Safety Assessment of Triphenyl Phosphate as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	May 11, 2018
Panel Meeting Date:	June 4-5, 2018

The 2018 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Christina L. Burnett, Senior Scientific Analyst/Writer.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst
Date: May 11, 2018
Subject: Draft Final Safety Assessment on Triphenyl Phosphate

Enclosed is the Draft Final Report of the Safety Assessment of Triphenyl Phosphate as Used in Cosmetics. (It is identified as *tripho062018rep* in the pdf document.)

At the March 2018 meeting, the Panel issued a Tentative Report with the conclusion that this ingredient is safe in cosmetics in the present practices of use and concentration described in the safety assessment.

Prior to the March meeting, the Council provided additive HRIPT data of Triphenyl Phosphate tested at up to 7.0% in nail products (identified as *tripho062018data*). This data has now been included in the report and highlighted in the appropriate table. No other unpublished data were provided. A recent published study on dermal uptake and penetration of Triphenyl Phosphate in human skin samples has been included in this draft Final Report and is denoted in the text with highlighting.

The Council provided comments on the draft report (prior to the March meeting) and the Tentative Report (*tripho062018pcpc1 and tripho062018pcpc2*, respectively). These comments have been addressed. The CIR Science and Support Committee have also supplied comments specific to the published references included in the "Other Relevant Studies-Endocrine Activity" section of this safety assessment (identified as *tripho062018cirssc*). CIR staff ask the Panel to consider the edits made in response to these comments to ensure they are consistent with the Panel's consensus (denoted in the text with highlighting).

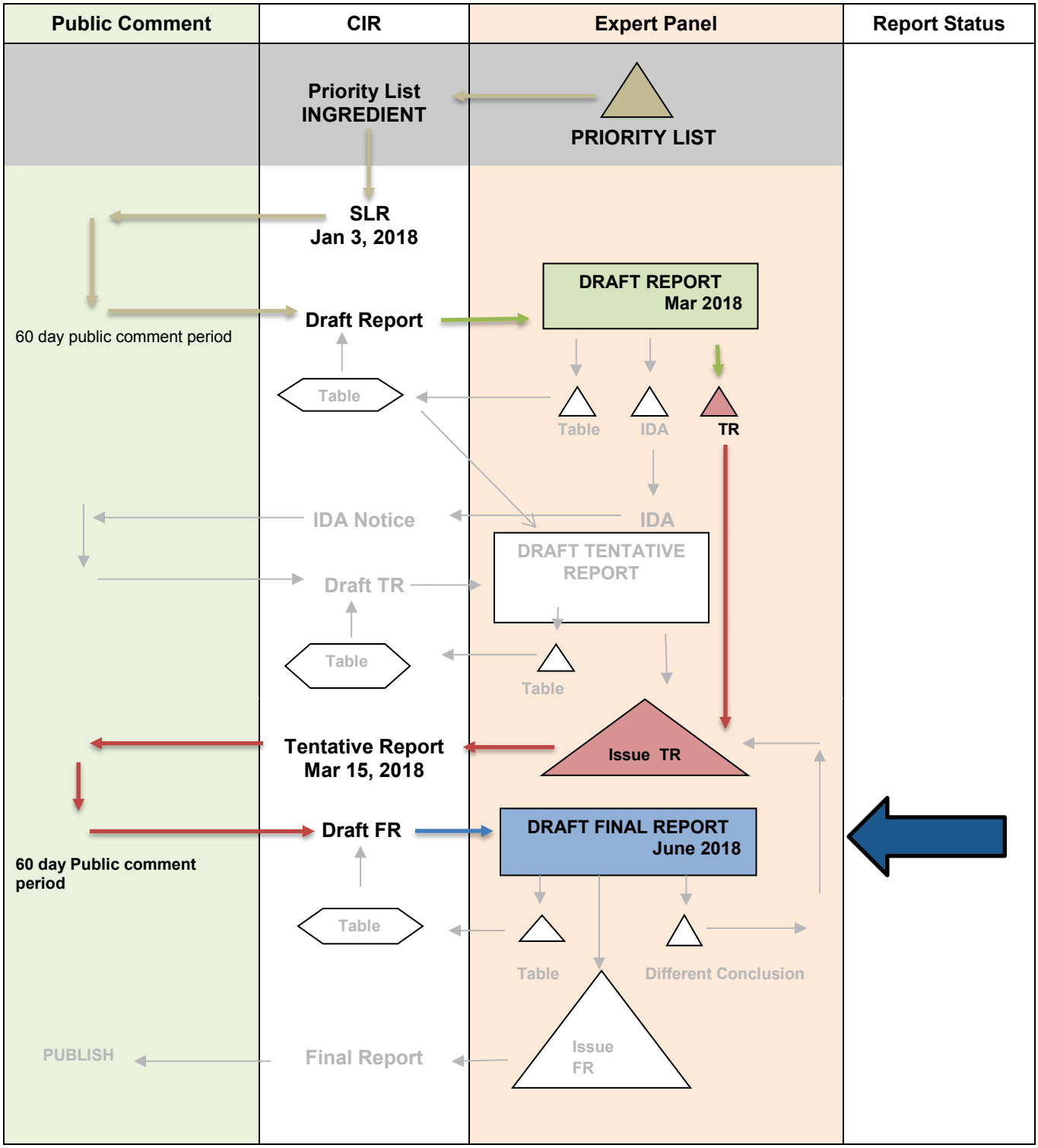
According to the recently obtained 2018 VCRP data, the number of uses of Triphenyl Phosphate has decreased by 41formulations (all in nail polishes and enamels) when compared to 2017 data. The total number of uses for Triphenyl Phosphate in personal care products is now 331.

