m^3$ for 6 h in 5 male CF-1 mice and 757 $mg/m^3$ for 2 h and 4 h in 7 male CF-1 mice, each; mice exposed in cylindrical glass battery jars; no further details provided | No cholinergic signs or symptoms observed; mean cholinesterase activity in treated groups lower than controls; significance only observed in the 757 $mg/m^3$ dose group for 2 h | Not an $LC_{50}$ study | [16] |
| 200 mg/L; administered as a powder | 200 mg/L in 5 male and 5 female Wistar rats for 1 h; no further details provided | No premature deaths and no clinical symptoms observed | > 200 mg/L/h | [4,14] |

**Table 3.** Short-term and subchronic toxicity studies for Triphenyl Phosphate

| Concentration/Dose/Vehicle | Species | Study Protocol/Duration | Results | Reference |
|---|---|---|---|---|
| | | ***Short-Term Dermal*** | | |
| 50% (w/v) in ethanol; 0, 100, or 1000 mg/kg bw/day | Groups of 10 male and 10 female New Zealand White rabbits | Repeated dose dermal toxicity study in accordance with EPA OPPTS 870.3200; half of the animals received 0.2 ml test material on clipped, intact skin and half on abraded skin for 6 hours/day, 5 times/week for 3 weeks; not occluded; animals were collared; control animals received ethanol alone | NOAEL = 1000 mg/kg bw/day; no significant differences in mortality, clinical signs, body weight, hematology, clinical chemistry, necropsy, organ weights, or histopathology of tissues, including reproductive organs, were observed when compared to controls; a depression of acetyl cholinesterase in plasma, erythrocytes and brain of treated rabbits had no clinical or histological correlations and was not considered toxicologically relevant | [4] |
| | | ***Short-Term Oral*** | | |
| 2% in aqueous tragacanth; 50 mg/kg bw/day | 4 cats; no further details provided | Gavage study; test material administered once daily for 5 - 10 days; no further details provided | All animals died within 10 days; dyspnea, weakness, and decreased body weight were observed; cholinesterase activity was measured and found to be 64% to 71% of normal values | [4,14] |
| 10-25 mg/kg bw/day; vehicle not reported | 2 cats/dose group; no further details provided | Gavage study; test material administered once daily for 30 days; no further details provided | No clinical signs of toxicity observed at 10 mg/kg bw/day; weakness, prostration, labored respiration, and severe reduction of body weight observed at 25 mg/kg bw/day; 1 death occurred in the high dose group on day 27; choline esterase activity was 77%-87% of normal value | [4,14] |
| 0, 250, 1000, or 4000 ppm in feed equating to 0, 23, 104, or 508 mg/kg bw/day in males and 0, 39, 161, or 701 mg/kg bw/day in females | Wistar rats in groups of 5 males and 5 females | 4 week dietary study in accordance with OECD TG 407 | NOEL = 250 ppm for males and 1000 ppm for females; NOAEL = 250 ppm for males and 4000 ppm for females based on effects on body weights; no treatment-related mortality observed; no clinical signs of toxicity observed; no signs of neurotoxicity were observed; body weight gain was slightly depressed in males at 1000 ppm (13%) and 4000 ppm (10%); feed consumption was increased when compared to controls at 4000 ppm for males (31%) and females (14%); mean aspartate aminotransferase activities were decreased in 1000 and 4000 ppm males; mean cholesterol was increased in 4000 ppm males; absolute and relative liver weights were statistically significantly increased in 4000 ppm rats of both sexes; distinct changes in liver function were observed at 1000 ppm and greater in males and at 4000 ppm in females; no toxicologically relevant changes to other organ weights were observed; no other gross or histopathological findings were observed | [14] |

