Safety Assessment of Bis-Trimethylbenzoyl Phenylphosphine Oxide, Ethyl Trimethylbenzoyl Phenylphosphinate, and Trimethylbenzoyl Diphenylphosphine Oxide

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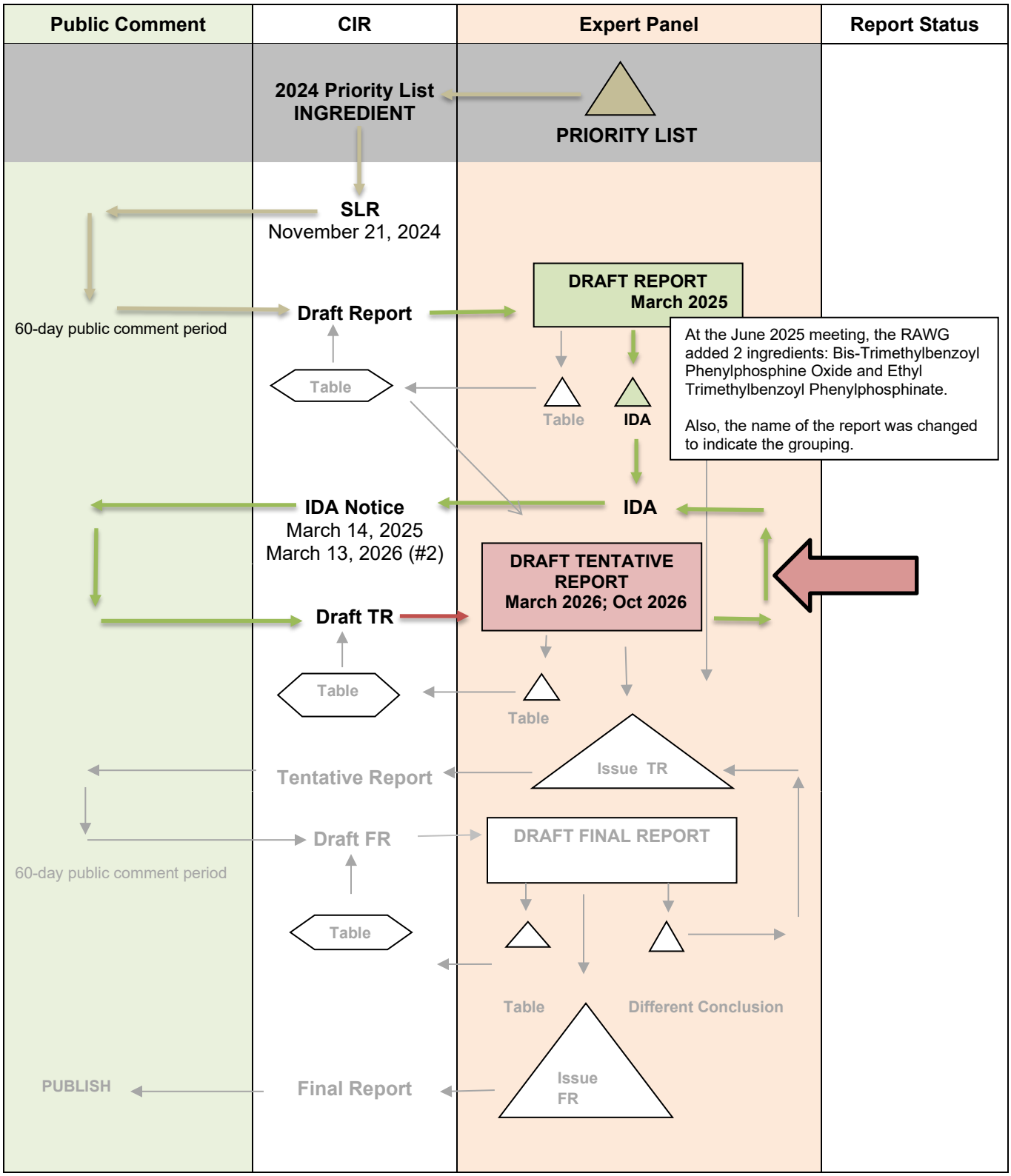
The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Bruce A. Brod, M.D., M.H.C.I., F.A.A.D.; Samuel M. Cohen, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel member involved in this assessment: David E. Cohen, M.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume, M.B.A. This safety assessment was prepared by Priya Ferguson, M.S., Associate Toxicologist & Senior Scientific Analyst/Writer, CIR, and Jinqiu Zhu, Ph.D., D.A.B.T., E.R.T., D.C.S.T., CIR Toxicologist.

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SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Phosphine Oxides & Phosphinate Ingredients
MEETING October 2026



COSMETIC INGREDIENT REVIEW
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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Ferguson, M.S.
Associate Toxicologist/Senior Scientific Analyst/Writer, CIR
Date: September 11, 2026
Subject: Safety Assessment of Bis-Trimethylbenzoyl Phenylphosphine Oxide, Ethyl Trimethylbenzoyl Phenylphosphinate, and Trimethylbenzoyl Diphenylphosphine Oxide

Enclosed is the Draft Tentative Report of the Safety Assessment of Bis-Trimethylbenzoyl Phenylphosphine Oxide, Ethyl Trimethylbenzoyl Phenylphosphinate, and Trimethylbenzoyl Diphenylphosphine Oxide as Used in Cosmetics (*report_PhosphineOxides_102026*). At the March 2025 meeting, the Panel reviewed the Draft Report on Trimethylbenzoyl Diphenylphosphine Oxide and issued an IDA for the following data:

- Concentration of use in non-nail products
- Dermal irritation and sensitization at maximum use concentration for the skin
- Ocular irritation data (preferably at concentrations for products resulting in eye exposure, once received)
- Margin of exposure (MOE) calculation
- Phototoxicity/photosensitization data

At the June 2025 meeting, the Read-Across Working Group (RAWG) determined that 2 structurally similar ingredients from the 2026 Priority List (Bis-Trimethylbenzoyl Phenylphosphine Oxide and Ethyl Trimethylbenzoyl Phenylphosphinate) should be added to the report. Accordingly, a Draft Tentative Report on these 3 ingredients was prepared and reviewed at the March 2026 meeting, and a second IDA was issued for the following data:

- For all ingredients:
  - Sensitization data at maximum use concentration
  - Phototoxicity/photosensitization data (not nail products)
  - Concentration of use in non-nail products
- For Bis-Trimethylbenzoyl Phenylphosphine Oxide and Ethyl Trimethylbenzoyl Phenylphosphinate:
  - Impurities
  - Method of manufacturing
- For Trimethylbenzoyl Diphenylphosphine Oxide:
  - Dermal irritation at maximum use concentration

Since the IDA was issued, CIR received an unpublished data submission that included systemic exposure and skin sensitization risk assessments for Bis-Trimethylbenzoyl Phenylphosphine Oxide and Ethyl Trimethylbenzoyl Phenylphosphinate as used in UV/LED-curable nail products (*data1_PhosphineOxides_102026*). The systemic exposure assessment considered incidental periungual exposure scenarios and applied model-derived adjustment factors to estimate exposure via the nail-plate; these factors were not based on experimentally measured nail permeation. In the MOE calculation, the submission used concentrations of 5.6% for Ethyl Trimethylbenzoyl Phenylphosphinate and 0.69% for Bis-Trimethylbenzoyl Phenylphosphine Oxide, although the sources of these concentrations were not identified. CIR staff further recalculated the MOE for Ethyl Trimethylbenzoyl Phenylphosphinate using the maximum concentration of 6.2% that was reported in the Council's 2025 survey; no concentration of use was reported for Bis-Trimethylbenzoyl Phenylphosphine Oxide in that survey. Two supporting published references concerning nail plate permeation and consumer exposure to nail cosmetics (Yin et al. 2024; Ficheux et al. 2014) were also submitted. These new data have been incorporated into the report in highlighted text.

Supporting documents for this report package include a flow chart (*flow_ PhosphineOxides_102026*), report history (*history_PhosphineOxides_102026*), a search strategy (*search_PhosphineOxides_102026*), a data profile (*dataprofile_PhosphineOxides_102026*), and transcripts from previous meetings (*transcripts_PhosphineOxides_102026*).

A draft Abstract and Discussion have been included in this report version. The Panel should carefully consider and discuss the data (or lack thereof) and be prepared to issue a Tentative Report with a safe, safe with qualifications, insufficient data, unsafe, or split conclusion, and identify any additional items for inclusion in the Discussion.

For the Panel's reference, tables summarizing the insufficiencies/data requests identified in both the first and second IDAs are provided below. Please note that several of the insufficiencies identified in the first IDA overlap with those identified in the second IDA.