The Panel should carefully review the Abstract, Discussion, and Conclusion of this safety assessment. If these are satisfactory, the Panel should issue a Final Report.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Triphenyl Phosphate

MEETING June 2018



Triphenyl Phosphate History

January 3, 2018 – Scientific Literature Review announced.

March 2018 - The Panel issued a tentative report for public comment with the conclusion that Triphenyl Phosphate is safe in cosmetics in the present practices of use and concentration described in the safety assessment.

The Panel found that the systemic toxicity data, including developmental and reproductive toxicity and short-term toxicity studies, and dermal irritation and sensitization data in this report were sufficient. The Panel noted the lack of carcinogenicity data, but this gap was mitigated by multiple genotoxicity studies that were negative. This ingredient is only used in nail products and the maximum reported use concentration is 14.5%.

Triphenyl Phosphate Data Profile –June 2018 – Writer, Christina Burnett															
	In-Use	Physical/Chemical Properties	Method of Manufacturing	Composition/Impurities	Acute Toxicity	Repeated Dose Toxicity	Genotoxicity	Reproductive and Developmental Toxicity	Carcinogenicity	Other Relevant Toxicity Studies	Irritation/Sensitization - Nonhuman	Irritation/Sensitization - Human	Ocular/Mucosal	Phototoxicity	Clinical Studies/Case Reports	Toxicokinetics
Triphenyl Phosphate	X	X	X	X	X	X	X	X		X	X	X	X		X	X

"X" indicates that data were available in the category for that ingredient.

Triphenyl Phosphate

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	FEMA	Web
Triphenyl Phosphate	115-86-6	√	√	√	√	√	√	√	√	√	√	√	√	√	√			

Search Strategy

PubMed = (triphenyl phosphate) OR 115-86-6 = 304 returns, 27 ordered or downloaded

Search updated April 2018 – No new pertinent references found.

LINKS

InfoBase (self-reminder that this info has been accessed; not a public website) - http://www.personalcarecouncil.org/science-safety/line-infobase
ScfFinder (usually a combined search for all ingredients in report; list # of this/# useful) - https://scifinder.cas.org/scifinder
PubMed (usually a combined search for all ingredients in report; list # of this/# useful) - http://www.ncbi.nlm.nih.gov/pubmed
Toxnet databases (usually a combined search for all ingredients in report; list # of this/# useful) – https://toxnet.nlm.nih.gov/ (includes Toxline; HSDB; ChemIDPlus; DAR; IRIS; CCRIS; CPDB; GENE-TOX)

FDA databases – http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm (CFR); then,
list of all databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm; then,
http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true (EAFUS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm (GRAS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm (SCOGS database);
http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives (indirect food additives list);
http://www.fda.gov/Drugs/InformationOnDrugs/default.htm (drug approvals and database);
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf (OTC ingredient list);
http://www.accessdata.fda.gov/scripts/cder/iig/ (inactive ingredients approved for drugs)

EU (European Union); check CosIng (cosmetic ingredient database) for restrictions and SCCS (Scientific Committee for Consumer Safety) opinions - http://ec.europa.eu/growth/tools-databases/cosing/
ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
OECD SIDS documents (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/
NTIS (National Technical Information Service) - http://www.ntis.gov/
NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/ (FAO);
FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
Web – perform general search; may find technical data sheets, published reports, etc

Botanical Websites, if applicable
Dr. Duke's https://phytochem.nal.usda.gov/phytochem/search
Taxonomy database - http://www.ncbi.nlm.nih.gov/taxonomy
GRIN (U.S. National Plant Germplasm System) - https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
Sigma Aldrich plant profiler http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html

Fragrance Websites, if applicable
IFRA (International Fragrance Association) – http://www.ifraorg.org/
the Research Institute for Fragrance Materials (RIFM) should be contacted

Triphenyl Phosphate
March 5-6, 2018

Dr. Belsito's Team
DR. BELSITO: Okay. We're doing triphenyl phosphate. This is the first time we're looking at it. It's a single ingredient report. And it's basically used in nails.

DR. SNYDER: Up to 14.5 percent.

