Science for Communities

HEALTH RISK ASSESSMENT:

TRIPHENYL PHOSPHATE IN NAIL POLISH

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TABLE OF CONTENTS

ACRONYMS AND ABBREVIATIONS

BW	Body weight
CDC	US Centers for Disease Control and Prevention
DBP	Di-n-butyl phthalate
ECHA	European Chemical Agency
ESR	Institute of Environmental Science and Research Limited
MOE	Margin of Exposure
NOAEL	No Observed Adverse Effect Level
RfD	Reference Dose
SCHEER	EU Scientific Committee on Health, Environmental, and Emerging Risks
TPP	Triphenyl Phosphate
USEPA	United States Environmental Protection Agency
WHO	World Health Organization

EXECUTIVE SUMMARY

Triphenyl phosphate (TPP) is an organophosphate chemical used in flame retardants and as a plasticiser in polymers. It has become more widely used in consumer products, including nail polish, as a substitute for dibutyl phthalate (DBP). This has been initiated by the recognition of the reproductive toxicity of DBP, designated as a substance of very high concern in Europe. The acute toxicity of TPP is low, but robust chronic studies are not available to evaluate potential carcinogenicity with suitable confidence. Some reproductive and developmental studies are available, and, while TPP is not currently considered to be a reproductive or developmental toxicant, recent studies in rodents and humans have suggested that TPP may alter cellular responses to oestrogen receptor activation, and also cause changes in carbohydrate and lipid metabolism, leading to increased body weight. An older publication on TPP toxicity in animals and humans concluded that a subchronic dose of 70 mg/kg bw via oral or inhalation routes was a no observed adverse effect level (NOAEL), based on acetylcholinesterase inhibition in humans and liver and kidney pathology in rodents.

Several recent studies have been published showing endocrine and developmental toxicities to mice as measured by alterations in insulin dependent cellular effects, carbohydrate and lipid metabolic effects, increases in body weight, oestrogen receptor mediated effects in females, and lowered testosterone production in males. These endocrine and metabolic effects of TPP have been reported to occur at doses as low as 0.01 mg/kg bw/day using oral dietary exposures, and down to 0.002 mg/kg bw/day using subcutaneous injection. Due to the much lower apparent thresholds for toxicity with these reports, a US EPA toxicological review of the potential hazard qualities of TPP is ongoing and expected to be completed in 2023.

The occurrence of TPP in nail polishes presents primarily a dermal and inhalation route of exposure to many people. The low volatility of TPP renders inhalation a minor route of exposure, and an empirical case study demonstrated that the dermal route is of greatest significance outside of occupational settings. It is unknown to what extent TPP can be absorbed directly through the fingernail or toenail, and published assessments have assumed that absorption takes place instead through the cuticle skin around the nail itself. It is also unclear what role, if any, a polymer base coat applied underneath the TPP-containing coloured enamel would have in slowing or preventing TPP absorption through the nail.

We examined two exposure scenarios: 1) a high use consumer, female 11 to 15 years old, using nail polish 3 times/week on fingernails and toenails, and using polish containing TPP at the highest reported range of TPP concentrations, and 2) a lower use consumer, adult female, using nail polish once/month, with a lesser TPP concentration in the product. Using currently available toxicological endpoints, and the published reference dose for TPP, risk characterisations using a margin of exposure (MOE) were performed. The MOE, using a published risk assessment approach, ranged from 1.0×10^4 to 2.0×10^4, indicating a low concern for consumer use of TPP to exceed current toxicological doses of concern. Alternative MOEs were calculated using more recent toxicology study findings, with MOEs ranging into values less than 1.0×10^2 indicating a potential risk of concern.

Due to the above-mentioned data gaps in the toxicology literature and the ongoing authoritative review of TPP toxicity by the US EPA and ECHA, it is recommended that the current assessment be revisited when authoritative reviews of TPP are completed.

1 INTRODUCTION

The purpose of this report is to develop a generic health risk assessment for dermal and inhalation exposure to triphenyl phosphate (TPP) from its use in nail polish. This report will only consider domestic, non-occupational, incidental exposure to TPP. Exposure scenarios will be developed for the most common or likely exposure events.

TPP is a crystalline low volatility solid at room temperature, primarily used as a chemical additive for plasticisers and fire retardants in industrial and consumer products including textiles, paint, lubricants, electronics, furniture, and personal care products, such as cosmetics (Merriam-Webster; National Center for Biotechnology Information 2022; US EPA 2020). Cosmetics, specifically nail polish, utilise TPP as a plasticiser to enhance flexibility and durability (Sharad 2019).

TPP has become more widely used in various consumer products in recent years, in part, as a substitute for chemicals with toxicity or persistence concerns, particularly polybrominated diphenyl ethers (PBDEs) in fire retardants as well as the reproductive toxicant dibutyl phthalate (DBP) in cosmetics, including in nail polish (Estill 2021; Howard 2014; Tokumura 2019). TPP is used in some nail polish and nail enamels, basecoats and undercoats, and manicuring products as a plasticiser or adhesive. TPP was found to be the most commonly used plasticiser in nail products when DBP was not present (DTSC 2016). Data on the toxicity of TPP in humans is scarce; however, an emerging toxicological literature indicates that exposure may be associated with endocrine impacts, reproductive and developmental toxicity, and genotoxicity (Mendelsohn 2016; DTSC 2016; USEPA 2020). These data gaps and recent findings have given rise to concerns over the exposure to and safety of TPP as it is currently used.

The purpose of this report is to review the current toxicological and regulatory literature for TPP, to identify critical toxicological hazards or data gaps and to construct exposure scenarios through which risks can be characterised. Only non-occupational exposure scenarios are discussed in this report.

1.1 REGULATORY STATUS

1.1.1 New Zealand

Triphenyl phosphate is in the inventory of chemicals, and does not have a specific approval status in New Zealand, but may be used under a group standard (NZ EPA, 2006).

New Zealand has a workplace standard for TPP of 3 mg/m^3, for an 8-hour time-weighted average air concentration (Worksafe NZ, 2022). The toxicological basis for this value was not found.

1.1.2 United States

In December 2019, the United States Environmental Protection Agency (US EPA) designated TPP as a high-priority substance for risk evaluation; however, since cosmetics are regulated under the Food and Drug Administration (FDA), the US EPA is not evaluating cosmetics as an exposure (US EPA 2020). Under the Food, Drug and Cosmetic Act, cosmetic products and ingredients do not require FDA pre-approval nor are companies required to file product formulations and this information is provided by the manufacturer on a voluntary basis (FDA). The Cosmetic Ingredient Review (CIR) panel, which acts as the

independent scientific body that periodically assesses cosmetic safety in the US, concluded that TPP is safe in cosmetics in the present practices of use and concentration (CIR 2018). The US EPA risk evaluation is yet to be completed (Cadova 2021; USEPA 2020).

1.1.3 European Union

In the European Union (EU), chemical safety regulations are largely governed by the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) and Classification, Labeling and Packaging (CLP) legislations. REACH, which is overseen by the European Chemical Agency (ECHA), provides hazard assessment document dossiers and also regulates the maximum amounts of toxic substances of concern in consumer products placed in the EU market, including cosmetics. Companies must register products on the cosmetic products notification portal and manufacturers are required to complete a safety assessment report as part of the manufacturer's technical dossier. The current status of TPP in ECHA is pending, based on a request for additional toxicological information to complete the TPP dossier evaluation process (ECHA 2021). Specific groups of chemicals, such as cosmetics, are also covered by separate legislation: Regulation (EC) No. 1223/2009. The Scientific Committee on Consumer Safety (SCCS) is responsible for reviewing all cosmetics ingredients that are forwarded to them by the EU member states for consideration and declaring if safe usage levels are approved.