IDA 1 on Trimethylbenzoyl Diphenylphosphine Oxide

Insufficiency/Data Requests (March 2025)	Data received/available?
concentrations of use in non-nail products	no
dermal irritation and sensitization at maximum use concentration for the skin	no
ocular irritation data (preferably at concentrations for products resulting in eye exposure, once received)	no
MOE calculation	yes
phototoxicity/photosensitization data	no

IDA 2 on Bis-Trimethylbenzoyl Phenylphosphine Oxide, Ethyl Trimethylbenzoyl Phenylphosphinate, and Trimethylbenzoyl Diphenylphosphine Oxide

Insufficiency/Data Requests (March 2026)	Data received/available?	Details
sensitization data at maximum use concentrations for all ingredients	no	Sensitization data at maximum use concentrations were not provided; however, a skin sensitization risk assessment for Bis-Trimethyl-benzoyl Phenylphosphine Oxide and Ethyl Trimethylbenzoyl Phenylphosphinate was submitted.
phototoxicity/photosensitization data (not nail products) for all ingredients	no	-
concentrations of use in non-nail products for all ingredients	no	-
impurities data on Bis-Trimethylbenzoyl Phenyl-phosphine Oxide and Ethyl Trimethylbenzoyl Phenylphosphinate	no	-
method of manufacturing data on Bis-Trimethyl-benzoyl Phenylphosphine Oxide and Ethyl Trimethylbenzoyl Phenylphosphinate	no	-
dermal irritation at maximum use concentration for Trimethylbenzoyl Diphenylphosphine Oxide	no	-

Phosphine Oxide and Phosphinate History

November 2024
- SLR posted

December 2024
- 6-wk use study received on products containing Trimethylbenzoyl Diphenylphosphine Oxide (base, color, and top coat containing 0.25, 3.65, and 1.5%, respectively)
- Comments on SLR received by Personal Care Products Council (PCPC)

March 2025
- Panel reviews Draft Report on Trimethylbenzoyl Diphenylphosphine Oxide and Panel issued IDA for following data:
  -Concentrations of use in non-nail products
  -Dermal irritation and sensitization data at maximum use concentration for the skin
  -Ocular irritation data (preferably at concentrations for products resulting in eye exposure, once received)
  -Margin of exposure (MOE) calculation
  -Phototoxicity/photosensitization data
- Comments on Draft Report received by PCPC

June 2025
- The Read-Across Working Group (RAWG) determines that 2 structurally-similar ingredients from the 2026 Priority List be added to the report (Bis-Trimethylbenzoyl Phenylphosphine Oxide and Ethyl Trimethylbenzoyl Phenylphosphinate)
- Concentration of used data received for the 2 new additions

October 2025
- updated concentration of use data received on TPO

November 2025
- Comments on Draft Tentative Report received from PCPC

March 2026
- Panel reviews a Draft Tentative Report on Bis-Trimethylbenzoyl Phenylphosphine Oxide, Ethyl Trimethylbenzoyl Phenylphosphinate, and Trimethylbenzoyl Diphenylphosphine Oxide and issues an IDA:
  - For all ingredients:
    - Sensitization data at maximum use concentration
    - Phototoxicity/photosensitization data (not nail products)
    - Concentration of use in non-nail products
  - For Bis-Trimethylbenzoyl Phenylphosphine Oxide and Ethyl Trimethylbenzoyl Phenylphosphinate:
    - Impurities
    - Method of manufacturing
  - For Trimethylbenzoyl Diphenylphosphine Oxide:
    - Dermal irritation at maximum use concentration

July 2026
- New data received: systemic exposure and skin sensitization risk assessment for Bis-Trimethylbenzoyl Phenylphosphine Oxide and Ethyl Trimethylbenzoyl Phenylphosphinate; nail and skin tolerability assessment received

October 2026
- Panel reviews Draft Tentative Report
- Dermal irritation data at maximum concentration of use

Phosphine Oxides and Phosphinate Ingredients Data Profile* – October 2026 – Writer, Priya Ferguson																														
				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	Method of Mfg	Impurities	log P/log K_{ow}	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Bis Trimethylbenzoyl Phenylphosphine Oxide	**X**			X			X	X			X			X	X					X	X			X					X		
Ethyl Trimethylbenzoyl Phenylphosphinate	**X**		X	X			X	X	X		X			X	X					X	X			X					X		
Trimethylbenzoyl Diphenylphosphine Oxide	**X**	**X**		X			X	X			X			X	X					X	X			X	X				X		

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

Phosphine Oxides and Phosphinate Ingredients

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
Bis-Trimethylbenzoyl Phenylphosphine Oxide	162881-26-7					X				X							
Ethyl Trimethylbenzoyl Phenylphosphinate	84434-11-7	X				X				X				X			
Trimethylbenzoyl Diphenylphosphine Oxide	75980-60-8	X		X		X			X	X			X	X			X

"X" indicates data were found

Search Strategy

- The following terms were searched in the links below:
  - Trimethylbenzoyl Diphenylphosphine Oxide
  - Diphenyl(2,4,6-Trimethylbenzoyl)Phosphine Oxide
  - 75980-60-8
  - Methanone, (diphenylphosphinyl)(2,4,6-trimethylphenyl)-
  - Bis-Trimethylbenzoyl Phenylphosphine Oxide
  - 162881-26-7
  - Ethyl Trimethylbenzoyl Phenylphosphinate
  - 84434-11-7

LINKS

Search Engines

- Pubmed - http://www.ncbi.nlm.nih.gov/pubmed
  - appropriate qualifiers are used as necessary
  - search results are reviewed to identify relevant documents
- Connected Papers - https://www.connectedpapers.com/

Pertinent Websites

- wINCI - https://incipedia.personalcarecouncil.org/winci/ingredient-custom-search/
- FDA Cosmetics page - https://www.fda.gov/cosmetics
- eCFR (Code of Federal Regulations) - https://www.ecfr.gov/
- FDA search databases: https://www.fda.gov/industry/fda-basics-industry/search-databases
- Substances Added to Food (formerly, EAFUS): https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus
- GRAS listing: https://www.fda.gov/food/food-ingredients-packaging/generally-recognized-safe-gras
- SCOGS database: https://www.fda.gov/food/generally-recognized-safe-gras/gras-substances-scogs-database
- Inventory of Food Contact Substances Listed in 21 CFR: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=IndirectAdditives
- Drug Approvals and Database: https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases

- FDA Orange Book: https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book
- OTC Monographs - https://dps.fda.gov/omuf
- Inactive Ingredients Approved For Drugs: https://www.accessdata.fda.gov/scripts/cder/iig/
- FEMA (Flavor & Extract Manufacturers Association) GRAS: https://www.femaflavor.org/fema-gras
- HPVIS (EPA High-Production Volume Info Systems) - https://iaspub.epa.gov/oppthpv/public_search.html_page
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
    - technical reports search page: https://ntrl.ntis.gov/NTRL/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- EUR-Lex - https://eur-lex.europa.eu/homepage.html
- Scientific Committees (SCCS, etc) opinions: https://health.ec.europa.eu/scientific-committees_en https://health.ec.europa.eu/scientific-committees/scientific-committee-consumer-safety-sccs_en
- ECHA (European Chemicals Agency – REACH dossiers) – https://echa.europa.eu/
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- EFSA (European Food Safety Authority) - https://www.efsa.europa.eu/en
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- AICIS (Australian Industrial Chemicals Introduction Scheme)- https://www.industrialchemicals.gov.au/
- International Programme on Chemical Safety http://www.inchem.org/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) IRIS library - https://apps.who.int/iris/
- a general Google and Google Scholar search should be performed for additional background information, to identify references that are available, and for other general information - www.google.com https://scholar.google.com/

MARCH 2025 MEETING – FIRST REVIEW/DRAFT REPORT

Belsito Team – March 13, 2025

DR. SNYDER: Trimethylbenzoyl Diphenylphosphine Oxide, that's a handful. Okay. All right. Okay. Is everything good, Priya?

MS. CHERIAN: Yes.

DR. SNYDER: You sure?

MS. CHERIAN: Yes.

DR. SNYDER: Okay. All right. So, this is a draft report. We issued an SLR in November of 2024. There is an irritation potential with gel nail application. This draft report, on PDF Page 4 of 52, there were comments from PCPC. There's new 2024 RLD data which says that the maximum concentration of use is four percent in nail polishes. There is an ingestion potential with lipstick use. There's eye area use.

There's children uses, inhalation potential, airbrush delivery, too. Airbrush delivery is also a reported use, and it's a restricted use in the EU on nails at five percent in professional use only. Okay. So I'll open it up for comments.

DR. SNYDER: Okay. So, what are your comments or issues?

DR. BELSITO: Well, I mean it's applied to the nails and 10-day rapidly consumed. So, do we need systemic endpoints or even sensitization? But it apparently has photo absorption. Right? And then, non-nail use I thought was insufficient. We don't have concentration and we'd need to do margin of exposure calculations. No?

DR. SNYDER: Yes, I agree.

DR. BELSITO: So, I thought it was potentially safe for nails except for the issue of the photo. Right? It says it absorb -- PDF Page 14. It absorbs ultraviolet light in UVA, UVB, and UVC bands with three primary peaks. All of them are important, 385, 290 and, 235. Or I'm sorry, two of them are important, 290 and 385.

DR. RETTIE: So, Don, when you irradiate this so that you get the photo initiation process underway for nail hardening, you split this thing in half. You still got chromophores, though. But the data that we have for UV absorption is for the whole molecule. And I think that's not relevant to the phototoxicity of the split products after UV or the rest of that.

DR. BELSITO: So, you think it occurs so quickly that it's not an issue? Is that what you're saying, Allan?

DR. RETTIE: I wanted to know what stoichiometry was and the rate and what's left. Is it like hair dyes where ultimately, after oxidation, we don't worry about the actual aromatic amine, the original one, because it's all been consumed. I don't know how much of this is consumed in the UV process. When they shine the light on, that's only for a few minutes, I believe, or even a few seconds. It's a very rapid process. In fact, these photo initiators are chosen in part for, my understanding, how fast they react.

So, we still need to consider UV absorption, but we might not need to consider UV absorption only for the intact molecule.

DR. SNYDER: Whole molecule. Got you.

DR. BELSITO: But we would need to consider for non-nail uses. Right?

DR. RETTIE: Yes.

DR. SNYDER: So, for non-nail uses, we're going to be insufficient, Don?

DR. BELSITO: Is this the one cosmetic use application where, in Europe, it's limited to nail salons?

DR. SNYDER: Yes, professional use only.

DR. BELSITO: Right.

DR. SNYDER: It's limited to 5 percent, professional use only. It's on Page 16. Yeah.

DR. BELSITO: Right. So, I guess my concern is that -- this gets back, as you recall, Paul, to our whole discussion on ethyl methacrylate in nail products. Right?