DR. BELSITO: Up to 14.5 percent. And the only concern I had was a nail lotion reported at 1 percent, which would be more likely to give you skin leave on. I thought what we really need to do is look at a 1 percent. It has a high-boiling point --

MS. BURNETT: I'm sorry, we have HRIPT data at 7 percent.

DR. BELSITO: No. I know. Yeah. I'm just going through my notes as I'm going through here. It has a high-boiling point, so I don't think respiratory is an issue here. For repro, there was a positive repro study, but it was a very high dose.

DR. SNYDER: There's a second study. He published two studies. We have one, we don't have the other, so probably just add that one to the report.

MS. BURNETT: Okay.

DR. BELSITO: But we didn't have a NOAEL or a LOAEL, so I didn't know how we wanted to deal with that. And I also didn't understand, under the immunology section, where they said the immunotoxicity was 1 percent and they gave a NOAEL; because the results didn't appear to me to be dose dependent at all. It was like a quirky study.

DR. SNYDER: Yeah. It wasn't a very good study. Immuno chemistry of lymph node, organ weights are very --

DR. BELSITO: And the cytotoxicity, do we need to discuss that at all?

DR. LIEBLER: Not really. I mean, this is another one where you dump that chemical in on cultured cells and I don't think it's particularly relevant. You know, the concentrations that inhibited cell growth were almost millimolar range. So, that's very high.

DR. BELSITO: Okay. So, the only thing we're missing here is UV? Do we need UV absorption?

DR. LIEBLER: Probably not. These are going to absorb in the UVA, not quite the UVB, in their isolated phenyl rings.

DR. BELSITO: But UVA is what you worried about?

DR. LIEBLER: Yeah. They're not going to -- I'm sorry, no, no, no, no. I'm sorry, UVC. I'm flipped on my UVs.

DR. BELSITO: Oh. Un-flip your UVs, it could be dangerous.

DR. LIEBLER: I don't think these are going to have absorption beyond about 260.

DR. BELSITO: Okay. So, do we just ignore it? Do we put that in the discussion? Dan Liebler doesn't think it will absorb above 260. What do we do?

DR. LIEBLER: It should be possible to find spectra in the literature of this compound or other phenolic esters.

DR. BELSITO: I mean, triphenyl phosphate is so widely used in the plastic industry, I'm surprised we don't have that data. Okay, well then, safe as used?

DR. LIEBLER: I think so. My question was, is the sensitization high enough for you?

DR. BELSITO: Yeah.

DR. LIEBLER: And if it is, then I thought it was safe as used.

DR. BELSITO: Now since it's only used in nail products, nail lotions, do we say just safe as used? Or do we say safe as used in nail products? Or how do we approach -- we're in triphenyl phosphate, Curt. How do we approach this?

MS. BURNETT: It would be safe in the current practices of use and concentration.

DR. BELSITO: Right. That covers it.

DR. SNYDER: Yup.

DR. LIEBLER: Yeah, here's the UV spectrum.

MS. BURNETT: Okay. What website are you on?

DR. LIEBLER: It's on NIST Webbook. I'll send you a link.

MS. BURNETT: Okay. Thank you.

DR. BELSITO: And it doesn't absorb?

DR. LIEBLER: It's got a max at about 265 and it falls off to nothing at about 275.

DR. BELSITO: Perfect. Okay. So, safe as used in the current -- what's our phrase now?

MS. BURNETT: Current practices of use and concentration. Is there anything for the discussion?

DR. BELSITO: I didn't have anything. That's why I was -- I said team do we have any --

DR. SNYDER: He was trying to come up with something.

DR. BELSITO: I mean, my discussion said see notes to team, and they shot those down. Cytotoxicity wasn't an issue. The repro wasn't an issue. I mean, I guess if we need to discussion something, we would could say why we didn't think they were issues. The immunotoxicity was all over the place.

MS. BURNETT: But the endocrine activity?

DR. BELSITO: It's not in aerosolized products. I don't even know that we need to bring in the respiratory aspect.

I mean, just comments on why we dismissed the high-dose no NOAEL for the repro, the lack of dose response for the immunotoxicity, and the dumping of materials into cell lines for the cytotoxicity. Those would be the only things if we have to discuss something.

DR. LIEBLER: I mean, I think the thing you can say with the cell models, is simply that concentrations that produced inhibition of cell growth were nearly millimolar, which is very high, which is equivalent to exposures far above what would be achieved with cosmetic products.

DR. BELSITO: Anything else?

DR. KLAASSEN: Majority of the uses are used as nail polish, et cetera.

DR. BELSITO: Right.

DR. KLAASSEN: And exposure is minimal.

Dr. Marks' Team

DR. MARKS: Next is triphenyl phosphate. Christina, yeah, you're here, good. We have a draft report, so this is the first time we've seen this ingredient. It's a single ingredient, the triphenyl phosphate used for nail products.

We don't have to decide whether we're going to include ingredients or not. We have one ingredient. Tom, Ron, needs?