2 HAZARD IDENTIFICATION

2.1 PREVIOUS ASSESSMENTS

No previous health risk assessments for TPP were found for New Zealand.

2.2 TOXICOLOGY OF TPP

2.2.1 Absorption and metabolism

It was previously considered that TPP was not well absorbed dermally, following observations that mice treated topically with TPP did not exhibit reduced cholinesterase activity (ATSDR 2012). However, TPP is only a comparatively weak cholinesterase inhibitor and human data confirm that TPP is, in fact, absorbed dermally, leading to measurably increased urinary levels in occupational settings over background exposures (Mendelsohn et al. 2016). The study design used by Mendelsohn was intended to inform the relative importance of dermal exposures as compared with inhalation exposures. The authors concluded that the dermal route was dominant for TPP exposure.

Jonsson and colleagues reported human plasma TPP concentrations to range from 0.12 to 0.14 µg/g, while Wang et al., estimated, based upon their review, that human (non-occupationally exposed) plasma can contain a concentration of up to approximately 0.4 µM TPP as a result of environmental exposures from all sources (Wang et al., 2018).

An elimination half-life for TPP of 9.58 days was estimated based on human urine and blood measurements (Wang et al., 2020). This slow elimination rate indicates that even a single dose of TPP would be expected to have protracted bioavailability over the course of several weeks.

2.2.2 Acute toxicity, allergenicity and irritation

Skin, eye, and respiratory irritation studies and a sensitisation study in guinea pigs found that TPP was neither irritating nor sensitising (UK Environment Agency 2009).

Examinations of small groups of operators in a TPP production plant did not reveal any unusual frequency of symptoms, or physical or laboratory findings, as compared to unexposed groups. The estimated weighted average concentration of TPP vapor mist and dust was 3.5 mg/m^3. A few individual cases of allergic dermal reactions to TPP have been reported. However, a much bigger study of 343 patients seen at a dermatology clinic reported that no individuals showed allergic reactions to TPP (ATSDR 2012).

2.2.3 Repeated dose toxicity

A 3-week study in rabbits exposed to TPP by skin application evaluated haematology and clinical chemistry parameters in addition to gross and microscopic morphology of tissues and found virtually no toxicity with daily dermal doses of up to 1,000 mg/kg bw/day (ATSDR, 2012).

In a 4-month dietary study, TPP doses of 345 mg/kg bw/day reduced weight gain of rats by 11%, but TPP doses of up to 711 mg/kg bw/day had no significant effect on the results of a battery of behavioural tests administered at monthly intervals during treatment (Sobotka et al. 1986). In a study in which male and female rats received TPP doses of up to 690 mg/kg bw/day for 90 days before mating and during gestation, there were no significant effects on

reproductive parameters or on foetal parameters assessed on gestation day (Gd) 20 (Welsh et al. 1987).

In a review of several earlier studies, TPP treatment caused a slight depression of body weight gain and an increase of liver weights at a level of 0.5 % (estimated dose: ~ 350 mg/kg bw/day) in the diet. No findings were recorded in clinical observation, haemoglobin content, cell volume, red cell count, total and differential white cell count and at necropsy. A concentration of 0.1 % in the diet (estimated dose: ~ 70 mg/kg bw/day) was without any effect (= NOEL) (Sutton et al., 1960; OECD SIAR).

The OECD concluded that only limited data were available for evaluating the toxicity hazards of TPP and a number of standard parameters of repeated dose toxicity are missing (e.g. organ weight measurement and histopathology of organs other than lymphoid organs, including spleen, thymus, lymph nodes, as well as haematology and clinical chemistry other than serum proteins). Nevertheless, the studies show that TPP did not interfere with the general well-being and behaviour of the animals at levels of up to 1 % in the diet for 4 months. At dose levels of 0.5 to 1 % a slight but statistically significant reduction of growth rate was detected as the only change in one of the two studies (Sobotka et al., 1986), whereas a reduced growth rate was recorded at the 1 % dose level in the other study (Hinton et al., 1987), leading to NOELs of 161 or 517 mg/kg bw/day.

No chronic-duration studies with TPP were located in the literature available for review.

2.2.4 Carcinogenicity and mutagenicity

Carcinogenicity was evaluated by several authorities and it was concluded that TPP was not carcinogenic (OECD). However, there are no long-term carcinogenicity bioassays available.

Theiss et al. (1977) studied the occurrence of lung adenomas in strain A/St male mice, 6 to 8 weeks old, using doses of 20, 40, or 80 mg TPP/kg bw injected intraperitoneally 1, 3, and 18 times, respectively, into groups of 20 mice. Twenty-four weeks after the first injection, the animals were sacrificed, and the frequency of lung tumours was compared with that in the control group of 50 animals treated with vehicle control. The pulmonary adenoma response to TPP was not significantly greater than the response of the control mice. This study was considered inadequate due to the low survival of animals in two of the three experimental groups and the short duration of the study (WHO 1991).

Tests for gene mutations in bacterial, as well as yeast and mammalian cells, did not reveal any evidence of mutagenicity (OECD SIAR; ECHA 2010).

2.2.5 Endocrine and Metabolic Effects

The European Chemicals Authority (ECHA) is currently evaluating TPP as a potential endocrine disrupting substance (ECHA 2022). In the European REACH registration dossier for TPP, an anonymous study from China in 2015 describes a male reproductive toxicity finding (decreased testes weight and testosterone production), but did not account for the concurrent reduction in body weight, making interpretation of the findings indeterminate (ECHA 2010). Wang and colleagues found a dose-related increase in body weight and insulin resistance in young offspring from adult mice fed TPP in the diet for 14 weeks, with TPP doses of 10, 100, or 1000 μg/kg bw/day, and with exposures lasting through gestation and lactation. Genetic expression of lipid metabolism enzymes was altered and the role of gut microbiome perturbation was implicated (Wang et al., 2019). More recently, this research group reported alterations in expression of an insulin-sensitising hormone

(adiponectin) in mice exposed to TPP (Wang et al., 2020). The same research group had previously reported that male mice exposed to 2 μg/kg bw of TPP for 10 days of lactation, displayed increased weight gain with low doses of TPP compared with control mice (Wang et al., 2018).

A study in zebra fish found that TPP interfered with DNA repair, and metabolic and cell cycle parameters (Du et al., 2016).

Guan and colleagues investigated adverse outcome pathways (AOP) for TPP, using in vitro omics-based models, and proposed an AOP framework with TPP activating the G-protein coupled Oestrogen Receptor (GPER) to influence cell proliferation, metastasis, and apoptosis. The GPER regulates gene transcription and kinase activity, leading to abnormal immune function, cancer and other oestrogen-dependent cell processes (Guan et al., 2022).

A different AOP for TPP toxicity has been proposed by Wang and colleagues (Wang et al., 2016). These authors observed that TPP stimulated pre-adipocyte (fat cells) differentiation of these cells to become lipid-laden adipocytes at a concentration that disrupted the peroxisome proliferation activation receptor (PPAR) signalling network. They found a dual activity of TPP, as an inhibitor of PPARα:RXRα signalling and an activator of PPARγ:RXRα signalling, and suggested that this provides a mode of action that could lead to weight gain and other symptoms of metabolic syndrome. In their study, the lowest TPP concentration that both inhibited the PPARα signalling pathway and stimulated the PPARγ signalling pathway was 10 μM.