DR. SNYDER: Yep. Yep.

DR. BELSITO: And, you know, protecting the application to the skin and not the nail and what happens when you get it on the skin? We actually were having that discussion on 9/11, if you recall.

DR. SNYDER: Yep.

DR. BELSITO: So, I mean, I would like to hear, from the Cohen team. I guess I get your point, Allan. When you apply to the nail, I don't think I'm worried about photo onycholysis, where you get the nail plate separating from the nail bed. I would worry about photo allergy on the skin from this application by consumers.

DR. RETTIE: Right.

DR. BELSITO: And is that our purview? Right? I mean, it's not intended to be applied to the skin, at least for nail products. I mean, I think it's insufficient for non-nail use. We need concentrations of use and margin of exposure calculations.

DR. RETTIE: I wondered about that, too, Don. And I had the question, since I don't frequent my local nail salon, when you get professional application of these things, do they not put something around? They don't? They just lather it on, and that's it?

MS. FIUME: Yes.

DR. SNYDER: Okay. I don't always say lather it on.

MS. FIUME: Professionals typically don't apply on your skin.

MS. CHERIAN: But you can purchase this, and you're doing it yourself, I'm going to tell you it gets on your skin.

DR. BELSITO: And I guess, in the PDF Page 22, where we have these other reported uses, when I looked at them my thought was, with the possible exception of eyelash adhesives, why would you be putting this in a lipstick or a makeup or children's foundation? I mean it's to accelerate an adhesive.

DR. ZANG: I have a question on Table 2. I believe you probably noticed that, too, this table has this as Inositol.

MS. CHERIAN: It's just a header. It's a typo. But the information is correct.

DR. ZANG: Got you.

MS. FIUME: We were just checking the information to make sure it is correct.

DR. ZANG: Okay.

MS. FIUME: And, those 27 other preparations, we have no idea what those are that are in the RLD now.

DR. BELSITO: Right.

MS. FIUME: They don't fit into any other category.

DR. BELSITO: But I guess we have to accept what the RLD tells us as where it's being used.

DR. SNYDER: Yeah.

DR. BELSITO: I think the data is insufficient. We need concentration of uses, and we need to look at risks. I think the biggest one would be photo.

DR. SNYDER: Yeah.

MS. FIUME: So, with that -- I'm sorry.

DR. BELSITO: Safe for nails. Insufficient for either.

DR. SNYDER: Yep.

MS. FIUME: But this is a draft report, so an IDA would need to go out first.

DR. SNYDER: Yep.

MS. FIUME: So, for the UV, would it be UV spectra and if absorbed?

DR. SNYDER: Yeah. Yeah.

DR. BELSITO: We have the spectra.

MS. FIUME: Okay.

DR. BELSITO: We know it's absorbed.

MS. FIUME: So, the phototox data.

DR. BELSITO: I just think that, you know, if you put it on the nail, I'm not concerned about photo effects. But how quickly is this being consumed? And, if you're using it in a sensitive area, like to apply artificial eyelash as an eyelash adhesive, how safe is that? How safe is it in the children's foundation?

DR. RETTIE: How you get it off? Isn't it permanent?

MS. FIUME: Makeup remover.

DR. ZANG: Yeah.

DR. BELSITO: What did you say, Allan? I'm sorry.

DR. RETTIE: Yeah. I read that you use it as an eyelash adhesive, and I just wondered about that.

DR. BELSITO: Yeah, for artificial eyelashes

MS. CHERIAN: There's some long-term ones, and there's some shorter term ones. I'm not sure which ones it's used in or both.

MS. FIUME: So, the IDA is for all four non-nail use?

DR. SNYDER: Yeah.

DR. BELSITO: Yes.

MS. FIUME: So, is it phototox?

DR. SNYDER: Since they're going out the first time.

MS. FIUME: So, is it phototox data?

DR. SNYDER: Yes, the UV spectra indicates that there's a potential for phototoxicity/photosensitization. So, you want that data in?

MS. FIUME: Okay. So phototox which is photosense?

DR. SNYDER: Yeah.

MS. FIUME: Okay.

DR. SNYDER: Right, Don?

DR. BELSITO: Yeah. I mean, I think we need use concentrations for all those categories.

DR. SNYDER: Yep.

DR. BELSITO: And then, you'll get a better idea of how quickly this photo initiator is consumed in those products. I'm very concerned about this being used other than it now is. It clearly is a UV absorber. I mean that's why it's put into the adhesive.

DR. SNYDER: Right. Yeah.

DR. BELSITO: It's the whole mechanism of the activation. Well, I was just curious. There were lots of DART effects seen. I didn't really think a lot about them but what was your thought?

DR. SNYDER: Same for me. I didn't see any reason to raise concern, Don, for the use. Yeah.

DR. BELSITO: Okay.

DR. RETTIE: Table 4 gave a pretty high NOAEL.

DR. SNYDER: Yeah.

MS. FIUME: So, the tox data are fine with that lips gloss use?

DR. SNYDER: Yeah. Yeah.

MS. FIUME: Okay. Great.

DR. RETTIE: You got a minor typo, Schlink, Schlip, Schlenk. You got Schluck (phonetic). I'll send it. It's no big deal.

MS. CHERIAN: Thank you.

DR. RETTIE: I had a question for the team. Maybe you guys can educate me about penetration through the nail plate. I never thought about penetration through the nail plate. But I found in the SCCS document where they say it's unlikely to penetrate the nail plate.

DR. KLAASSEN: Correct.

DR. RETTIE: I look at it, and I would say ,hey, it's pretty hydrophobic. Hasn't it got a shot at getting through membranes? But I guess a nail plate is not a membrane.

DR. SNYDER: No. No.

DR. BELSITO: No. Nail plate is pretty dead and pretty impermeable.

DR. RETTIE: And then, AI told me that small polar molecules tend to penetrate the nail plate better. Is that right?

DR. SNYDER: Out of my expertise.

DR. BELSITO: What was your comment, Allan?

DR. RETTIE: It was just a comment for my own edification. I wondered if it was correct that small polar molecules tended to get through the nail plate better because that's what AI told me. I had no way to evaluate that, but I thought somebody here would.

DR. BELSITO: I think AI is just saying the smaller the molecule the greater the chance it'll penetrate. But the nail bed, the nail plate, I don't think it's an issue.

DR. RETTIE: It was a polarity that I had an issue with. But this is not important. I don't believe AI for everything.

DR. SNYDER: Okay. so we're gonna go safe for nail use, and then we're gonna go non-nail uses is insufficient date announcement. We need concentration of use for the non-nail uses, possibly a margin of exposure calculation. And then, based on the phototox data, we need phototox and photosensitization data for those non-nail uses.

DR. BELSITO: Correct.

DR. SNYDER: Okay. Thank you.

Cohen Team – March 13, 2025

DR. DAVID COHEN: Okay. We have a draft report for Trimethylbenzoyl Diphenylphosphine Oxide. And so this may bring up another conversation.

This ingredient is reported to function in cosmetics as an artificial nail builder. The RLD indicates that Trimethylbenzoyl Diphenylphosphine Oxide is used in over 1,800 formulations, including manicuring preparations, make-up, fragrances, eye make-up preparations, children make-up preparations, not eye. So one point for discussion, when we open it, is as a function as a nail builder and wind up with all of these uses, right? So that's something. It's used in products that may be incidentally ingested. It's used near the eyes, in eyelash, eyebrow adhesives, glues, and sealants. And it's used in children, in children's foundations.

The VCRP had it in 127 formulations. And in 2023, the maximum use was 4 percent in nail polishes and enamel. We have sensitization study, but I think we need to discuss that further. LLNA suggests that it would be sensitizing and it's irritating to the eyes. So before I go to my conclusions, why don't we just open it up? Sam, you want to lead off?

DR. SAMUEL COHEN: Yeah. This one, I found it a bit confusing because it was mainly as the artificial nail builder, and that's really as a polymer, and is of really little toxicity issues because the polymer is not going to be absorbed. It's not going to be an issue.

The LD-50 of the chemical itself is very high, so this is not a toxic chemical. In the tox studies that we have, it was generally a NOAEL of about 100 milligrams per kilogram, so it's not very toxic. There's a 90-day rat study.

Developmental tox didn't show any developmental or repro tox. Genotox was generally negative. There was a common assay in vitro that was positive, but I don't know how to interpret in vitro common assays, because you always have a cytotoxicity issue there, which if you kill cells, you're going to damage DNA, so I don't put much stock in that.

It was sensitizing in mice at high concentrations, but the data in humans seemed to indicate that it wasn't sensitizing, so I had some issue there. But it did indicate there's some ocular irritation, so I would be concerned about this in baby products or in eye products related to that.

There really is not much data there for what the levels are in other products besides the nail products, so I thought that there was insufficient data for that. And we need that kind of information for these other products.

DR. DAVID COHEN: When we issue an Insufficient Data Announcement, we need to hold our own feet to the fire, specifically what we're asking for. So, in your IDA, what do you want to know?

DR. SAMUEL COHEN: I'd like to know what the levels are in the products that are not the nail.

DR. DAVID COHEN: Concentrations in non-nail products?

DR. SAMUEL COHEN: Right.

DR. DAVID COHEN: Okay.

DR. SAMUEL COHEN: Because I couldn't find it in there.

DR. DAVID COHEN: Yeah.

DR. SAMUEL COHEN: If it was there, I couldn't find it. But other than that, I think this is a very non-toxic substance, but I would be concerned about ocular irritation based on the studies that we were provided.

DR. DAVID COHEN: You would not be?

DR. SAMUEL COHEN: I would be.

DR. DAVID COHEN: Okay. I didn't know if I heard you right. Susan?