DR. SLAGA: Sufficient data and safe as used.

DR. HILL: The only need I had is on page 9. It's probably just a clarification. What we have is the purity of triphenyl phosphate is reported to be greater than X, 99.6 percent. Impurities may include water, phenol and esters. I wanted to know, are those just diesters, maybe some monoester or -- because we have information that these -- I'm wondering if they're produced by transesterification; in which case we could have some carboxylic acid esters mixed in there, so I wanted information about what those esters were. This is -- reference 4 was not going to enlighten us as I remember right.

MS. BURNETT: I wrote what was in the reference.

DR. HILL: I assumed that was the case. It was the OECD screening information. I didn't go out and look at it to see, but I'm guessing there's nothing specific about that. I wanted to see if we could find out from industry what those are. I had no other needs. I thought the report was really solid and I felt, other than that, no reason to conclude other than safe.

DR. MARKS: Is that need enough to have an insufficient data announcement? Or do we move forward with a tentative report, safe conclusion and then see what Christina can find possibly?

DR. HILL: I like tentative report, safe conclusion, but flag that as a pending request for further information.

DR. MARKS: Okay. Ron Shank, I feel like I have the card and I'm opening up the envelope with Ron Shank's conclusions here after we've discussed it. Ron Shank concurs the conclusion as okay with no restrictions, so safe. Actually, his conclusion is, okay. I translated, okay, as meaning safe.

Discussion. Sufficient toxicity data in this report; short-term, DART, genotox irritation, sensitization. These data support the safety of triphenyl phosphate as an ingredient in manicuring products. There is no need for additional data.

Then we'll see what tumbles out with the esters, Ron.

DR. BERGFELD: Are you adding a discussion to this report? I don't see one.

DR. MARKS: I think, yes.

DR. SLAGA: This is the first time.

MS. BURNETT: I need -- yeah. This is the first time.

DR. BERGFELD: I know, but are we adding a discussion?

DR. HILL: I would assume so.

DR. MARKS: Sure. It will be just what --

MS. BURNETT: I can go by what Dr. Shank has written and expand upon that. The other group had difficulties too. No worries.

DR. MARKS: Exactly. Yes. I'm not worried. I figured you can expand, Christina, on what he wrote. Tomorrow I'll be moving a tentative report be issued with a conclusion of safe as used.

Okay. Any other comments?

DR. HILL: Just that what I appreciated about some of the data in here was that there was work that was done at multiple doses, enough that you could get some sense of the range of things that they tested and that was very helpful in trying to reach some conclusions.

Full Panel Meeting

DR. MARKS: Well, this should be less exciting than ginkgo. This is a first review on this single ingredient, which is used for nail products. And our team felt that we could progress. I move that we issue a tentative report with a safe conclusion.

DR. BELSITO: Second.

DR. BERGFELD: Second. Any discussion regarding this ingredient?

DR. BELSITO: There was no UV absorption in the report, but Dan looked it up and it doesn't absorb, so we would just incorporate that into the report. Thank you.

DR. BERGFELD: Ron Hill had his hand up.

DR. HILL: Yeah. This was something that I requested information about, but that I thought did not need to be a formal insufficiency. In our information about impurities -- I'm sorry -- what I have written here, and there's a reference to esters as potential impurities. And it wasn't clear to me, is that phosphodiester and phosphomonoester, mixed in with the triester, or was it other possible esters if the substance is made by transesterification?

I'd hope without holding it up -- I guess I'm putting a request to the industry and to satisfy what are those esters that are in there, to move forward.

DR. BERGFELD: Any other comments before I call to question? All those in favor of safe for this ingredient, please indicate by raising your hand. Thank you. Unanimous.

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.

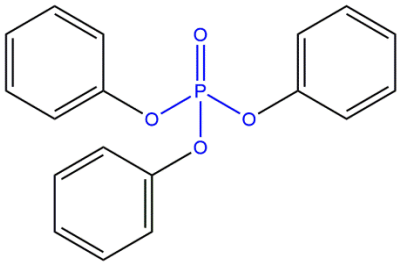

Figure 1. Triphenyl Phosphate

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 UV-A and UV-B 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 in 331 leave-on manicuring preparations, 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 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 has been approved for use as an 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 small 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) 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 also painted their own nails or 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 Organization for Economic Co-operation and Development Test Guideline (OECD 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

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. These results demonstrated that Triphenyl Phosphate could induce oxidative stress and reduce the expression of main genes related to testosterone synthesis in TM3Leydig cells.

The same researchers evaluated the effects of Triphenyl Phosphate (> 99% pure) on the induction of oxidative stress and gene expression in groups of 7 ICR male mice.[22] 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, catalase, and glutathione *S*-transferase 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. These results demonstrated that Triphenyl Phosphate induced oxidative stress and reduce the expression of main genes related to testosterone synthesis in mice.[22]

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.[23] 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%.[4,14,24] 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.[25-29] No adverse events were reported in an in-use safety evaluation of a nail polish containing 1.0041% Triphenyl Phosphate.[30]

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.[31] 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.[32] 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.[33] 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.[34] 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).[35] 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 in 331 leave-on manicuring preparations, 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 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 has been approved for use as an indirect food additive in substances for use only as components of adhesives.