TPP concentrations in house dust were measured for 50 men recruited through a US fertility clinic. An inter-quartile range increase in house dust TPP was associated with a 10% increase in occupant prolactin and a 19% decrease in sperm concentration (Meeker and Stapleton, 2010). Only men were included in the study.

The practical significance of the low dose findings in rodents, is that, if verified, and found to be relevant to human health, the NOAEL for TPP used in risk assessment could effectively change to a vastly lower value of several orders of magnitude difference. This is one reason why the current US EPA re-evaluation of these relatively recent findings is of such importance for the risk assessment of TPP.

2.2.6 Neurological effects

Like many organophosphate compounds, TPP is an acetylcholinesterase (AChE) inhibitor (USEPA 2020). Additional hazardous traits for TPP include potential neurotoxicity, reproductive toxicity, and endocrine disruption (DTSC 2016). An older study examined acute and repeated dose toxicity parameters in rodents, primates, birds, and human workers exposed to TPP. Red blood cell (RBC) AChE inhibition was studied in humans, animals, and cells in vitro. A time-weighted average of 3.5 mg/m^3 was concluded to be a No Observable Adverse Effect Concentration (NOAEC) for RBC cholinesterase in workers exposed to TPP via dust inhalation for up to 10 years (Sutton et al., 1960).

2.2.7 Reproduction and development

In studies by Welsh et al. (1987), male and female Sprague-Dawley rats (40 per sex per group) were fed dietary levels of 0, 0.25, 0.5, 0.75, or 1.0% TPP in feed from 4 weeks post weaning for 91 days, through mating and gestation. The daily intake of TPP during pregnancy was 0, 166, 341, 516, and 690 mg/kg bw, respectively. TPP exposure had no treatment related effects on mothers or offspring at these dosages. The types of

developmental anomalies were similar in both treated and control animals, and no significant increase in the incidence of anomalies was seen in the treated groups as compared to control values. TPP was not teratogenic in Sprague-Dawley rats at the levels tested.

The NOEL given by the authors for male and female fertility, maternal toxicity, and developmental toxicity was 1 % in the diet (690 mg/kg bw/day) (Welsh et al., 1987).

Conclusion: No signs of developmental toxicity were seen for TPP up to the highest tested dose of 690 mg/kg bw/day daily in the rat.

2.2.8 Immunotoxicity

Five groups of 10 male and 10 female Sprague-Dawley rats were fed diets containing 0, 0.25, 0.5, 0.75, and 1% of TPP for 120 days. The animals were observed for clinical symptoms. Body weights and food consumption were recorded weekly. Blood samples were analysed for total protein and by electrophoresis of plasma proteins. Immunotoxicity was assessed by measurements of the weights of lymphoid organs, immuno-histochemical evaluation of spleen, thymus, lymph nodes, and the humoral response to antigens. At the 1% dose level, reduced growth rate was detected. There were no significant differences between immunised and non-immunised animals. The weights of lymphoid organs (spleen, thymus) varied in a non-dose-dependent way. No significant changes were found in these organs and lymph nodes by histopathologic examination and no significant alterations of serum protein were detected. Electrophoresis revealed increased levels of alpha- and beta-globulin in rats but effects were similar at all dose levels, relative to the control group.

Indices of immunocompetence, including the humoral response to immunisation with sheep red blood cells (SRBC) were also not significantly affected in rats exposed to TPP at up to 711 mg/kg bw/day for 120 days (Hinton et al. 1996).

Conclusion: In a subchronic bioassay, no effects were observed in a range of parameters of immune function in rats receiving oral doses up to 700 mg/kg bw/day (1 %). The NOAEL for immunotoxicity was 1% (700 mg/kg bw) of TPP in the diet and a NOAEL of 0.75% (517 mg/kg bw) for all effects due to a slight reduction of body weight gain at the highest dose level. The significance of these results at high doses, with respect to human health at environmental exposure levels, is questionable.

Table 1. Summary of Critical Toxicology Studies for TPP

Study type, species	Doses (mg/kg/day)	Findings	Reference
12-week, oral (dietary), C57BL/6J mice	0, 0.01, 1.0	Increased inflammatory markers and apoptosis in kidney; LOAEL = 0.01 mg/kg	Cui et al., 2020
PND 1-10, s.c., ICR mice	0, 0.002, 0.2	Altered lipid metabolism in males; LOAEL = 0.002 mg/kg (s.c.)	Wang et al., 2018
GD 6 through lactation day 21, gavage, followed by low fat or high fat diets, ICR mice	0, 0.01, 0.1, 1.0	Increased body weights with all doses. 1.0 mg/kg dose studied for metabolic effects (LOAEL = 1.0 mg/kg)	Wang et al., 2019
Acute oral lethality, CF1 mice (males); Holtzman rats (males); albino guinea pigs (males)	3000 or 4000	Deaths: 0/10 Guinea pigs 1/11 rats 0/10 mice	Sutton et al., 1960
35-day study, oral (dietary), rats	0, 0.1%, 0.5% in diet	No mortality, or body weight changes. Relative liver weight was increased to 4.9% vs 3.9% in controls. LOAEL = 0.5% in diet.	
Acute dose acetyl cholinesterase inhibition, gavage, mice	0, 10, 25, 50, 100, 200, 500	Dose dependent inhibition of AChE after 4 hours. LOAEL = 10 mg/kg	

s.c. = subcutaneous injection administration; PND = post-natal day; GD = gestation day

2.3 HAZARD CLASSIFICATIONS

The toxicity hazard classifications for TPP relevant to human health in New Zealand are limited to Acute Toxicity Category 4, and Eye Irritation Category 2 (Table 2). No indication for a repeated dose classification currently exists in the regulations, but this may change pending the review of endocrine and epigenetic effects of TPP by US EPA or ECHA.

Table 2. GHS Hazard Classifications for TPP in New Zealand.

Hazard Classification	WHO GHS Description
6.1D (all)	Acute toxicity Category 4
6.4A	Eye irritation Category 2
9.1A (all)	Hazardous to the aquatic environment Category 1
9.3C	Hazardous to terrestrial vertebrates

NZ EPA 2022.

3 DOSE-RESPONSE

3.1 REFERENCE DOSES FOR TPP

A Reference Dose (RfD) for TPP was derived by Tokumura et al. (2019), to estimate margins of exposure for various exposure doses arising from nail polish consumer use (Tokumura et al., 2019). The RfD of 70 mg/kg bw/day was used by these authors based on an older animal and human study (Sutton et al., 1960).

The experimental and review paper by Sutton and associates, examined both human and animal acute and repeated dose toxicity studies, as well as in vitro cholinesterase inhibition, and concluded that a time-weighted average concentration of 3.5 mg/m^3, over a chronic exposure period, did not affect workers exposed to TPP via dust. A statistically significant ($p < 0.05$) reduction in red blood cell cholinesterase activity was found in a group of men regularly engaged in the manufacture of TPP, however there was no evidence of adverse clinical effects in men exposed to TPP in the workplace for up to 10 years to an estimated mean level of 3.5 mg/m^3. The ATSDR evaluated the Sutton study and concluded that the lack of information regarding the total number of workers that participated in the health surveys, lack of detailed presentation of the results of the surveys, and uncertainty regarding the estimation of exposure levels made this study unsuitable for minimal risk level (MRL) derivation (ATSDR 2012).