DR. TILTON: I agree with those comments. I guess I did note some reproductive toxicity. Again, this is at milligrams per kilogram. But in terms of use, majority of uses are manicuring products. And we really are missing information about concentrations for how it might be used in any other product. And so, I would say we're certainly insufficient for considering use outside of nail products.

DR. DAVID COHEN: Concentrations of use in non-nail products? You guys aligned? David?

DR. ROSS: Yeah, exactly the same. I think all of us had the same reading of this. When I looked at 1837 over 1845 uses were in nail, manicuring perhaps. So there's very few uses, but we got no information on the other uses at all. We need concentrations of the non-manicuring preparations.

The MOE agent adjusted it to 4 percent, I think, and I went through that calculation, and it looked okay. So thank you for doing that. And I think I had a couple of editorial changes; sections need to be deleted; sections need to be moved.

DR. DAVID COHEN: Sections need to be deleted?

DR. ROSS: Yeah, I had a couple of editorial things. There was a sensitization studies in nails section, PDF Page 18, and there was no concentrations. We didn't know what the concentrations were being used there. So I didn't see that as particularly helpful.

DR. DAVID COHEN: PDF what?

DR. ROSS: PDF Page 18. I didn't see that section as being particularly helpful to me unless I missed the concentration. But it was on sensitization in nails. So if we don't know the concentration, should we really put it in?

DR. DAVID COHEN: And so some of my issues were I think we need to pay more attention to how it's listed as a function, right? We always breeze by that. It functions as a nail builder. I'm not exactly sure how to define that in my head, but I got an ethereal understanding of what that means.

So, if it's a nail builder, what's it doing in lip glosses? What's it doing in children's foundation, right? It's a disconnect, and it's an irreconcilable disconnect.

DR. HELDRETH: I do think we have to be careful relying on functions, really, at all, honestly, for looking at risk and safety. We have to remember we're getting our functions for the report from the cosmetic ingredient dictionary. Those functions end up there not for safety, not for really any purposes of trying to evaluate the risk of these materials. But it's really for the purpose of a submitter is trying to get a name for their ingredient to go into the product. And they've submitted, oh, this is a nail builder. There's no vetting to that. There's no going back and checking to see if that's what everybody's doing.

And so, instead, I think we have to look to the RLD because that tell us, okay. There's these product categories out there. Because someone could put in, say, for example, something simple like citric acid, put it out there and say that this is there as a pH adjuster. Okay? It works very well as a pH adjuster. Carboxylic acid could do that. But it could also be a preservative. But if it's not listed as a function there, does that mean it's not a preservative?

I think what we have to do instead of looking at those functions for a risk assessment, we need to look at well, what's the product category? And then what do we think is going to be the worst-case scenario of human exposure for that ingredient in that product category instead of the function. Because, yeah, you're right, the functions often just don't make sense. And we even have functions like skin conditioning agent miscellaneous, which we know means nothing at all.

DR. DAVID COHEN: Right.

DR. HELDRETH: It's to replace the not reported use.

DR. DAVID COHEN: We open the report with it. I mean, it's the headline, right? And so maybe we shouldn't headline it that way.

DR. BERGFELD: We could say primary function because that's what we have.

DR. DAVID COHEN: I don't know if that's always -- in this case it is, but maybe it should be somewhere else, and we open the report that is used in these categories.

DR. HELDRETH: We could say it is primarily in nail products.

DR. DAVID COHEN: Primarily in these products. Because that got me all worked up. I looked at the sensitization study, and there's a nail sensitization study at 2.6 percent, right? And the LLNA is suggesting it's sensitizing.

And how they did this study, they applied a single coat using a brush on the nail, left on for ten minutes and wiped off. What kind of maximum use study is that where you leave it on de-vitalized keratinaceous material for ten minutes and then remove it, and then just do that a couple of times, and that's your sensitization study? I don't think that's how you would do a sensitization study.

DR. ROSS: Yeah, neither one had no concentration. There was two studies. Neither one had no concentration. Not one.

DR. EISENMANN: Well, I think it was like a six-week use study where they sent the product home with people and they had to break up --

DR. DAVID COHEN: Yeah, they changed it every two weeks.

DR. EISENMANN: Right.

DR. DAVID COHEN: But that's not sufficient for all the other uses.

DR. EISENMANN: Right. We're not supporting the other uses.

DR. DAVID COHEN: Right.

DR. EISENMANN: But traditionally, nail products, HRIPTs are not done on nail polish.

DR. DAVID COHEN: No, no, no. Yeah. Listen, if this was just on the nails, we probably wouldn't have the conversation. It's nail-building product, and then the next paragraph is, here are all the other places, including children's foundation. I didn't even know there was a product category called children's. Like, I don't know there's an aisle in the store that says, like, children's foundations.

DR. ROSS: I thought it was a charity organization. I had to look it up.

DR. DAVID COHEN: Come pick up your bag of Trimethylbenzoyl Diphenylphosphine Oxide at the door. I think we need irritation and sensitization at max use. And it's predicated on the concentration to non-nail products. All right? Otherwise, I don't see how we could --

DR. BERGFELD: No, this is a primary draft that we're looking at.

DR. DAVID COHEN: Yeah, it's early days.

DR. BERGFELD: Yeah. But at the present time, it's insufficient for children/baby products in eye.

DR. DAVID COHEN: Well, I have an IDA for concentration in non-nail products and irritation and sensitization at max use.

DR. ROSS: So, David, can I ask a question on that too?

DR. BERGFELD: You need to be specific. You'll do another nail study.

DR. ROSS: I mean, as you pointed out, we have that study at 3.69 percent, and that's not enough?

DR. DAVID COHEN: Which one?

DR. ROSS: Dermal, 50 percent was slightly irritating in rabbits, 3.69 percent in individuals three times a week for six weeks. That's the one I would refer to.

DR. DAVID COHEN: No, but that's on nails.

DR. ROSS: That's on nails?

DR. DAVID COHEN: That's on nails. But we have use in (inaudible) Skin.

DR. ROSS: Yeah.

DR. DAVID COHEN: Right? We have use on lips.

DR. ROSS: So the only dermal data we have is on rats.

DR. SAMUEL COHEN: Mice.

DR. ROSS: With some on rats and from this, Sam says there's some on mice.

DR. SAMUEL COHEN: High concentrations, that's what it says it was.

DR. ROSS: And then 50 percent was slightly irritating in rabbits.

DR. SAMUEL COHEN: But then it says that it was not sensitizing in humans.

DR. DAVID COHEN: The LLNA was sensitizing, right?

DR. ROSS: The LLNA sensitizing.

DR. DAVID COHEN: Sensitizing.

DR. TILTON: At 40 to 50 percent.

DR. ROSS: 27 percent.

DR. SAMUEL COHEN: But the data in humans was listed as nonsensitizing.

DR. DAVID COHEN: What data in humans do we have?

DR. SAMUEL COHEN: Not much.

DR. DAVID COHEN: Well, we have the nail stuff.

DR. ROSS: Yeah, the nail data.

DR. DAVID COHEN: You're applying it to non-immunologically-competent components, right? And the only way you'll detect allergies ectopically -- and I don't know when they're doing this study. Are they looking at lips, neck, eyelids, where you're going to passively transfer allergens up to the face, right?

So when you look at formaldehyde resins in nail polish, they present with eyelid dermatitis, lip, and face dermatitis, not around the cuticle or the fingers. When you're looking at acrylates on the nails, they typically present with cuticle and fingertip dermatitis. So, if they're just applying it to nails and wiping it off after ten minutes, I don't know what I'm supposed to be looking for from that.

DR. SAMUEL COHEN: Yeah, I would support irritation and sensitization at max use.

DR. DAVID COHEN: Yeah.

DR. BERGFELD: For the nail?

DR. DAVID COHEN: No.

DR. BERGFELD: No, for the other?

DR. DAVID COHEN: On skin.

DR. ROSS: Yeah.

DR. BERGFELD: Skin.

DR. DAVID COHEN: I'll put skin in the IDA because you mentioned that.

DR. ROSS: We have that and then the concentrations of use in the other products.

DR. DAVID COHEN: Concentration in non-nail products.

DR. ROSS: Yeah.

DR. BERGFELD: So you're actually saying safe for nail products and, at this point in time, insufficient for others?

DR. DAVID COHEN: No, actually, I'm not ready for that yet.

DR. BERGFELD: Okay.

DR. DAVID COHEN: I'm not ready for it because what if I get sensitization data at a certain concentration on the skin? We already know that you can transfer that if you don't properly use it. And we might want to caveat the conclusion a little bit.

DR. HELDRETH: Yeah, since it's an IDA, we don't have to make any kind of a conclusion anyway.

DR. DAVID COHEN: No. It's Phase 1 we're looking at.

DR. SRINIVASAN: Would you also like ocular irritation data as part of the IDA? I know you don't have a concentration, but if you had -- if you say that you are requesting concentrations in products that are not nail products, and you get a concentration on an ocular product, would you like ocular irritation?

DR. DAVID COHEN: Oh, yeah. I think that's a very good point. David, what do you think?

DR. ROSS: Sorry. I was drifting off there. Could you just repeat that?

DR. SRINIVASAN: Would you like to add ocular irritation data as part of the IDA? And if you get a concentration of use for ocular irritation, we can request that concentration.

DR. DAVID COHEN: Yeah, we would then come back and ask for it, right?

DR. SRINIVASAN: Yeah.

DR. ROSS: Yep. Yeah. I mean, in a new study like a HET-CAM or something. Yeah.

DR. DAVID COHEN: I have to go back, but I think it said it's in eye makeup preparations. And then it's in children's makeup preparations, parenthesis, not eye. By definition it is eye.