**Table 3.** Short-term and subchronic toxicity studies for Triphenyl Phosphate

| Concentration/Dose/Vehicle | Species | Study Protocol/Duration | Results | Reference |
|---|---|---|---|---|
| 0, 0.5, or 5.0% (350 - 3500 mg/kg bw/day) in feed; because high dose animals refused feed and lost weight, dose was reduced to 0.1% after 3 days | Male Holtzman rats in groups of 5 | 35 day dietary study; parameters recorded were clinical observations; body weights (3 times/week), feed consumption, and hematology; 2 rats/group were kept for recovery examination; all animals subjected to gross necropsy; organ weights were recorded | NOEL = 0.1% (~70 mg/kg bw/day); slight depression of body weight gain and an increase in liver weights in the 0.5% dose group were observed; no clinical signs of toxicity or adverse effects in hemoglobin content, cell volume, red cell count, or total and differential white cell count were observed; no toxicologically significant findings were reported at necropsy | [16] |
| | | ***Subchronic Oral*** | | |
| 0, 300, 1500, or 7500 ppm in feed equating to 0, 20, 105, or 583 mg/kg bw/day for males and 0, 22, 117, or 632 mg/kg bw/day females | Wistar rats in groups of 10 males and 10 females | 90 day dietary study in accordance with OECD TG 408; reproductive organs were examined (see DART studies) | NOAEL = 1500 ppm based on liver weight increase at 7500 ppm; no treatment-related mortality observed; no toxicologically relevant clinical signs observed; approximately 30% and 21% increase in liver weight observed at 7500 ppm in males and females, respectively; no adverse changes noted in liver during histopathological examination | [14] |
| 0, 0.25%, 0.50%, 0.75%, or 1.0% in feed equating to 0, 161, 345, 517, and 711 mg/kg/day | Groups of 10 male Sprague-Dawley rats | 4 month dietary study on neuromotor function (see Other Relevant Studies - Neurotoxicity); body weight and feed consumption were measured weekly | Body weight gains were significantly reduced in the 0.5% and 1.0% dose groups; significant decreases in cumulative body weight gains were observed in the first 2 months in the 0.75% dose group, but not in the last 2 months; no significant effects on body weight gains were observed in the 0.25% dose group; body weight gain reductions were not accompanied by significant changes in feed intake | [17] |
| 0, 0.25%, 0.5%, 0.75%, and 1% in feed | Groups of 10 male and 10 female Spartan Sprague-Dawley rats | 120 day dietary study on immunotoxic effects (see Other Relevant Studies – Immunotoxicity); clinical signs of toxicity and body weights and feed consumption were recorded weekly | NOEL for non-immunotoxic effects was 0.75% due to the slight reduction of body weight gain in the high dose group | [14,18] |

**Table 4.** Genotoxicity studies of Triphenyl Phosphate

| Concentration/Dose | Species/Strain/Cell | Method | Results | Reference |
|---|---|---|---|---|
| | | ***In Vitro*** | | |
| Up to 5000 µg/plate in DMSO | *Salmonella typhimurium* TA 1535, TA 100, TA 1537, TA 98 and TA 102. | Ames test with and without metabolic activation in accordance with OECD TG 471 | Not mutagenic | [14] |
| Up to 1000 µg/plate; vehicle not reported | *S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538 and *Saccharomyces cerevisiae* D4 | Ames test with and without metabolic activation in accordance with OECD TG 471 | Not mutagenic | [4,14] |
| 34% in a mixture; 0.1 ml/plate at 0.01%, 0.1%, 1%, 10%, and 100%; vehicle not reported | *S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538 | Ames test with and without metabolic activation | Not mutagenic | [4,14] |
| 19% in a mixture; 0.1 ml/plate at 0.001%, 0.01%, 0.1%, 1%, and 10%; vehicle not reported | *S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538 | Ames test with and without metabolic activation | Not mutagenic | [4,14] |
| >98% pure; up to 10,000 µg/plate in 95% ethanol | *S. typhimurium* TA98, TA100, TA1535, and TA 1537 | Ames test with and without metabolic activation | Not mutagenic | [20] |
| Details not provided | *S. cerevisiae* D4 | Ames test with and without metabolic activation | Not mutagenic | [4,14] |
| 99.6% pure; up to 21 µg/ml without metabolic activation and up to 60 µg/ml with metabolic activation; vehicle not reported | Chinese hamster V79 cells | Chromosome aberration test in accordance with OECD TG 473; cells exposed without metabolic activation at concentrations up to 21 ug/ml or with metabolic activation at concentrations up to 60 ug/ml and harvested after 18 h or 30 h of treatment | Not clastogenic | [14] |
| 3.13 to 75 µg/ml dissolved in DMSO | Mouse lymphoma L5178Y cells | Mouse lymphoma assay with and without metabolic activation in accordance with OECD TG 476 | Not mutagenic; cytotoxicity occurred in highest concentrations tested in cultures with and without metabolic activation | [4,14] |