The calculation of the margin of safety in the Tokumura paper is based on the stated human NOAEC by Sutton et al. (1960), assuming an adult inhalation rate of 20 m^3/day, assuming 100% absorption by inhalation, to achieve an **RfD of 70 mg/kg bw/day**. The same NOAEL was derived from dietary exposures that found no adverse effects in rodents fed 0.1% TPP (approximately 70 mg/kg bw/day) in the diet for 35 days. The latter case, being derived from animal data, lacked safety factors to account for species differences.

An alternative RfD could be derived from a NOAEL based on the recent studies in mice from Wang et al. (Wang et al., 2018, 2019, 2020). The 10-day LOAEL of 10 μg/kg bw/day for endocrine effects related to obesity is over a thousand-fold lower than the NOAEL from the Sutton et al. (1960) study. However, this subtle biochemical effect of TPP has not been thoroughly evaluated by authoritative bodies, and due to the present uncertainties about these lower dose effects, the published RfD from Tokumura et al. (2019) has been selected in the current risk assessment.

3.1.1 USEPA

There is currently no USEPA RfD for TPP available. The USEPA RfD will be available when the agency review is complete, which is anticipated to occur in 2023.

3.1.2 Europe

Derived No Effect Levels (DNELs) are estimates of safe exposure doses for the purpose of risk assessments, under various scenarios. These estimates are provided by industries in registering their chemicals under the European REACH system (ECHA 2010).

The DNELs are intended to serve as a basis for risk assessments for consumers and workers. These are shown below:

DNELs for TPP:

Dermal Route - Workers
DNEL 1.05 mg/kg bw/day
NOAEL 105 mg/kg bw/day

Dermal Route - General Population
DNEL 0.525 mg/kg bw/day
NOAEL 105 mg/kg bw/day

3.1.3 Summary of reference doses

TPP is an organophosphate flame retardant and plasticiser of low acute toxicity, used in nail polish as a replacement for DBP, a Substance of Very High Concern in Europe and with substantial use restrictions. While studies are available that demonstrate TPP is less hazardous to reproduction compared to DBP, there are animal and human studies that suggest a possible endocrine effect on male reproductive systems. This possibility is currently under review by the USEPA and ECHA. The toxicological reference doses for TPP are currently based on repeated dose toxicity outcomes on the liver of rodents, or from blood cholinesterase assessments in human workers, and not on the low dose effects recently reported by Wang and colleagues. For the purposes of this report, the published RfD (NOAEL) of 70 mg/kg/day is used as a comparison value for risk assessment.

TPP is a substance currently under review for its potential as an endocrine active chemical with reported effects on male reproductive hormones and tissues. While no authoritative toxicological threshold value exists for assessing the risk of TPP, a reference dose of 70 mg/kg bw/day has been published based on toxicological findings in animals, but while the authors use the term RfD, in fact the comparison value used is an experimental NOAEL and also a measured NOAEC from human workers, both arriving at the same value.

If one were to instead use the dose levels from the Wang et al., (2018, 2019) studies as a basis for comparison, the resulting RfD would be expected to be lower, by a factor of up to 10,000.

4 EXPOSURE ASSESSMENT

TPP is a low volatility plasticiser chemical (Table 3) which has been shown to be commonly found in house dust from its use in consumer household products (ATSDR 2012; CPSC 2016).

Table 3. Physical/Chemical Properties of TPP

Molecular Formula	$C_{18}H_{15}O_4P$
Molecular Weight	326.29 g/mol
Melting Point	49-50℃ (ICSC, 2000)
Boiling Point	370 °C (ICSC, 2000)
Density	1.2055 g/cu cm @ 50℃ (HSDB, 2013)
Solubility (in water)	0.2 mg/L – 1.9 mg/L @ 20℃ (CPSC 2016)
Log Kow	4.59 (HSDB, 2013)
Vapor Pressure	6.28 x 10^{-6} torr @ 25℃ (CPSC 2016)
Henry's Law Constant	3.31 x 10-6 atm-m^3/mol @ 25℃ (CPSC 2016)

According to the Consumer Product Safety Commission, the vapor pressure (VP) of pure TPP can be misleading in estimating its potential to become airborne as a vapor (CPSC 2006). Using the measured vapor pressure at typical room temperature of 25 °C results in the following estimation of a maximum or saturated airborne concentration:

(6.3x10^{-6} torr/760 torr) (1,000,000) (326.3/24.4) = 111 µg/m^3

In reality, TPP would not be expected to exist as a pure material in ambient air. Initially, it is in the polymer, typically a polyvinyl chloride (PVC) or polyurethane matrix and, after it diffuses out of the matrix, it comes to the surface, where it is then associated with house dust, which is primarily an organic material composed of human skin cells that have been shed. Thus, one would expect only a small portion of the saturation airborne concentration to occur in indoor air. Indeed, most of the measured indoor air values agree with this expectation (CPSC 2006).

While inhalation of volatilised TPP is considered to be a minor route of exposure, inhalation, dermal absorption, and oral ingestion of TPP in house dust all represent environmental routes of TPP exposure.

4.1 EXPOSURE TO TPP FROM OTHER SOURCES

Stapleton et al. (2009) measured concentrations of various organophosphate flame retardants, including TDCPP, TCPP and TPP in house dust extracts from 50 Boston homes. They estimated cumulative exposure to these organophosphate flame retardants, using the geometric mean concentration for each chemical and using lower bound dust ingestion rates from U.S. EPA (100 mg dust/day for a child; 20 mg dust/day for an adult). For children, the average estimated cumulative exposure to all of these chemicals was 1600 ng/day; for the adult it was 325 ng/day, with a majority of the exposure from TPP, TDCPP and PBDEs (Stapleton et al., 2009; CPSC 2016).

The ranges of expected exposures to TPP through food are generally considered to be 0.5–20 ng/kg bw/day for adults and 0.1– 40 ng/kg bw/day for children under 2 years of age (ATSDR 2012).

4.2 PREVIOUS ESTIMATES OF EXPOSURE TO TPP FROM NAIL POLISH

Tokumura et al. (2019) found that dermal absorption was a significant route of exposure, contributing at least as much to overall exposure as oral ingestion or inhalation of household dust. In addition, the direct application of nail polish, containing highly concentrated TPP, provided for a more than 1700-fold higher TPP exposure than oral, dermal, or inhalation exposures to TPP in house dust (Tokumura et al., 2019). The explanation for this difference in exposure by route, is due to the vastly higher concentration of TPP in polish (approximately 10,000,000 to 20,000,000 μg TPP/kg polish) vs dust (981 and 600 μg/kg dust). The authors discussed the role of Fick's Law to explain the very high dermal absorption rate when the concentration is very high.

4.3 TPP IN NAIL POLISH

According to a safety assessment from the Cosmetic Ingredient Review Expert Panel (CIR), TPP was reported in 331 nail products in the US, including 286 nail polishes and enamels, with a concentration range of 1% to 14.5% (CIR 2018).

The concentration (weight %) of TPP in nail polishes from Japan were 1.1% to 1.8% in the 3 out of 45 sampled nail polish products tested (Tokumura et al., 2019). This range is consistent with a previously reported range of TPP of 0.46% to 1.68% in 8 out of 10 sampled U.S. nail polish products (Mendelsohn et al., 2015).