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 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 other relevant studies, 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. No neurotoxicity was observed in a subchronic dietary rat study of this ingredient at up to 1.0%. In a 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.

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 local effects data, including dermal irritation and sensitization studies, in this report were sufficient. The Panel noted that Triphenyl Phosphate can be absorbed, but the safety profile 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 studies on TM3 Leydig cells and mouse testicular testosterone levels following exposure to Triphenyl Phosphate and determined that the results were not sufficient to characterize this ingredient as an endocrine disrupting chemical.

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)	7.50×10^{-6}	[14]
Melting Point º(C)	49-50	[2]
Boiling Point (ºC at 11 mm Hg)	245	[2]
Water Solubility (mg/L @ 25ºC)	1.9	[36]
Log P (@ 20ºC)	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 or 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	[14,24]
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	[30]
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	[26]
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	[28]
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	[25]
5.85% in nail color (1 shade); neat	100 human subjects	HRIPT; semi-occlusive patch; no further details provided	No dermal irritation or sensitization	[25]
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	[27]
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	[29]

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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2018 FDA Raw Data

08A - Basecoats and Undercoats	115866	TRIPHENYL PHOSPHATE	19
08E - Nail Polish and Enamel	115866	TRIPHENYL PHOSPHATE	286
08G - Other Manicuring Preparations	115866	TRIPHENYL PHOSPHATE	26

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: February 12, 2018

SUBJECT: Triphenyl Phosphate

Clinical Research Laboratories, Inc. 2006. Repeated insult patch test of a nail lacquer containing 7% Triphenyl Phosphate.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

Clinical
Research
Laboratories, Inc.

Final Report

Repeated Insult Patch Test

CLIENT: [redacted]

ATTENTION: [redacted]

TEST MATERIAL: Nail Lacquer [redacted]023.001 Containing 7% Triphenyl Phosphate

CRL STUDY NUMBER: CRL19606-4

AUTHORIZED SIGNATURES:

Bruce E. Kanengiser, M.D.
President/Medical Director

Michael J. Muscatiello, Ph.D.
Executive Vice President/COO

George J. Neumaier, M.D.
Diplomate American Board
of Dermatology

REPORT DATE: April 21, 2006

371 Hoes Lane • Piscataway, NJ 08854 • (732) 981-1616 • FAX (732) 981-0520

Clinical
Research
Laboratories, Inc.

Good Clinical Practice
Quality Assurance Audit Statement

Clinical Study Number: CRL19606-4

Start Date: March 3, 2006

Completion Date: April 7, 2006

The clinical study listed above was conducted in accordance with Clinical Research Laboratories, Inc. Standard Operating Procedures, which incorporate the principles of Good Clinical Practice defined by applicable guidelines and regulations established by U.S. Regulatory Agencies. The conduct of the study was monitored for compliance, and the associated records, including source documents or raw data, were reviewed for documentation practices and accuracy by a Project Manager/Study Director and/or a Quality Assurance Representative. Standard Quality Assurance audit procedures for this final report and study related documents were conducted, as indicated below.

Signature of QA Auditor

4/21/06
Date

FINAL REPORT

REPEATED INSULT PATCH TEST

PURPOSE

The purpose of this study was to determine the dermal irritation and sensitization potential of a test material.

INVESTIGATIVE SITE

Clinical Research Laboratories, Inc.
371 Hoes Lane
Piscataway, New Jersey 08854
732-981-1616

TEST MATERIAL

The following test material was provided by [redacted] and was received by Clinical Research Laboratories, Inc. on February 21, 2006:

Test Material	Test Condition	Patch Type
Nail Lacquer [redacted]023.001	Applied to the patch as received. Allowed to air dry.	Semi-occlusive *

The test material was coded with the following CRL identification number:

CRL19606-4

STUDY DATES

This study was initiated on March 3, 2006 and was completed on April 7, 2006.

* Semi-occlusive Strip (TruMed Technologies Inc., Burnsville, Minnesota)

PANEL SELECTION

Each subject was assigned a permanent CRL identification number. All subjects signed an Informed Consent Form in compliance with 21 CFR Part 50: "Protection of Human Subjects" and a HIPAA Authorization Form in compliance with 45 CFR Parts 160 and 164. All subjects completed a Subject Profile/Medical History Form provided by Clinical Research Laboratories, Inc. prior to the study (Subject Demographics - Appendix I). Subjects who met the following criteria were impaneled:

- Male and female panelists between the ages of 18 and 70;
- Subjects who have completed a Panelist Profile/Medical History;
- Subjects who are in general good health as determined by a Panelist Profile/Medical History;
- Subjects who do not exhibit any skin diseases that might be confused with a skin reaction from the test material;
- Subjects willing to sign an Informed Consent Form in conformance with 21 CFR Part 50: "Protection of Human Subjects";
- Subjects who have completed a HIPAA Authorization Form in conformance with 45 CFR Parts 160 and 164;
- Females who are not pregnant or lactating;
- Subjects who demonstrate dependability and intelligence in following directions;
- Subjects who are not currently using any systemic or topical corticosteroids, anti-inflammatory drugs or antihistamines.