**Table 5.** Dermal irritation and sensitization studies with Triphenyl Phosphate

| Concentration/Dose/Vehicle | Test System | Method | Results | Reference |
|---|---|---|---|---|
| ***Irritation - Animal*** | | | | |
| 99.7% pure; 500 mg; in water | 3 New Zealand White rabbits; sex not reported | Dermal irritation/corrosion study in accordance with OECD TG 404; test material applied to shaved rabbit skin for 4 h and semi-occluded; test area = 6 $cm^2$ | Not irritating | [4,14] |
| 500 mg; concentration and vehicle not reported | 6 albino rabbits; sex not reported | Dermal irritation/corrosion study in accordance with OECD TG 404; test material applied to shaved intact and abraded skin for 24 h and semi-occluded | Not irritating | [4,14] |
| 50 mg/ml suspension in 1.0 ml/patch; 50% aqueous solution of polyethylene glycol | 6 New Zealand White rabbits; 3/sex | Dermal irritation/corrosion study in accordance with OECD TG 404 ; test material applied to shaved intact and abraded skin for 24 h and occluded | Not irritating | [4,14] |
| 70% solution in alcohol | 25 male CF-1 mice | Dermal irritation study; semi-occluded patch for 24 to 72 h; no further details provided | Not irritating | [16] |
| ***Sensitization - Animal*** | | | | |
| 5% intracutaneous induction; 75% dermal induction; 75% dermal challenge; administered in peanut oil | 10 guinea pigs; no further details provided | Guinea pig maximization test; dermal patches occluded | Non-sensitizing | [4] |
| 5% in arachis oil or with Freund's complete adjuvant for intradermal induction; 75% in arachis oil for dermal induction; 50% and 75% in arachis oil for dermal challenge | 10 Dunkin-Hartley guinea pigs received test material, 5 served as controls | Guinea pig maximization test in accordance with OECD TG 406; test sites were clipped skin on should region | Non-sensitizing | [14] |
| 0%, 1.0%, 3.0% or 10% solution following pretreatment with Freund's complete adjuvant; challenge with 30% solution; positive control 0.5% 2,4-dinitrofluorobenzene | Female B6C3F1 mice; 8 mice per group | Mouse ear swelling test; the applicant noted this test is not a validated method and that it did not follow accepted procedures | Significant and dose-dependent allergic contact hypersensitivity observed | [14,29] |
| ***Sensitization - Human*** | | | | |
| 1.0041% in a nail polish | 30 human subjects | 4 week in-use safety evaluation; polish applied to nails every 7 days; removed and reapplied | No adverse events | [35] |
| 3% in a nail lacquer | 52 human subjects | HRIPT; 0.2 ml applied to upper back with 1 $in^2$ pad and semi-occluded | No dermal irritation or sensitization | [31] |
| 4.65% in a nail enamel | 110 human subjects | HRIPT; 0.2 ml applied to upper back with 1 $in^2$ pad and semi-occluded | No dermal irritation or sensitization; one subject had mild edema on induction days 4 and another subject had mild to moderate dryness and edema on induction days 2 through 4 and did not continue with study | [33] |
| 5.85% in nail color (2 shades tested in shared panel); neat | 104 human subjects | HRIPT; semi-occlusive patch; no further details provided | No dermal irritation or sensitization | [30] |
| 5.85% in nail color (1 shade); neat | 100 human subjects | HRIPT; semi-occlusive patch; no further details provided | No dermal irritation or sensitization | [30] |
| 7% in a nail lacquer | 50 human subjects | HRIPT; 0.2 ml applied to upper back with 1 $in^2$ pad and semi-occluded | No dermal irritation or sensitization | [32] |
| 7% in a nail lacquer; neat | 108 human subjects | HRIPT; applied to upper back; semi-occluded; no further details provided | No dermal irritation or sensitization | [34] |

**Table 6.** Ocular irritation studies with Triphenyl Phosphate

| Concentration/Dose | Test System | Method | Results | Reference |
|---|---|---|---|---|
| | | ***Animal*** | | |
| 100 mg/eye; neat | 9 albino rabbits; sex not specified | Ocular irritation study; 3 eyes washed 4 seconds after instillation; eyes examined 24 h, 28 h, 72 h, and 7 days post-instillation; eyes scored according to 16 CFR 1500.42 | Minimally irritating in rabbit eyes; mild conjunctival effects (slight redness 6/6, slight discharge 4/6) at 24 h in unwashed eyes which cleared by 72 h; no effects in washed eyes | [4,14] |
| 99.7% pure; 70 mg; neat | 3 New Zealand White rabbits; sex not specified | Ocular irritation study in accordance with OECD TG 405; test material applied for 24 h; eyes washed after 24 h and examined for 7 days post-application | Not irritating; mild reactions of the mucous membranes and the cornea observed immediately after exposure were considered mechanically induced effects | [4,14] |
| 100 mg; neat | 6 New Zealand White rabbits; 3/sex | Ocular irritation study in accordance with OECD TG 405; test material was washed in 3/6 eyes after 30 seconds | Minimally irritating in rabbit eyes; mild conjunctival effects (slight redness in all rabbits) observed 24 h post-instillation which cleared in all but 1 unwashed eye by 72 h (remaining eye cleared by day 6); slight corneal opacity observed in 1 unwashed eye at 24 h which cleared by 48 h | [4,14] |

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