For the purpose of this risk assessment, a TPP concentration of 14.5% was chosen to represent a worst case scenario, using the highest reported TPP concentration in the CIR report (CIR 2018).

4.4 NAIL ANATOMY AND DERMAL ABSORPTION

The nail plate is a durable keratinised structure that exhibits various features to ensure the integrity and health of the nail. It consists of multiple layers of cells structured in three-layers, in which the outer layer is only a few cells thick. The cuticle acts as a barrier and provides protection to the nail matrix. Nail permeability characteristics include both hydrophilic and hydrophobic properties and the nail unit itself possesses a complex and abundant vascular network to ensure adequate blood supply (Berker 2007).

Dermal absorption through nails is observed through topical drug application for ailments of nail diseases. For effective therapy, permeation must be enhanced, which can be achieved by disrupting the nail plate using physical or mechanical techniques such as nail abrasion (filing the nail plate) or by using chemical agents (thiols, sulphides, hydrogen peroxide, urea, water, and enzymes) (Bedanta 2021).

4.5 MANICURE PROCESS

Permeation methods, both physical and chemical, occur during the manicure process in order to achieve the desired finished look. For example, the nails are soaked in warm water to absorb moisture and become soft (Newman 2004). Cuticles are cut or pushed back from the dorsal nail plate, which will ensure an even coat of nail polish (Sharad 2019). The nail plate is filed to allow for better adhesion of the enamel coating. This process can weaken the integrity of the nail and therefore potentially increase exposure. Nail polish application is the last step and includes three coats: a base layer, enamel (color), and a top coat. Base

coats, which have a high resin content, may contain titanium-silicone-zirconium polymers, polytef, nylon, calcium and biotin, and are developed to create a stronger bond with the natural nail and help to form a barrier between the nail and the polish (Chandra 2019; Madnani 2012; Newman 2004). TPP is not reported to occur in the base layer, but only in the enamel.

4.6 EXPOSURE FREQUENCY

Generally, a basic manicure with the application of nail polish will last approximately seven days (Newman 2004; SallyBeauty 2022). SallyBeauty recommends a professional manicure once a week to maintain perfect polish for medium to long nails and a professional manicure every two weeks with at-home touch-ups for short nails (SallyBeauty 2022). Aside from the quality of the polish and application of coats, fingernail growth rate can affect the frequency of application. Fingernails grow faster than toenails. As an average guide, nails grow at the rate of approximately 3 mm per month and it takes approximately 5–6 months for a fingernail to grow from the matrix to the free edge and up to a year for a toe nail (Berker 2007; Bedanta et al. 2021; Newman 2004).

The above information provides context that nails can be a route of absorption, with enhanced permeability in some situations. Nail polish application is common and a frequency of once per month is not an unreasonable assumption for a long-term exposure scenario.

4.7 DERMAL TPP ABSORPTION

The results from the Mendelsohn et al. (2016) study indicate that nail polish is a likely source of both dermal and inhalation exposure to TPP by consumers. Two cohorts were assessed during the application of nail polish while wearing gloves and while directly applying polish to the nail. Urine concentrations of diphenyl phosphate (DPP), a TPP metabolite and biomarker of exposure, were analysed both before and after each application. Urinary DPP concentrations were found to increase nearly seven-fold 10-14 hours after nail polish application on the fingernails, while those wearing gloves had significantly lower concentrations (Mendelsohn 2016). Based on the results of this study, the dermal route was found to be the primary route of exposure, suggesting a significant short-term exposure and a potential source of chronic exposure for frequent users.

Concerns have arisen for occupational hazards among nail salon technicians exposed to TPP during nail polish application. Estill and associates found that nail salon technicians had higher urine concentrations of DPP post-shift as compared to pre-shift (Estill, et al. 2021). The study measured air samples as well as hand wipes and concluded that hand wipe concentrations directly correlated to urine concentrations indicating that dermal absorption was the primary route of TPP exposure.

These more recent exposure studies appear to contradict the earlier statements by Sutton and associates, who concluded that TPP was effectively not absorbed dermally due to a lack of cholinesterase inhibition in rodents dermally exposed to TPP (Sutton et al. 1960). However, since TPP is only a weak cholinesterase inhibitor, the basis for this conclusion is not robust.

4.8 EXPOSURE SCENARIOS

The basic equation for the estimation of daily exposures to TPP from nail polishes is as follows:

$D_i = ((C_p \times V \times Abs \times AR) / (30 * BW)) \times 1000$ µg/mg

Where:

Di = internal daily dose (µg/kg bw/day)
Cp = concentration of TPP in product (mg/g)
V = volume of product applied per application event (g)
Abs = fraction of applied TPP absorbed
AR = application rate (per 30 day month)
BW = body weight of subject (kg)

The parameters used in the exposure calculations are shown in Tables 4 and 5 below:

Table 4. Exposure Scenario 1: High use rate, 15 yo female, fingernails + toenails

TPP in nail polish:	14.5% (wt%) or 145 mg/g (CIR 2018)
Application rate:	156/year (Bremmer 2006; Tokumura 2019)
Nail polish used/application	0.3 g (fingernails) (Mendelsohn 2016)
TPP applied/ application	43.5 mg (fingernails only)
TPP applied/ application + toenails	87 mg (+ toenails assumed equal to fingernails)
TPP applied / week	261 mg (fingernails + toenails)
TPP applied / day	37.3 mg/day
Body weight (11 to 15 yo female)	53 kg (Cressey and Horn, 2016)
External dose TPP/week	4,930 µg/kg bw
External dose TPP/day	704 µg/kg bw
Dermal absorption fraction	0.5% (Mendelsohn 2016)
Inernal dose TPP/day	**3.52 µg/kg bw**

Table 5. Exposure Scenario 2: Lower use rate, adult female, fingernails only

TPP in nail polish:	0.97% (wt%) or 9.7 mg/g (Mendelsohn 2016)
Application rate:	1x per month (online literature reviewed in this report)
Nail polish used/application	0.05 g (fingernails only) (Tokumura 2019)
TPP applied/ application	0.49 mg (fingernails only)
TPP applied/day	0.016 mg/day
Body weight (adult female)	74 kg (Cressey and Horn, 2016)
External dose TPP/ application	0.22 µg/kg bw
Dermal absorption fraction	0.5% (Mendelsohn 2016)
Inernal dose TPP /application	**0.001 µg/kg bw/day**

Tokumura and colleagues investigated the specific scenario of TPP absorption and risk with dermal exposure from nail polish through contact with nail beds (Tokumura et al., 2019). In their study, TPP exposures ranged from 0.2 – 6.8 µg/kg bw/day for the 5th to 95th percentile of exposures, using the European ConsExpo exposure assessment program (Table 6, also see Appendix A for parameters used in the ConsExpo simulation). The ConsExpo exposure model used QSAR predictions of dermal permeability rate for TPP, using molecular weight and octanol/water partition coefficients, and the resulting absorption rate was estimated to be 0.089 cm/hr (Tokumura et al., 2019).

5 RISK CHARACTERISATION

The risk of the above exposure scenarios can be expressed as a margin of exposure (MOE), as shown in Table 6. The MOE is the ratio between a defined point on the dose-response curve for the adverse effect and the estimated human exposure. In this case the NOAEL has been taken as the point of departure.