You ever see a -- many years ago when my five-year-old daughter was putting on makeup, it gets everywhere than where it's supposed to be, right? So, okay. We good on that?

DR. BERGFELD: Can I ask a question? I had some questions on the genotox studies. Were they okay?

DR. SAMUEL COHEN: Yeah, I think that the genotox were negative except for this one in the fibroblasts, which was an in vitro comment, which I don't think it is interpretable.

DR. BERGFELD: Thank you.

DR. SAMUEL COHEN: I think the others are much more meaningful, and they were across the board negative.

DR. ROSS: I would agree with that statement.

DR. SAMUEL COHEN: Well, in vitro should never be done.

DR. ROSS: Yeah.

DR. HELDRETH: Should we remove it from the report or just include in the discussion how we think it's not valid?

DR. SAMUEL COHEN: No, I think that it's data. You have to leave it in there so we're complete, but I think a comment saying that this can't -- in face of the other negatives, this is probably not meaningful.

DR. HELDRETH: Okay. Thank you.

DR. ROSS: On balance.

DR. TILTON: Just a question about the MOE. And we may get to this when we discuss the MOE resource document, but when we don't have absorption data, had we discussed defaulting to 100 percent absorption as a Tier 1?

DR. ROSS: I think it's a back-of-the-envelope calculation. I think you could as a Tier 1. I think SCCS -- Jinqiu, correct me if I'm wrong. SCCS had 50 percent as a default, if you do not have absorption data?

DR. TILTON: Yeah. And this is just an amended calculation of the SCCS based on 4 percent max concentration.

DR. ROSS: Yeah, I think -- do you want to comment, Jinqiu, about how you did that? I think you just extrapolated, right? Yeah. So that data was at 5 percent, and we had 4 percent. And so while he's setting up.

MR. ZHU: Yeah. It's 4 percent and not 100 percent. It's based on the actual dermal absorption data. But if you prefer to use the conservative value, we can recalculate that.

DR. ROSS: Susan's question was on the 100 percent, though, I think, right?

DR. TILTON: Just on the discussion that we had had for the MOE resource document about implementing 100 percent absorption or bioavailability where we had no other data.

DR. ROSS: I think we tried a few things with that. We've done Tier 1 where we've assumed 100 percent, and if it clears at a 100 percent, you're golden. I think you could go to 50 percent, which was SCCS recommendations?

MR. ZHU: Yeah. That's the default value from SCCS.

DR. ROSS: And then, previously, PCPC had said, well, if you've got concentrations which are much closer to that -- not the exact concentration. But if you've got concentrations that are much closer to the concentration that was used in the actual product, why not use that? And we've done that also if we've got concentrations that bracket the concentrations. And I think we've said in previous transcripts that we would go with that as well.

DR. DAVID COHEN: Yeah.

DR. ROSS: So I think this various approach is to do a Tier 1 and --

DR. TILTON: I mean there's no concern here.

MR. ZHU: It's also dependent on the route of exposure.

DR. EISENMANN: What troubled me that the -- this is an older SCCS opinion, I think. And I think they used 100 percent for dermal, but they adjusted the oral by 50 percent. And to me, it doesn't make sense to adjust the oral and then assume through the nails is going to be 100 percent.

DR. ROSS: Correct.

DR. EISENMANN: To me, you either use 100 for both or 50 percent for both. It doesn't matter. I think either way it comes out the same. But to me, does this make sense? And to me, no.

DR. ROSS: For Tier 1, I don't mind what you use. I think if I see a Tier 1 that's 100 percent, then it's fine. That's great.

DR. EISENMANN: I just didn't like 50 oral and 100 for nails.

DR. ROSS: It doesn't make intuitive sense, does it? No. But we can discuss that in the MOE document. I don't think it's specific to this document really.

DR. DAVID COHEN: Are we okay to move on?

DR. TILTON: Yes, I'm good.

DR. ROSS: I think so.

DR. DAVID COHEN: Okay. That was a good discussion.

Full Panel – March 14, 2025

DR. SNYDER: We issued an SLR in November of 2024, and then we received this report. We got updated 2024 RLD data of 2,024 uses. This is a photo-initiator. It's applied to the nails. So the Belsito Team had a split conclusion saying that it's safe for nails, and that its non-nail uses, it's an Insufficient Data Announcement. And the data needs would be concentration of use, a margin of exposure calculation and phototox data. Since we have a UV spectra that suggest that it's absorbs, we need phototox and photosensitization data.

DR. BERGFELD: So your motion is?

DR. SNYDER: Insufficient Data Announcement.

DR. BERGFELD: Comment?

DR. DAVID COHEN: I heard a split conclusion.

DR. SNYDER: I guess I retracted the initial one; we'll go Insufficient Data Announcement. And then in the Discussion, I should have left that for the Discussion.

DR. DAVID COHEN: Okay, so, what are the data needs that you guys -- I can give you our data. We suggested an IDA. We wanted concentration of use in non-nail products, irritation and sensitization at max use on skin product, and ocular irritation.

DR. BERGFELD: Did you have any other?

DR. DAVID COHEN: So maybe we could just merge our lists and create a unified motion.

DR. SNYDER: Yes, exactly, we wanted a margin of exposure calculation for the non-nail uses. And, then, because of that UV spectra on non-nail use prep, we thought we needed the phototox and photosensitization data.

DR. DAVID COHEN: That's a great idea. So, if your motion could be the IDA with those and ours?

DR. SNYDER: We agree.

DR. DAVID COHEN: Second.

DR. BERGFELD: Any further discussion then regarding an Insufficient Data Announcement? Seeing none, I'll call the question. All those in favor of the IDA? Unanimous again, thank you. And the next ingredient is a botanical -- I hope I pronounce it right -- Nelumbo nucifera, Dr. Cohen.

JUNE 2025 MEETING – RAWG DISCUSSION

RAWG – June 9, 2025

DR. RETTIE: Okay. Good. So the last time we met, and we looked at the priorities, a suggestion was made that we take the two light stabilizers that were not in the Trimethylbenzoyl Diphenylphosphine Oxide report -- no, the report we had in front of us was for the Phosphinates and the Phosphinate Oxide. So we were happy with the grouping of the phosphinates and the phosphinate oxide.

And the suggestion was made that we would add in the Diphenylphosphine Oxide into that report, because the structurally similarities are just very, very, very close. We've just replaced a phenyl group with an ester group. And certainly there'll be a little bit of metabolic difference, but it's a phosphine ester. It shouldn't be that huge. So the Read-Across Working Group recommended that you add in those two to that one report.

And, of course, we've got quite a few light stabilizers in the priorities report. There's the crylenes, the Tocrylene and Octocrylene, which are rather interesting compounds. They look very much like something that might bind to peptides to me. There are two of them in the proposed grouping, Tocrylene and Octocrylene. And I think that's good that they're grouped together.

But I think they're sufficiently different from the phosphinates that we should not add them in. We should leave them as a separate report with two crylenes. Anybody want to weigh in on that?

Okay. And so, before we finish with the light stabilizers there's Diethylhexyl Syringylidenemalonate, and I've been practicing that. And it's structurally even further away than the original phosphinate so I don't think we should be grouping them as a use group. They're distinct chemicals and so they should be left alone.

And then a final one I had is the Toluene-2,5 Diamine Sulfate, the allergen of the year for 2025. And the question posed to the read-across group was, how should we group Toluene-3,4 Diamine? Or should we look at it independently and consider a conclusion that commutes it to use not supported because it has no uses. The Panel is asked if they would like to adopt the strategy in the Admin Memo. For me, I'm happy with the strategy that was proposed, which I think Dr. Heldreth put together. So, I was good with that. You guys in the same boat?

DR. ROSS: Good with me.

DR. TILTON: Yes, I support.

DR. KLAASSEN: Yes.

DR. RETTIE: And that was really all I had in terms of read-across for the Priorities. We may identify others as we keep looking at them, but those are the ones with answers that popped out immediately.

DR. HELDRETH: That's all I was hoping for.

DR. RETTIE: Okay.

DR. ROSS: Was there a phthalate question? That's a different question. Do we have to cover that or not?

DR. RETTIE: Where's the phthalate question?

DR. HELDRETH: That's the Strategy Memo. That'll be on the agenda this afternoon.

DR. ROSS: Okay.

DR. RETTIE: Yeah, but it's separately. Okay, so if there are no more comments the RAWG group will disband for lunch. Thank you.

DR. HELDRETH: Thanks. And those of you that are a part of the lunch group, the Panel, the liaisons and the CIR Staff, the lunch is actually in a separate room on another floor. It's on the promenade floor. If you need help finding there, Carla or a CIR staff member will be happy to help you find it.

MARCH 2026 MEETING – SECOND REVIEW/DRAFT TENTATIVE REPORT

Belsito Team – March 12, 2026

DR. BELSITO: Okay, next we're moving on to the Phosphinates, which are Phosphine ingredients in the December report. So, at the June 2025 meeting, the Read Across Working Group determined that the two additional ingredients from the 2026 Priority list, Bis-Trimethylbenzoyl Phenylphosphine Oxide, Ethyl Trimethylbenzoyl Phenylphosphinate should be added to this report because they were structurally similar to the Trimethylbenzoyl Diphenylphosphine Oxide. And when we reviewed this in March of 2025, with only the Phosphine Oxide, we thought that there were insufficiencies for concentration of use in non-nail products, dermal irritation and sensitization data at maximum use concentration for skin, ocular irritation, margin of exposure calculations, and phototoxicity photosensitization.

Since that IDA, we've not received any of the requested data, but we do have updated 2025 concentration of use data for the Trimethylbenzoyl Diphenylphosphine Oxide. And because that value aligns with what the SCCS used in their margin of error calculation for the Dimethyl Phosphine Oxide, we used the same method of calculation.