TEST METHOD

Prior to the application of the patch, the test area was wiped with 70% isopropyl alcohol and allowed to dry. The test material, which was prepared as described in the Test Material section of the report, was applied to the upper back (between the scapulae) and was allowed to remain in direct skin contact for a period of 24 hours.

TEST METHOD (Continued)

Patches were applied to the same site on Monday, Wednesday, and Friday for a total of 9 applications during the Induction Period. This schedule may have been modified to allow for missed visits or holidays. If a subject was unable to report on an assigned test date, the test material was applied on 2 consecutive days during the Induction Phase and/or a makeup day was added at the end of the Induction Phase.

The sites were graded by a CRL technician for dermal irritation 24 hours after removal of the patches by the subjects on Tuesday and Thursday and 48 hours after removal of the patches on Saturday, unless the patching schedule was altered as described above.

The sites were graded according to the following scoring system:

Dermal Scoring Scale

0 No visible skin reaction
± Barely perceptible erythema (minimal)
1+ Mild erythema (diffuse)
2+ Well defined erythema
3+ Erythema and edema
4+ Erythema and edema with vesiculation

If a "2+" reaction or greater occurred, the test material was applied to an adjacent virgin site. If a "2+" reaction or greater occurred on the new site, the subject was not patched again during the Induction Phase but was challenged on the appropriate day of the study. At the discretion of the Study Director, patch sites with scores less than a "2+" may have been changed.

Following approximately a 2-week rest period, the challenge patches were applied to previously untreated test sites on the back. After 24 hours, the patches were removed by a CRL technician and the test sites were evaluated for dermal reactions. The test sites were re-evaluated at 48 and 72 hours. Subjects exhibiting reactions during the Challenge Phase of the study may have been asked to return for a 96-hour reading.

RESULTS

This study was initiated with 110 subjects. Two subjects discontinued study participation for reasons unrelated to the test material. A total of 108 subjects completed the study.

Individual dermal scores recorded during the Induction and Challenge Phases appear in Table I.

CONCLUSION

Based on the test population of 108 subjects and under the conditions of this study, the sample identified as Nail Lacquer [redacted].023.001 did not demonstrate a potential for eliciting dermal irritation or sensitization.

RETENTION

Test materials and all original forms of this study will be retained by Clinical Research Laboratories, Inc. as specified in CRL Standard Operating Procedure 30.6C, unless designated otherwise by the Sponsor.

TABLE I

Summary of Dermal Scores

Test Material:	Nail Lacquer [redacted]023.001

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	Discontinued										
3	0	0	0	0	0	0	0	0	0	0	0	0
4	±	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0
16	±	0	0	0	0	0	0	0	0	0	0	0
17	±	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	Nail Lacquer [redacted]023.001

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
26	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0
41	±	±	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	Discontinued									
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	Nail Lacquer [redacted].023.001

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
51	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0
57	0	0	0	0	0	0	0	0	0	0	0	0
58	0	0	0	0	0	0	0	0	0	0	0	0
59	0	0	0	0	0	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0	0	0	0	0	0
61	0	0	0	0	0	0	0	0	0	0	0	0
62	0	0	0	0	0	0	0	0	0	0	0	0
63	0	0	0	0	0	0	0	0	0	0	0	0
64	±	±	0	0	0	0	0	0	0	0	0	0
65	0	0	0	0	0	0	0	0	0	0	0	0
66	0	0	0	0	0	0	0	0	0	0	0	0
67	0	0	0	0	0	0	0	0	0	0	0	0
68	0	0	0	0	0	0	0	0	0	0	0	0
69	0	0	0	0	0	0	0	0	0	0	0	0
70	0	0	0	0	0	0	0	0	0	0	0	0
71	0	0	0	0	0	0	0	0	0	0	0	0
72	0	0	0	0	0	0	0	0	0	0	0	0
73	0	0	0	0	0	0	0	0	0	0	0	0
74	0	0	0	0	0	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0	0	0	0	0	0

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	Nail Lacquer [redacted].023.001