Table 6. Summary of Dose Estimates and Margins of Exposure for TPP in Nail Polish

Scenario	Internal Dose Estimate (μg TPP/kg BW/day)	NOAEL (μg/kg/day)*	MOE
High use, fingernails + toenails, 15 yo female	3.54	70,000** 525*** 10****	2.0E+04 1.5E+02 2.8E+00
Lower use, fingernails only, adult female	0.001	70,000 525 10	7.0E+06 5.3E+04 1.0E+03
Adult female*	0.2 (5th percentile) 0.8 (25th percentile) 1.7 (50th percentile) 3.1 (75th percentile) 5.0 (95th percentile) 6.8 (99th percentile)	70,000	3.6E+05 8.8E+04 4.1E+04 2.2E+04 1.4E+04 1.0E+04

* Tokumura et al., 2019, ConsExpo Model; **RfD based on Sutton et al., 1960; *** DNEL from REACH; ****NOAEL of Cui et al., 2020. All NOAELs are external doses; 100% absorption by the oral route is assumed.

Table 6 shows the outcome of the exposure assumptions for high use frequency and TPP concentration, as compared with the lower use frequency and TPP concentration. The published assessment by Tokumura is provided for comparison. The large range of MOE values reflects the dose range from the recent toxicology studies compared with the older studies from Sutton et al. (1960).

The MOEs calculated by Tokumura et al. (2019) were based on comparison to toxicity endpoints derived from Sutton (Table 1). Typically, a MOE greater than 100 is considered to represent a low level of toxicological concern for compounds other than genotoxic carcinogens.

As shown in Table 6, Tokumura found that an accepted exposure model used in Europe (ConsExpo), considering even the most highly exposed consumers do not approach the RfD, with a MOE that is comfortably greater than 100 (Tokumura et al., 2019).

If, however, an RfD of 10 μg/kg bw/day were to be adopted, based on the more recent findings on insulin and endocrine effects in mice (i.e. from Wang et al., 2018; Wang et al., 2019; Ciu et al., 2020; Guan et al., 2022), then the MOE would be close to or below 1.0, or over 100-fold below a typically acceptable MOE.

6 DISCUSSION

Triphenyl phosphate is a flame retardant and plasticiser chemical that has been increasing used in consumer products to replace persistent and hazardous chemicals, including polybrominated diphenyl ethers (PBDEs), and phthalates. While it is not known what the prevalence of TPP in nail polishes used in New Zealand is, several published reports indicate a high prevalence in products available overseas.

Triphenyl phosphate is absorbed dermally, orally and through inhalation. The dermal absorption route has been shown, in a published human case study, to be significant (Mendelsohn et al., 2016). The acute toxicity, irritancy, and sensitisation potential of TPP is low, and although many data gaps exist in the toxicology profile of TPP, the few older human and animal studies that have been conducted have not found evidence of carcinogenicity or low dose effects of concern (ATSDR 2012). However, there are no long-term studies with TPP that allow for a thorough evaluation of chronic, low dose effects that have been published in the last several years. As an organophosphate, TPP inhibits acetylcholinesterase, with a low potency and at high doses.

The data gaps in the TPP toxicity assessment present a large uncertainty in the present risk assessment. To illustrate this problem, a comparatively recent series of peer-reviewed publications by several research groups in China have collectively found very low dose, subtle effects *in vitro* and *in vivo*, involving endocrine perturbations with ensuing effects that involve the regulation of estrogen receptor downstream events as one of multiple proposed adverse outcome pathways (Wang et al, 2020; Cui et al., 2020; Guan et al., 2022). Other papers reported alterations in insulin regulation in rodents with varying effects on obesity depending on diet (Wang et al., 2018; Wang et al., 2019). These recent findings are currently under consideration in Europe and the U.S. as they re-evaluate the toxicity hazards of TPP. The doses at which these endocrine responses have been reported are approximately 3 to 4 orders of magnitude lower than NOAELs previously reported in more conventional toxicology studies.

Dermal TPP exposure through nail polish has been demonstrated in a controlled study of human volunteers, and is estimated to be a significant route of exposure in comparison with the more environmentally prevalent house dust oral, inhalation, and dermal routes of exposure, due to the high concentration of TPP used as a plasticiser in some polishes. This may be particularly true in the case of frequent applications of polishes, and exposure to cuticle surrounding nail beds, and even through the nail itself, if nails are not coated with a base layer prior to polishing. The optimally precise application methods and role of nail polish base coating in mitigating TPP exposure have not been scientifically established.

A risk assessment on TPP in nail polish, peer reviewed and published in 2019, using a NOAEL of 70 mg/kg bw/day, combined with an exposure assessment using the European ConsExpo model, found that estimated exposures have a satisfactory MOE, well above 100, using conservative exposure assumptions and TPP concentrations at the high end of the published range.

We examined two exposure scenarios: 1) a high use consumer, female 11 to 15 years old, using nail polish 3 times/week on fingernails and toenails, and using polish containing TPP at the highest reported range of TPP concentrations, and 2) a lower use consumer, adult female, using nail polish once/month, with a lesser TPP concentration in the product. Using currently available toxicological endpoints, and the published reference dose for TPP, risk characterisation using a margin of exposure (MOE) was performed. The MOE, using a

published risk assessment approach, ranged from 1000 to 20,000, indicating a low concern for consumer use of TPP to exceed current toxicological doses of concern.

Alternative MOEs were calculated using more recent toxicology study findings, with MOEs ranging into values less than 100 indicating a potential cause for concern.

7 CONCLUSIONS

TPP is currently used in some cosmetic nail polish products available overseas and this is expected to be true also in New Zealand. The current risk assessment has shown that exposure to TPP in nail polish does not present a risk of toxicity even to people using products with high concentrations of TPP and with great frequency. A maximum dose of 3.54 μg TPP/kg bw/day was estimated, using conservative absorption assumptions. While consumer exposure to TPP is expected to occur through the skin and possibly also through the nails, the toxicity of TPP is sufficiently low that exposures will be well below dose levels of concern.

This conclusion may require revisiting in the near future when a peer-reviewed assessment of the recent literature suggesting potential toxic effects of TPP at lower doses becomes available by the U.S. EPA, ECHA, or a similar regulatory authority.

8 REFERENCES

Agency for Toxic Substances and Disease Registry (ATSDR). 2012. Toxicological profile for phosphate ester flame retardants. www.atsdr.cdc.gov.

Bedanta, et al. 2021. Understanding the drug delivery through nails: a comprehensive review. *Journal of Drug Delivery and Therapeutics.* 11(4):116-131. Retrieved May 21, 2022 from DOI: http://dx.doi.org/10.22270/jddt.v11i4.4941.

Berker, D., et al. 2007. Nail biology and nail science. *International Journal of Cosmetic Science.* 29 (4): 241-275. https://doi.org/10.1111/j.1467-2494.2007.00372.x.

Bremmer H, Prudehomme de Lodder L, and Van Engelen J. 2006. Cosmetics Fact Sheet. To assess the risk to the consumer: Updated version for ConsExpo4. ConsExpo Fact Sheets. https://www.rivm.nl/bibliotheek/rapporten/320104001.pdf. [Link accessed May 2022].