In addition, CIR staff performed margin of exposures for Ethyl Trimethyl Diphenylphosphine Oxide, which used a concentration of 6.2 percent, nail polishes and enamels. And in terms of what's changed between 2024 and 2025, they were pretty similar but the Bis Trimethylbenzoyl Phenylphosphine Oxide now have reports in non-coloring hair preparations.

So, that's where we're at. Since that time, we've not received any concentration of use in non-nail products; we've not received irritation or sensitization at maximum concentration of use; we've not received ocular irritation; we do have a margin of exposure calculation, and we have no phototoxicity or photosensitization.

The margin of exposure, though, was for nail use and it wasn't for other uses, so I think that's important to keep in mind because it is used in kids' cosmetics, the Ethyl Trimethylbenzoyl Phenylphosphinate and the Trimethylbenzoyl Diphenylphosphine Oxide.

In addition, with the addition of the two new ingredients, we don't have method of manufacture for the Bis Trimethylbenzoyl Phenylphosphine Oxide or the Ethyl Trimethylbenzoyl Phenylphosphinate, so the two materials that we added in based on the Read Across Working Group. And impurities we don't have for the Bis Trimethylbenzoyl Phenylphosphine Oxide. We have data on 95 percent of Ethyl Trimethylbenzoyl Phenylphosphinate if that's sufficient for you.

In a one-gen reproductive toxicity study, Trimethylbenzoyl Diphenylphosphine Oxide, up to 600 mg/kg/bw, had an overall reproductive NOAEL that was sort of low at 60 mg/kg per day of body weight. And I think that material -- I didn't make a note on, but isn't that one that the EU has not approved? The SCCS? China?

DR. EISENMANN: Trimethylbenzoyl Diphenylphosphine is no longer allowed to be used in Europe. They haven't ruled on the other two.

DR. BELSITO: Right. It's classified as -- I guess it was the endocrine effect at 60 milligrams per kg per body weight, with reduced fertility, testicular abnormalities observed at the higher doses.

DR. SNYDER: Don, my notes say that EU classified it as a carcinogen, it's mutagenic and reprotoxin -- all three.

DR. BELSITO: No, "or." It's a CMR of 1B for toxic -- toxic for reproduction. So, it was the reproductive effect.

DR. SNYDER: Okay.

DR. BELSITO: That's all one class, muto and repro, and in this case it was repro that got classified.

DR. SNYDER: Okay, thank you for that clarification.

DR. BELSITO: Yeah, there's an "or." The other thing I want to hear from Sam, what NOAEL we use for a margin of exposure, unless the Comet assay makes this genotox. Because the genotox stuff was really pretty clear except for that Comet assay. I don't know if anyone here wants to comment or we want to hear what Sam has to say.

DR. RETTIE: Yeah, that was my note around the genotox, but of course I'd be interested to see what Sam has to say about it tomorrow.

DR. KLAASSEN: Other than that, it's pretty clean. But the Comet assay is a well-accepted assay, so let's see what he has to say.

DR. BELSITO: Yeah, and it's also, again, on the Trimethylbenzoyl Diphenylphosphine Oxide, the one that the EU has banned. The question is if we're doing margins of exposure, which one will we use for the -- would it be for the repro or the genotox if we couldn't get it with a Comet assay?

So, the cytotoxicity, it's really phototoxic. It says Bis Trimethylbenzoyl Phenylphosphine Oxide exhibited the highest cytotoxicity among the evaluator initiators. And at 50 mics, cell viability was approximately 40-45 under non-irradiated, and under irradiated, 35. So, there was a photo effect. And then the Ethyl Trimethylbenzoyl Phenylphosphinate also had a photo effect.

So, I think we have evidence that these are photo absorbers, so I also thought that they were insufficient for photosensitization and photo-irritation on the skin at concentrations of use.

DR. SNYDER: So we still have, basically, five insufficiencies: non-nail use, concentration of use, irritation and sensitization at maximum concentration, ocular irritation, phototox and photosensitization and irritation. Is that right?

DR. BELSITO: Yeah. And we need a margin of exposure, either for the DART or the genotox, depending upon which endpoint is most sensitive and what Sam thinks about the Comet assay versus all the other negative genotox studies. So, I had, for insufficiencies, method of manufacture for Bis Trimethylbenzoyl Phenylphosphine Oxide, Ethyl Trimethylbenzoyl Phenylphosphinate, impurities for the Bis Trimethyl, and if we're not happy with only having 95 percent of the Ethyl Trimethyl, we need that as well.

We need a calculation of margin of exposure, I thought, for the reproductive at 60 milligrams per kilogram per body weight per day for the Trimethylbenzoyl Diphenylphosphine oxide. We needed irritation at use concentration for Trimethylbenzoyl Phosphine oxide and need sensitization at use concentration for all three, phototox/photosensitization data for all three. That's what I had. Did you add something else that I missed, Paul?

DR. SNYDER: I had non-nail concentration of use.

DR. BELSITO: Oh, okay.

DR. SNYDER: And ocular irritation.

DR. BELSITO: Okay. Yeah, concentration of use in non-nail products, I had that; I guess I didn't mention that.

DR. SNYDER: I think that's it.

DR. EISENMANN: So my question is, do you need all these for the nail use? Because that's what our members really care about, the nail use, and that's all. I know there are other uses reported to FDA, but --

DR. BELSITO: Well, these are our needs, Carol. And then I think we can end up with a conclusion, safe for use in nails and insufficient for other reported uses, right?

DR. EISENMANN: Right.

DR. BELSITO: But at this point, we're going out with an insufficient conclusion based upon how we're told this material is being used, and we're being told that it's not just nail, right?

DR. EISENMANN: Right, but this is a tentative report, I think. So, if you change the conclusion the next time, you might have to go out again.

DR. HELDRETH: Yeah, I mean, what I'm hearing in the data needs, at least some of these are new data needs that were not in our original IDA. With the addition of the fact that we've added two ingredients since that IDA, I would suggest, instead of a Insufficient Data Conclusion, issuing a second IDA. That way, those that want to be part of the process have time to submit that information.

DR. BELSITO: Yeah. I think, obviously, we have to because we've gotten two new materials in which we're missing some data, and that's part of our data request, right? So, it wouldn't be fair to put this report on the same time schedule as the one where it was just the phosphine oxide we were looking at.

DR. HELDRETH: Right. So, it'll come back still as a Draft TR.

DR. BELSITO: Right.

DR. SNYDER: I'm okay with that.

DR. BELSITO: Okay. Let me just repeat the data needs so I make sure that we have them all. Non-nail concentration of use, manufacturing and impurities for Bis Trimethylbenzoyl Phenylphosphine Oxide and Ethyl Trimethylbenzoyl Phenylphosphinate, the latter only if we're not happy with the 95 percent. Are we happy with the 95 percent?

DR. RETTIE: I don't think so. There's some nasty things that go into making these, so we should err on the side of caution.

DR. BELSITO: Okay. Need impurities -- yeah, we need a margin of exposure, either for the repro or geno effect, concentration of use in non-nail products, irritation at use concentration for Trimethylbenzoyl Phenylphosphine Oxide, sensitization at use concentration for all three, phototox, photosensitization data for all three, and ocular irritation at concentration of use. Did I get everything, Paul?

DR. SNYDER: Yep, that matched up with what I had, Don. Nice job.

DR. BELSITO: Okay. Curt, Allan, anything else on this?

DR. KLAASSEN: No.

DR. RETTIE: No for me either.

Cohen Team – March 12, 2026

DR. DAVID COHEN: Let's see the next one. Okay. So, this is a Draft Tentative Report on Bis Trimethylbenzoyl Phenylphosphine Oxide, Ethyl Trimethylbenzoyl Phenylphosphinate, and Trimethylbenzoyl Diphenylphosphine Oxide. In addition, the report has been expanded to include two structurally related ingredients, Bis Trimethylbenzoyl Phenylphosphine Oxide, and Ethyl Trimethylbenzoyl Phenylphosphinate, based on structural similarities. Looking at cosmetic use, these ingredients are used primarily in nail products functioning as photo-initiators in UV-cured nail systems. They also have limited reported uses in other products.

At the March 2025 meeting, we issued an Insufficient Data Announcement, asking for concentration of use in non-nail products, dermal irritation and sensitization at max use, ocular irritation data for products that may be used around the eye, phototox and photosensitization, and a margin of exposure calculation.

Since the IDA was issued, most of these requested data have not been received. We have updated concentration of use for Trimethylbenzoyl Diphenylphosphine Oxide, which is used at 5 percent in nail polish and enamel, and Ethyl Trimethylbenzoyl Phenylphosphinate is used 6.2 percent in nail polish and enamel. We have some relatively low acute tox, right, generally negative genotox, some sensitization signals in animal models, but we don't have irritation and sensitization at max use, and phototox and photosensitization data.

So, why don't we open it up? It's as much of the summary as I could muster. Susan, you want to start?

DR. TILTON: Yeah, I mean, I think, importantly, we still don't have concentration of use for -- just going to --

DR. DAVID COHEN: Nail products.

DR. TILTON: (Inaudible) the TPO, but we also don't have concentration of use for the others in non-nail uses.

DR. ROSS: Correct, I would support that request.

DR. BERGFELD: You don't think that you could deal just with the nail ingredients alone? I mean, they harden, they're polymerized, little skin touch.

DR. ROSS: They're polymerized very quickly, aren't they, Wilma?

DR. BERGFELD: Yeah. They're light stabilizers, so they don't really, probably, not going to have a photosensitization.

DR. TILTON: I consider the nail use for TPO and ETP separately from non-nail use. And because we now have an MOE for DART, based on potential exposure, I didn't have concerns about those specific uses in nail products at the concentrations reported.