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
76	0	0	0	0	0	0	0	0	0	0	0	0
77	0	0	0	0	0	0	0	0	0	0	0	0
78	0	0	0	0	0	0	0	0	0	0	0	0
79	0	0	0	0	0	0	0	0	0	0	0	0
80	0	0	0	0	0	0	0	0	0	0	0	0
81	0	0	0	0	0	0	0	0	0	0	0	0
82	0	0	0	0	0	0	0	0	0	0	0	0
83	0	0	0	0	0	0	0	0	0	0	0	0
84	0	0	0	0	0	0	0	0	0	0	0	0
85	0	0	0	0	0	0	0	0	0	0	0	0
86	0	0	0	0	0	0	0	0	0	0	0	0
87	0	0	0	0	0	0	0	0	0	0	0	0
88	0	0	0	0	0	0	0	0	0	0	0	0
89	0	0	0	Discontinued								
90	0	0	0	0	0	0	0	0	0	0	0	0
91	0	0	0	0	0	0	0	0	0	0	0	0
92	0	0	0	0	0	0	0	0	0	0	0	0
93	0	0	0	0	0	0	0	0	0	0	0	0
94	0	0	0	0	0	0	0	0	0	0	0	0
95	±	0	0	0	0	0	0	0	0	0	0	0
96	±	0	0	0	0	0	0	0	0	0	0	0
97	0	0	0	0	0	0	0	0	0	0	0	0
98	0	0	0	0	0	0	0	0	0	0	0	0
99	0	0	0	0	0	0	0	0	0	0	0	0
100	0	0	0	0	0	0	0	0	0	0	0	0

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	Nail Lacquer [redacted].023.001

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
101	0	0	0	0	0	0	0	0	0	0	0	0
102	0	0	0	0	0	0	0	0	0	0	0	0
103	0	0	0	0	0	0	0	0	0	0	0	0
104	0	0	0	0	0	0	0	0	0	0	0	0
105	0	0	0	0	0	0	0	0	0	0	0	0
106	±	0	0	0	0	0	0	0	0	0	0	0
107	0	0	0	0	0	0	0	0	0	0	0	0
108	0	0	0	0	0	0	0	0	0	0	0	0
109	0	0	0	0	0	0	0	0	0	0	0	0
110	0	0	0	0	0	0	0	0	0	0	0	0

Appendix I

Subject Demographics

Subject Number	Subject Initials	CRL ID #	Age	Sex
1	JY	01655	66	F
2	DM	13166	33	F
3	MS	13172	69	M
4	JE	04267	54	M
5	PC	01267	42	F
6	SH	13159	41	F
7	DH	13160	43	M
8	CM	00741	54	F
9	IN	03306	53	F
10	DB	07917	56	F
11	LH	06760	50	F
12	LD	06451	49	F
13	NQ	10096	53	F
14	SP	07635	52	F
15	DP	07845	25	F
16	SS	07667	22	F
17	BA	11465	40	F
18	RB	08755	33	M
19	HM	05830	54	M
20	EK	12838	43	F
21	JK	12839	51	M
22	KT	06277	44	F
23	PT	12224	38	F
24	IS	05528	58	F
25	DT	11225	29	F

Subject Number	Subject Initials	CRL ID #	Age	Sex
26	DK	12361	44	F
27	DC	12622	43	F
28	MW	06787	41	F
29	JH	10856	43	M
30	TH	00133	39	F
31	NW	11974	66	F
32	EM	12300	65	F
33	MG	13064	48	F
34	NS	13134	26	F
35	MO	13180	38	F
36	SG	11518	42	F
37	LC	04359	40	F
38	CS	06243	64	F
39	JM	08727	48	F
40	LT	12033	52	F
41	ST	04268	39	M
42	LH	13156	39	M
43	PF	05623	38	F
44	ES	09428	51	F
45	GD	04511	55	F
46	JR	01117	34	M
47	LC	05000	37	F
48	CW	13178	53	F
49	AS	05552	46	F
50	GE	12153	34	F

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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Alexandra Kowcz
Industry Liaison to the CIR Expert Panel

DATE: February 23, 2018

SUBJECT: Draft Report: Safety Assessment of Triphenyl Phosphate as Used in Cosmetics (draft prepared for the March 5-6, 2018 CIR Expert Panel Meeting)

The Council respectfully submits the following comments on the draft report, Safety Assessment of Triphenyl Phosphate as Used in Cosmetics.

Key Issues

It would be helpful to note in the Introduction that NTP has a number of ongoing studies on Triphenyl Phosphate including a 2-week dietary study in rats and a one generation dietary study in rats (see: https://ntp.niehs.nih.gov/testing/status/agents/ts-11042-j.html).

The mouse sensitization study cited to the OECD SIDs data set (reference 4) and ECHA (reference 12) in the text and to ECHA in Table 5 appears to be an NTP study (IMM92060) for which a summary is available at: https://ntp.niehs.nih.gov/testing/types/imm/abstracts/imm92060/index.html . This summary indicates that there were 8 mice in each group.

The following recently published studies should be added to the CIR report:

Frederiksen M, Stapleton HM, Vorkamp K et al. 2018. Dermal uptake and percutaneous penetration of organophosphate esters in a human skin ex vivo model. *Chemosphere* 197: 185-192 (Epub 2018 Jan 10) (DOI: 10.1016/j.chemosphere.2018.01.032).