Businesswire. 2020. COVID-19 Impacts: Nail Care Products Market Will Accelerate at a CAGR of Over 4% Through 2020-2024 | Growing Interest in Nail Art and Manicure to Boost Growth | Technavio. Retrieved May 21, 2022. https://www.businesswire.com/news/home/20200730005339/en/COVID-19-Impacts-Nail-Care-Products-Market-Will-Accelerate-at-a-CAGR-of-Over-4-Through-2020-2024-Growing-Interest-in-Nail-Art-and-Manicure-to-Boost-Growth-Technavio.

Cadova, Petra Leroy. Annual Forum on Endocrine Disruptors Virtual Conference 21-22 September 2021. EU Commission. Retrieved May 8, 2022 from https://ec.europa.eu/environment/pdf/endocrine/Petra_Leroy_Cadova.pdf.

California Department of Toxic Substances Control (DTSC). 2016. Potential health and safety impacts of chemicals in nail products. https://dtsc.ca.gov/wp-content/uploads/sites/31/2018/04/DTSC-Work-Plan-Implementation-Potential-Health-and-Safety-Impacts-of-Chemicals-in-Nail-Products-11-15-16.pdf [site accessed May 2022].

Chandra, S., & Das, A. 2019. The Science of Nail Polish, Nail Polish Remover and Nail Moisturizers: A Comprehensive Approach. DOI: 10.1201/9781351139724-35.

Consumer Product Safety Commission (CPSC). 2006. CPSC staff preliminary risk assessment of flame retardant (FR) chemicals in upholstered furniture foam. https://www.cpsc.gov/s3fs-public/pdfs/ufurn2.pdf [site accessed June 2022].

Cosmetic Ingredient Review Expert Panel [CIR]. 2018. Safety Assessment of Triphenyl Phosphate as Used in Cosmetics. Final Report. Retrieved May 8, 2022 from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR760.pdf.

Cui H, Chang Y, Jiang X, and Li M. 2020. Triphenyl phosphate exposure induces kidney structural damage and gut microbiota disorders in mice under different diets. *Environ. Int.* 144:106054.

Du Z, Zhang Y, Wang G, Peng J, Wang Z, and Gao S. 2016. TPhP exposure disturbs carbohydrate metabolism, lipid metabolism, and the DNA damage repair system in zebra fish liver. *Scientific Reports*. www.nature.com/articles/srep21827.pdf.

Estill, Cheryl, et al. 2021. Assessment of Triphenyl Phosphate (TPhP) Exposure to Nail Salon Workers by Air, Hand Wipe, and Urine Analysis. *Int J Hyg Environ Health.* 231:113630. DOI:10.1016/j.ijheh.2020.113630.

European Chemical Agency [ECHA]. 2010. REACH registration dossier for triphenyl phosphate (CAS No. 115-86-6). https://echa.europa.eu/registration-dossier/-/registered-dossier/15972/7/9/4

European Chemical Agency [ECHA]. 2021. Decision on Testing Proposal. Retrieved May 8, 2022 from https://echa.europa.eu/documents/10162/77795ee5-cb7e-4723-0b8a-08a0ca031038.

European Union Commission [EU Commission]. Cosmetics. Retrieved May 8, 2022 from https://ec.europa.eu/growth/sectors/cosmetics_en.

Food and Drug Administration [FDA]. Cosmetics & U.S. Law. Retrieved May 7, 2022 from https://www.fda.gov/cosmetics/cosmetics-laws-regulations/cosmetics-us-law.

Gjorgievska, Ljubica. 2022. 20+ Australian Beauty Industry Statistics (2022 Edition). Take a Tumble. 2022 March 28. Retrieved May 8, 2022 from https://takeatumble.com.au/insights/lifestyle/australian-beauty-industry-statistics/.

Guan R, Li N, Wang W, Liu W, Li X, and Zhao C. 2022. The adverse outcome pathway (AOP) of estrogen interference effect induced by triphenyl phosphate (TPP): Integrated multi-omics and molecular dynamics apporaches. *Ecotoxicol Environ Safety* 234:113387.

Hinton DM, Jessop JJ, Arnold A, Albert RH, Hines FA. 1987, Evaluation of immunotoxicity in a subchronic feeding study of triphenyl phosphate. *Toxicol Ind Health*. 3(1):71-89. doi: 10.1177/074823378700300103. PMID: 3495907.

Howard, Gregory J. 2014. Chemical Alternatives Assessment: The Case of Flame Retardants. Dickinson College Faculty Publications. Paper 37. https://scholar.dickinson.edu/faculty_publications/37

Jonsson O, Dyremark E, and Nilsson U. 2001. Development of a microporous membrane liquid-liquid extractor for organophosphate esters in human blood plasma: identification of triphenyl phosphate in donor plasma. *J. Chromatog. B: Biomed. Sci. Appl*. 755(1-2):157-164. ISSN: 0378-4347. https://doi.org/10.1016/S0378-4347(01)00055-X.

Madnani, Nina & Khan, Kaleem. 2012. Nail Cosmetics. *Indian J Dermatol Venereol Leprol.* 78:309-17. DOI: 10.4103/0378-6323.95445.

Meeker JD, & Stapleton HM. 2010. House dust concentrations of organophosphate flame retardants in relation to hormone levels and semen quality parameters. *Environmental Health Perspectives*, 118(3), 318–323. https://doi.org/10.1289/ehp.0901332.

Mendelsohn, Emma, et al. 2016. Nail Polish as a Source of Exposure to Triphenyl Phosphate. *Environ Int.* 86:45-51. DOI:10.1016/j.envint.2015.10.005.

Merriam-Webster. (n.d.). Triphenyl phosphate. In Merriam-Webster.com dictionary. Retrieved May 7, 2022, from https://www.merriam-webster.com/dictionary/triphenyl%20phosphate.

National Center for Biotechnology Information. 2022. PubChem Compound Summary for CID 8289, Triphenyl phosphate. Retrieved May 7, 2022 from https://pubchem.ncbi.nlm.nih.gov/compound/Triphenyl-phosphate.

Newman, Marian. 2004. The Complete Nail Technician. Cengage Learning, UK. ISBN 13: 9781844801398.

New Zealand Environmental Protection Authority. 2006. https://www.epa.govt.nz/database-search/new-zealand-inventory-of-chemicals-nzioc/view/9B717D80-B3AB-4520-B151-CBD87A85A646

New Zealand Environmental Protection Authority (NZ EPA). 2022. New Zealand's Hazard Classification System. https://www.epa.govt.nz/industry-areas/hazardous-substances/new-zealands-new-hazard-classification-system/ [site accessed May 2022].

Organization for Economic Cooperation and Development (OECD). 2002. SIDS Initial Assessment Report (SIAR) for triphenyl phosphate. https://hpvchemicals.oecd.org/ui/handler.axd?id=e23395dc-ed57-4822-b9c4-7178045c3c97

SallyBeauty. 2022. How often should I get a professional manicure? Retrieved May 21, 2022 https://www.sallybeauty.com/FAQ_NAILS_048.html.

Sharad, Jaishree, et al. 2019. *Aesthetic Dermatology: Current Perspectives*. Jaypee Brothers Medical Publishers. New Delhi, India. Pp 57.

Stapleton HM, Klosterhaus S, Eagle S, Fuh J, Meeker JD, Blum A, and Webster TF. 2009. Detection of organophosphate flame retardants in furniture foam and US house dust. *Environ Sci Technol* 43, 7490-7495.

Statistica. 2020. Retrieved May 17, 2022 from https://www.statista.com/markets/415/topic/467/cosmetics-personal-care/#overview.