DR. DAVID COHEN: But you know we have some of the children's cosmetics and mucous membrane exposure -- like, there's a lot of --

DR. TILTON: But that's these other uses that we don't have any information on.

DR. DAVID COHEN: That's right.

DR. BERGFELD: I just thought you could clear the nail for use.

DR. DAVID COHEN: You're talking about splitting the decision.

DR. BERGFELD: Yeah. Mm-hmm.

DR. DAVID COHEN: This was a Draft Tentative Report. Okay.

DR. ROSS: With respect to splitting there, I think -- Jinqiu is on the call, maybe; maybe not. But I think the MOE was done at the -- was it done at 5 percent? Is that SCCS, let me have a quick look.

MS. FIUME: It's Page 34.

DR. TILTON: TPO.

DR. ROSS: Yeah, you're assuming, Monice, I got the right document.

MS. FIUME: I'm confident you do. I'm confident you do.

DR. ROSS: Sorry, the PDF was?

MS. FIUME: Thirty-four.

DR. ROSS: Getting there, getting there. Okay, got it. Yeah, so I remember, 15.15. What was the concentration, yeah. Yeah, 5 percent. So, the MOE was done at the 5 percent max. So, presumably the other uses are not going to be above that 5 percent, so you're probably okay there. And then the Ethyl was -- I think Jinqiu did that -- the concentration of use, which I think was 6.2, wasn't it? Yeah.

DR. SAM COHEN: David, I'm going to have to go off for just a minute because my earphone is stuck. It's not hearing very well. I'm going to have to recharge it. I'll be off for about five minutes.

DR. DAVID COHEN: Okay. any comments that you want to do before, as we can hear you?

DR. SAM COHEN: No.

DR. DAVID COHEN: Okay.

DR. ROSS: So, yeah, I think you could -- even if you didn't get those, it gets to a discussion we had earlier, you could probably get away with just the maximum concentration of use. I think it would be nice to have -- it's nice versus essential, but it would be nice to have the concentrations of use for non-nail applications; but I think we requested that in the original IDA and we didn't get it, right, the maximum concentration used of the Bis derivative, I think Susan has already said that.

David pointed out we don't have dermal sensitization at max, which is still needed for all the compounds, I believe. The phototoxicity and sensitization, I think Wilma commented she didn't think that was going to happen. But I think Allan was looking into that from the last meeting we had on this. So, maybe he should comment on the phototox tomorrow.

DR. DAVID COHEN: Well, they use this photo-initiators, right?

DR. ROSS: Yeah.

DR. BERGFELD: Right.

DR. ROSS: Maybe we don't worry about that and ask them to bring it up if it's an issue for them.

DR. DAVID COHEN: Well, I mean, if they're photo-initiated, are they photoactive?

DR. ROSS: Well, they're going to form reactive species.

DR. BERGFELD: They polymerize, I thought, with photoactivation.

DR. ROSS: Yeah, it would. It'd sort of cross-link. But we'll probably get input on the phototoxicity tomorrow from the other team, because I know that they were looking at that with respect to the cutoff for the phototoxicity OECD assay. So, that was from last time we met on this.

And then the only other comment I had was we have the NOEL in here; we've just gone through those, and the MOEs -- sorry, the MOE values we have in here on the risk assessment. But unlike the last one, the Dimer Dilinoleates, this one does have reproductive concerns. It's a CMR 1B for reproductive concerns, the TPO, the Trimethyl compound. So, you could keep the original risk assessment.

And I did note there was a DART NOAEL of 60 mgs per kg. We have used 100 mgs per kg.

DR. TILTON: For TPO?

DR. ROSS: For TPO, yeah. And we could just include that as an extra line. Jinqiu could -- not even -- you wouldn't have to go through all the calculation. You could include that as an extra line. So, using the DART are much more potent, and it's actually a really conservative DART study. It's not just days 9 through 20, it's an atypical DART study; it's a one-generation study where it was dosed for 10 to 12 weeks.

So, you could keep that in at 60 mgs per kg; and given the reproductive concerns that have been raised in the EU, the MOE would still come in above 900, if you want to go that way. It doesn't have to be in there, but it's a possibility.

So, they would be my main thing. So, concentration use at the best, the dermal sensitization at max, maybe the DART MOE, using a very conservative NOAEL, and then we'll get some input on phototox from the other team. That's what I had on this.

DR. DAVID COHEN: Can we just go through the list again so I have everything? We don't have concentration of use for non-nail products. We don't have dermal irritation and sensitization at max use. We only have some animal studies data. And the phototoxs you think we're going to get from the other group, even though it didn't make it into the report here?

DR. ROSS: That's my notes, that they were looking at it last time. Let me just triple check that. I'm not too worried about the phototox.

DR. TILTON: I mean, for dermal irritation and sensitization, we do have -- you know, I recognize that they're animal studies, but they were applied neat, and there was no indication of irritation. I'm just wondering if we need additional.

DR. ROSS: No, it was sensitization, I think.

DR. TILTON: Okay.

DR. ROSS: Did I say irritation and sensitization? I meant sensitization.

DR. DAVID COHEN: But there are animal sensitization studies. There's a guinea pig maximization and there's a local lymph node assay.

DR. ROSS: So, David, do you feel you need sensitization on this? The LLNA, I believe, is okay at 10 percent.

DR. DAVID COHEN: The LLNA went up to 50 percent, didn't it?

DR. ROSS: It did, but it was sensitizing at 50.

DR. DAVID COHEN: Yeah.

DR. ROSS: My notes say it was okay at 10.

DR. BERGFELD: (Inaudible) concentration hovers around 6.

DR. ROSS: Yeah.

DR. DAVID COHEN: You know, this is going to get down to what we were talking about today. First of all, are these adequate studies to draw that conclusion, right? We just have these animal studies, there's no in silico studies to corroborate them. There's no human.

DR. BERGFELD: We have used animal before in place of human.

DR. DAVID COHEN: I know.

DR. ROSS: And was that -- that was in the original data request?

DR. DAVID COHEN: It was.

DR. ROSS: Yeah.

DR. DAVID COHEN: So, are we not asking for con- -- I mean, are your concerns assuaged over the MOE, that we don't need concentration of use in non-nail products?

DR. ROSS: I think that that would be a nice to have, I don't think it's necessarily an essential, given that we have the MOE value down at the maximum concentration of use. Presumably, if we got those other concentrations, this is turning the argument you had given me before, would it make any difference to our conclusion? Right?

I mean, because we've done the MOE at maximum concentration of use. So, let's assume it comes in at 4.9 or 4.7, would it make any difference to our conclusions? Probably not.

DR. DAVID COHEN: Well, I suppose the question is use on children's skin and use on mucous membranes.

DR. ROSS: That would be a different -- children's skin, yeah, yeah.

DR. DAVID COHEN: Okay.

DR. BERGFELD: That's the other use.

DR. DAVID COHEN: Huh?

DR. BERGFELD: Those are other uses, other than nail.

DR. DAVID COHEN: Right. So, Wilma, will you -- it seemed like we were meandering to a safe as used without a split conclusion there. Where's the group on that? So, Wilma, I get it completely, a split conclusion, safe as used in nails, and then you're saying split off with non-nail.

DR. BERGFELD: Well, if you're concerned about what you have here, yeah, split it off because the nail looks okay to me.

DR. ROSS: Are we concerned about children's products? I guess we are.

DR. TILTON: I mean, the MOE would be based on adult exposure.

DR. ROSS: Absolutely. There's nothing about children in that MOE.

DR. TILTON: Yeah.

DR. DAVID COHEN: And what about mucous membrane?

DR. ROSS: I think the major concern here would be children, but I think you could ask -- you could lump together the other things, David, and say concentrations of use for non-nail applications are still needed.

DR. BERGFELD: Including children.

DR. ROSS: And emphasize the children's aspect, yeah.

DR. DAVID COHEN: And I'm sure we'll get into a discussion tomorrow, but I'd like to keep the dermal irritation and sensitization if this is going to be used in children. And on mucous membrane, I don't know how assuaged I am that the guinea pigs were good.

DR. ROSS: I'm going to leave that to my expert dermatologists.

DR. DAVID COHEN: I'm sure it'll be a discussion. And what about ocular irritation and phototox? I just need a little more on why we don't think it's a photo concerning agent.

DR. ROSS: Ocular, I didn't have too much of a concern. There were reversible toxicities when applied neat, so probably okay. This was the case where you had a different interpretation of the same study by SCCS and ECHA. But, given that these are all

neat concentrations, I thought that looked all right. Would it have been preferred to have concentrations of use and ocular irritation at the max? Yeah, of course. But we've got neat, and I think it's probably okay, the ocular.

With respect to the other issue, the dermal irritation, I think, Susan, you thought that was okay, right, with the animal irritation?

DR. TILTON: Yes, I didn't have any concerns. And it was tested across all of them.

DR. ROSS: I thought so, too, on the irritation, David. The sensitizing was a different issue.

DR. DAVID COHEN: Yeah, no, no, I'm often less concerned about the irritation than I am about sensitization. Not always. I'm just saying I think once you're sensitized the concentration you need to elicit is a lot lower.

DR. ROSS: I'll let you make that call and come up with what you want to do.

DR. BERGFELD: So, what are you doing? Are you going insufficient for the other uses and clearing the nail, or are you going insufficient for everything?

DR. DAVID COHEN: I think we could clear the nail, right?

DR. BERGFELD: Thank you.

DR. DAVID COHEN: What do you guys think?

DR. SAM COHEN: I think so.

DR. TILTON: I would support that. And that would be for TPO and ETP.

DR. ROSS: It's mainly TPO, I think, isn't it? But BTP also, yeah. Yeah, no, I'm okay with that.