Philbrook NA, Restivo VE Belanger CL et al. 2018. Gestational triphenyl phosphate exposure in C57Bl/6 mice perturbs expression of insulin-like growth factor signaling genes in maternal and fetal liver. *Birth Defects Res* Jan 8 doi: 10.1002/bdr2.1185.

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Additional Considerations

Definition - Please revise: "function as a plasticizer in cosmetic ingredients" to "function as a plasticizer in cosmetic products"

Cosmetic Use - As Triphenyl Phosphate is only used in 4 FDA product categories, a table showing the reported uses in these four categories should be added to the report.

Please revise the following sentence: "Nail enamels were reported to be up used at up to 11.9% and nail lotions were reported to be used at up to 1%." It was Triphenyl Phosphate that was reported to be used at concentrations up to 11.9% in nail polish and up to 1% in nail lotions.

ADME - Please also state the average urinary concentrations of diphenyl phosphate that were found when the subjects applied the nail polish to synthetic nails on gloves.

DART - In the second paragraph describing the rabbit study, it states: "visceral and skeletal developmental malformations or variations, visceral variations". The last "visceral variations" needs to be deleted.

Endocrine Activity - Please delete "endocrine disruption" from this section and state what they examined. They looked at testosterone levels in the testes and effects on genes related to testosterone synthesis, other endocrine-related endpoints were not examined.

Immunotoxicity - How did the lymphoid organ weights vary? Did they see increases or decreases in organ weights?

Summary - Instead of saying that Triphenyl Phosphate "was found to induce oxidative stress and endocrine activity", the Summary should state that Triphenyl Phosphate decreased testicular testosterone levels at 300 mg/kg.

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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Alexandra Kowcz
Industry Liaison to the CIR Expert Panel

DATE: April 4, 2018

SUBJECT: Tentative Report: Safety Assessment of Triphenyl Phosphate as Used in Cosmetics (released March 15, 2018)

The Council respectfully submits the following comments on the draft report, Safety Assessment of Triphenyl Phosphate as Used in Cosmetics.

Provocative Studies - Please correct: "no sensitization was not observed in 174 patients with suspected occupational dermatosis" (delete not)

Table 2, Oral - Four studies in the oral subsection of Table 2 say: "route of administration not reported." If it was not clear that these studies were oral exposure, they should not be included in the oral subsection. If the studies were oral, but the method of oral exposure was not stated, "route" of administration should be changed to "method" of administration, or as is stated for other studies, it could say: "no further details provided."

Table 2, Inhalation - "LD_{50}" should be changed to "LC_{50}"

Table 3, Short-Term Oral - Please correct "no other gross histopathological findings were observed". As "gross" is used for effects observed directly (with out magnification), and histopathological effects are those observed with a microscope, it is likely that "or" is missing between "gross" and "histopathological".

Please correct: "increase in livers weight"; and there seems to be something missing from the following: "...total and differential white cell count, or during necropsy were observed"

Table 4 - Please use the symbol "μ" for micro rather then the letter "u" throughout Table 4.

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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: CIR Science and Support Committee of the Personal Care Products Council

DATE: April 10, 2018

SUBJECT: Tentative Report: Safety Assessment of Triphenyl Phosphate as Used in Cosmetics (release date March 15, 2018)

We appreciate the opportunity to comment on the tentative report, Safety Assessment of Triphenyl Phosphate as Used in Cosmetics.

The descriptions of studies in the Endocrine Activity section should be consistent with the CIR Precedents Document titled "Endocrine Activity" found at https://www.cir-safety.org/sites/default/files/CIR%20Precedents%20-%20Endocrine%20Activity.pdf. This document states: "In 2002, the World Health Organization (WHO) International Program on Chemical Safety (IPCS) defined an EDC [endocrine disrupting chemical] as "an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations." By this definition, EDCs cause adverse health effects in living organisms specifically by altering the function of the endocrine system.

This definition has three important elements:

- The substance must act through an endocrine MOA that alters the function of the endocrine system
- The substance must cause an adverse health effect
- The adverse effect must be causally related to, and occur as a consequence of, the altered endocrine function

All three of these elements are necessary to identify a chemical as an EDC."

Although, references 20 and 21 in the CIR tentative report on Triphenyl Phosphate, used the term "endocrine disruption", they did not determine if the effect on testosterone was through an endocrine mode of action. When describing these studies it is not necessary to repeat the authors conclusion, e.g., Triphenyl Phosphate could induce oxidative stress and endocrine disruption. In

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addition, the term "endocrine activation" is not an appropriate replacement for "endocrine disruption". In the Endocrine Activity and Summary sections, please describe what was examined and the results (e.g., decreases in body weight and testes weight and decreased testosterone) without adding a label to indicate what was observed.