Sutton WL, Terhaar CJ, Miller FA, Scherberger RF Riley EC, Roudabush RL, and Fassett DW. 1960. Studies on the industrial hygiene and toxicology of triphenyl phosphate. *Arch Environ. Health.* 1:33-46.

Theiss J, Stoner G, Shimkin M, and Weisburger E. 1977. Test for carcinogenicity of organic contaminants of United States drinking waters by pulmonary tumor response in strain A mice. *Cancer Res.,* 37: 2717- 2720.

Tokumura, Masahiro, et al. 2019. Dermal exposure to plasticisers in nail polishes: An alternative major exposure pathway of phosphorus-based compounds. *Chemosphere.* 226:316-320. ISSN 0045-6535, https://doi.org/10.1016/j.chemosphere.2019.03.108.

UK Environment Agency. 2009. Environmental risk evaluation report: Triphenyl phosphate. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/290862/scho0809bquk-e-e.pdf

US Consumer Product Safety Commission (CPSC). 2016. Toxicology Excellence in Risk Assessment (TERA): Flame retardant exposure assessment database. Task Order 15, Contract CPSC-D12-001 https://www.cpsc.gov/s3fs-

public/FR%20exposure%20database.contractor%20report%2015.01062016.with%20cover.pdf?WgfzcVUPirdr5RkjwY4qXFbowunjr5s9. [site accessed June 2022].

US Environmental Protection Agency [US EPA]. 2020. Final Scope of the Risk Evaluation for Triphenyl Phosphate. Office of Chemical Safety and Pollution Prevention. Retrieved May 7, 2022, from https://www.epa.gov/sites/default/files/2020-09/documents/casrn_115-86-6_triphenyl_phosphate_tpp_final_scope.pdf.

Wang D, Le Y, Lu D, Zhao M, Dou X, and Zhang Q. 2020. Triphenyl phosphate causes a sexually dimorphic metabolism dysfunction associated with disordered adiponectin receptors in pubertal mice. *J. Hazard. Mater.* 388:121732.

Wang D, Yan S, Yan J, Teng M, Meng Z, Li R, Zhou Z, Zhu W. 2019. Effects of triphenyl phosphate exposure during fetal development on obesity and metabolic dysfunctions in adult mice: Impaired lipid metabolism and intestinal dysbiosis. *Environ Pollut*. 246:630-638. doi: 10.1016/j.envpol.2018.12.053

Wang D, Zhu W, Chen L, Yan J, Teng M, and Zhou Z. 2018. Neonatal triphenyl phosphate and its metabolite diphenyl phosphate exposure induce sex- and dose-dependent metabolic disruptions in adult mice. *Environ Pollut.* 237:10-17. https://doi.org/10.1016/j.envpol.2018.01.047

Wang X, Liu Q, Zhong W, Yang L, Yang J, Covaci A, and Zhu L. 2020. Estimating renal and hepatic clearance rates of organophosphate esters in humans: Impacts of intrinsic metabolism and binding affinity with plasma proteins. *Environ. Int*. 134:105321.

Wang Y, Kwon G, An L, Holmes C, Haeba M, and LeBlanc G. 2016. Differential interactions of the flame retardant triphenyl phosphate within the PPAR signaling network. *MOJ Toxicology*. https://medcraveonline.com/mojt/mojt-02-00039.pdf.

Welsh J, Collins T, Whitby K, Black T, and Arnold A. 1987. Teratogenic potential of triphenyl phosphate in Sprague-Dawley (Spartan) rats. *Toxicol. ind. Health,* 3(3): 357-369.

Worksafe New Zealand. 2022. Workplace Exposure Standards and Biological Exposure Indices. Worksafe.govt.nz

World Health Organization (WHO). 1991. International Programme on Chemical Safety (IPCS). Environmental Health Criteria 111. Triphenyl Phosphate. https://apps.who.int/iris/bitstream/handle/10665/40299/924157111X-eng.pdf?sequence=1&isAllowed=y [site accessed June 2022].

Young A, Allen J, Kim U, Seller S, Webster T, Kannan K, and Ceballos D. 2018. Phthalate and organophosphate plasticisers in nail polish: Evaluation of labels and ingredients. *Environ. Sci. Technol*. 52:12841-12850.

APPENDIX A RIVM CONSEXPO DEFAULT PARAMETERS

Nail Polish Composition and use

Nail polish is applied to the nails of the hands and feet using a very fine brush.
The general composition of ordinary nail polish is given in reference:

72% organic solvents
10% cellulose nitrate
5% plasticiser
10% synthetic resin
3% colouring

The composition of the mixture of solvents depends on the ingredients used in the nail polish. The solvents must be able to dissolve cellulose nitrate, resins and plasticisers. The viscosity must be suitable to allow the polish to be applied to the nails easily; the evaporation speed is also important. The drying time of nail polish should be between 3 and 5 minutes.

References show that nail polish contains 75% organic solvents:

20% ethyl acetate
15% butyl acetate
5% ethyl alcohol
35% toluene

Other possible solvents in nail polish are butanol, amyl acetate, and isopropyl alcohol. Cellulose nitrate is used as a film polymer in nail polish. The addition of plasticisers gives the film polymer more flexibility and makes it more resistant to breaking. These days acetyltributyl citrate is usually used as the plasticiser. Camphor is still used because it is a good plasticiser; phthalates are sometimes used. An important constituent of nail polish is resins such as alkyd, sulphonamide and acrylic resins. Used together with cellulose nitrate they increase the bond and the shine of the nail polish.

To colour nails, pigments are usually added to nail polish, in the same way as for blusher and eye shadow. Both organic pigments and inorganic pigments such as titanium oxide are used. Pigments are coloured, solid substances whose particles disperse in the solvent; they are physically or chemically inert.

Nail polish is available in various forms, such as base coat and topcoat. Base coat consists of more than 10% synthetic resin. Topcoat contains more cellulose nitrate and plasticiser but less synthetic resin than normal nail polish. They are used in this order: base coat, nail polish and then top coat.

Scenario

The amount of nail polish used per application is given in reference as 0.25 g. For the dermal exposure the amount applied to the nail is not important, only the amount that is applied to the skin. It is assumed that a fingernail has an area of 1 x 1.5 cm, then the total

fingernail area is 15 cm^2. For the contact of nail polish with the skin, a nail perimeter (i.e. the two sides of the nail and the nail bed) of 4 cm is assumed with a breadth of 1 mm. This gives an exposed area of 4 cm^2 for the skin around the fingernails. The amount of product that gets onto the skin is then 0.25 x 4 / 19 = 0.05 g.

Table A.1. Exposure Parameters for the Consexpo Model of Triphenyl Phosphate in Nail Polish

Parameter	Function	Value	Reference
Temperature (°C)	Constant	25	–
Body weight of 11 – 15 yo girl (kg)	Constant	53	ESR 2016
Concentration (wt%)	Triangle distribution	1.1–1.4–1.8	Tokumura et al., (2019)
Applied surface area for stray nail polish (cm^2)	Triangle distribution	0–0.1–4	Bremmer 2006
Amount of product applied (g)	Triangle distribution	0–0.001–0.05	
Exposure time (day)	Constant	2.3	
Use frequency ($year^{-1}$)	Constant	160	
Dermal permeation coefficient (cm h^{-1})	Constant	0.089	

Adapted from Tokumura et al. (2019)

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