DR. DAVID COHEN: So, the verbiage would be safe as used in nail cosmetics?

DR. ROSS: Nail products, yeah.

DR. DAVID COHEN: Nail products. So, this is a split conclusion? And then we have an Insufficient Data Conclusion, right?

DR. ROSS: Yeah.

DR. DAVID COHEN: For non-nail products. Does that sound right to you all?

DR. ROSS: Yeah.

DR. BERGFELD: Yes.

DR. DAVID COHEN: Sam, any other comments since you came off? I just wanted to see if we had --

DR. SAM COHEN: No, I think I got back on, and I agree with what your summary is here.

DR. DAVID COHEN: So, can I just recap our needs?

DR. BERGFELD: Yeah.

DR. ROSS: Just one comment, David, before you do that. About 98 percent of the uses -- I haven't done the calculation -- but it's certainly more than 95 percent on nail products, right?

DR. DAVID COHEN: Yeah, yeah, that's right, but the problem is there are non-nail products reported.

DR. ROSS: Yeah, yeah, absolutely.

DR. SAM COHEN: In the children.

DR. ROSS: That's the key points. Yeah.

DR. DAVID COHEN: Yeah. So, our Insufficient Data Conclusion for non-nail products are concentration of use in non-nail products, dermal irritation and sensitization at max use, we'll discuss, phototox or photosensitization data?

DR. ROSS: I think that's a discussion. Open that for discussion with the other team. Do you have this one tomorrow? Yes, you do, looking at it, yeah. Okay.

DR. DAVID COHEN: Wait, what was that? It sounded like you were discussing something.

DR. ROSS: No, I'm just looking at you're presenting it tomorrow, you could ask for discussion on the phototox, photosensitization.

DR. DAVID COHEN: Yes. But you had a note that you thought it was going to come from the other team and, Priya, do you have any insight into that? Is there any forthcoming --

MS. FERGUSON: I was going to make a point, that since this is a TR and there's two new ingredients, you can do a second IDA if you wished, since there's two new ingredients. I'm not sure if there needs to be more data needs than the IDA, but from what I understand, you can do a second IDA instead of a split conclusion, or you can go this way.

DR. DAVID COHEN: Well, look, I think it's just a timing issue for the companies to respond. If we do an Insufficient Data Conclusion, when would this come back?

MS. FIUME: It would come back in October. It would skip the June meeting, because there's really not time in between, and it would come back in October.

DR. DAVID COHEN: And if we did an IDA, it would come back in October and then come back again in March?

MS. FIUME: December or March -- probably March, based on the timing of the meetings. Yep. And the thing to consider is, if you don't have additional data needs. When these two ingredients were added, I believe the comment was made that even though it's an IDA, they would have the same -- the needs would follow because they could all be grouped together. I think that was mentioned when the two ingredients were added. Is that correct, Priya?

MS. FERGUSON: I'm not sure.

MS. FIUME: Okay.

MS. FERGUSON: I think it was implied.

MS. FIUME: Because it read across so that they would all have the same data needs.

MS. FERGUSON: Right. I think it's implied, but I'm not sure if that formally requests data, if that makes sense, for those two ingredients.

DR. ROSS: I mean, there's a lot of data in this dossier. I'm not sure you need to read across when you look at the actual amount of data in here.

MS. FIUME: I meant for the IDA needs.

DR. ROSS: Oh, I see.

MS. FIUME: That when the two were added, that they didn't have separate needs on their own.

DR. ROSS: Okay.

DR. DAVID COHEN: Any other comment on the Phosphinates? Okay.

DR. ROSS: You could comment that if an additional MOE with a DART NOAEL was desired, that could be incorporated. It's not necessary, but it's only --

DR. DAVID COHEN: Would it be helpful?

DR. ROSS: Yeah, it's just because the TPO was a CMR 1B for repro in Europe.

DR. DAVID COHEN: And this becomes an Insufficient Data Announcement, right? Because you're asking for a new need.

DR. ROSS: No, no, no, we have all -- we have all -- we have the data; so, we'll just be putting it in.

DR. DAVID COHEN: Then why would you ask for it? Why wouldn't we do it in-house?

DR. ROSS: We'd do it in-house; you wouldn't ask for it.

MS. FIUME: I think, David, you're just saying to include it in the next iteration?

DR. ROSS: Yeah.

DR. DAVID COHEN: Yeah. I guess that's what he means, right? That's what you mean, David, include it in the next iteration?

DR. ROSS: Exactly. We have all the data, you don't need to go out for this.

DR. DAVID COHEN: So, what is it? You're going to include an MOE for what?

DR. ROSS: It's open for discussion. Given the EU classification as a CMR 1B, as reproductive concerns, do we want to include a DART NOAEL for the TPO compound, the Trimethyl compound, in the risk assessment as well? We have a NOAEL for a DART endpoint, and it can just be added as a single sentence using this more sensitive NOAEL for a DART endpoint, and MOE was calculated and was 909. I did that calculation.

DR. DAVID COHEN: Is that right?

DR. ROSS: Yeah, yeah. But you don't -- I mean, it's not needed, but it may be worth discussing tomorrow. It's just an item for discussion.

DR. DAVID COHEN: All right, I'll put it in the discussion point after the motion.

DR. ROSS: Yeah.

DR. TILTON: I mean, it may not be needed, but I would also support it. In reading through the report and looking at the MOE, we have it calculated with a DART NOAEL for ETP, but not for TPO.

DR. ROSS: Correct.

DR. TILTON: I agree with Dave; given the concerns, it seems like we should be focused on that endpoint.

DR. SAM COHEN: I also agree. It's not necessary, but it would be helpful.

DR. DAVID COHEN: The Trimethyl as well, or just the TPO?

DR. ROSS: That is the TPO, yeah.

DR. SAM COHEN: TPO.

DR. DAVID COHEN: Yes. Okay. Yeah. Got it. Sorry.

Full Panel – March 13, 2026

DR. DAVID COHEN: Yes. This is a Draft Tentative Report on Bis-Trimethylbenzoyl Phenylphosphine Oxide, Ethyl Trimethylbenzoyl Phenylphosphinate, and Trimethylbenzoyl Diphenylphosphine Oxide. Since the prior review, the report has been expanded to include the two structurally related ingredients, and the use data continue to show that these materials are predominantly used in UV-cured nail products with some limited use outside the nail category.

At the prior review, the Panel requested additional data focused largely on non-nail exposure scenarios, including non-nail concentration of use, dermal irritation and sensitization at max use on the skin, ocular irritation were relevant, phototoxicity and photosensitization, and MOE. The MOE issues for the principal nail uses have now been addressed, and most of the non-nail data requests remain outstanding.

Accordingly, my motion is that Ethyl Trimethylbenzoyl Phenylphosphinate and Trimethylbenzoyl Diphenylphosphine Oxide ingredients are safe in the present practices of use and concentration when used in nail products. And that the data are insufficient to determine the safety for non-nail uses for all of them, and for Bis-Trimethylbenzoyl Phenylphosphine Oxide in nail uses as well.

So, for Bis-Trimethyl we have no concentration of use, and the team felt read-across was not sufficient to drag it across and in. We don’t have concentration of use for non-nail products, and we note that it’s being used for children’s products, dermal irritation and sensitization at max use concentration for skin exposure. And we wanted to have a discussion about the phototox and photosensitization. There was discussion that, Don, you and your team were going to address some of this and we didn't know where you stood on that.

DR. BERGFELD: So, are you not proposing a motion? You're just posing a discussion of a motion?

DR. DAVID COHEN: Well, I suppose, yes. Because the motion was safe as used for two of the products, the nail products, and insufficient on the others. I guess the reason the motion can't be complete is because I haven't enumerated every data need precisely, so I'd ask Don for comment.

DR. BERGFELD: Good.

DR. BELSITO: Yeah. Well, I'm still concerned about the reports of photocytotoxicity and the issue, therefore, of photo-irritants and photo-allergy. I mean, you can get photo-onycholysis of the nails, right?

DR. DAVID COHEN: You could.

DR. BERGFELD: Yeah.

DR. BELSITO: So, can we clear even nail until we have an understanding of the absorption spectra? Is it below Henry's Law? Is it below the -- you know, so I was like more --

DR. DAVID COHEN: So, you're still at an IDA across the board? Our discussion (inaudible) phototox things.

DR. BELSITO: Yeah, for nails I need more information on photo irritation and photosensitization. And for the other products, non-nail concentration of use, manufacturing of Bis-Trimethylbenzoyl and Ethyl Trimethylbenzoyl, impurities of Bis-Trimethylbenzoyl, and Ethyl Trimethylbenzoyl we didn't feel the 95 percent we got was adequate. Allan was concerned that the other 5 percent could have highly reactive molecules.

Why the DART NOAEL was used over -- let's see. Why the DART NOAEL was corrected to 150 milligrams from 600 milligrams? Maybe David Ross can address that question. Irritation at use concentration for Trimethylbenzoyl. Sensitization at use concentration for all three. Phototoxicity, photosensitization data, especially given the evidence of photo exacerbated cytotoxicity and ocular irritation at concentration of use for eye products.

So we had a huge list for everything other than nail; and for nail the basic issue was the photo.

DR. DAVID COHEN: For the eye, did we have some material on exposure to the eye? I got to go back and look at the PDF, that is.

DR. BELSITO: We have Bis-Trimethylbenzoyl Phenylphosphine Oxide in eyelash, eyebrow, glues and mascaras.

DR. DAVID COHEN: No, I meant what data we had on it?

DR. BELSITO: Ocular irritation is in Table 9.

DR. DAVID COHEN: So Bis was at neat, right?

DR. BERGFELD: You have them all at neat.

DR. DAVID COHEN: We had eye and then we pulled the eye out. So, Don, what was the -- I mean, we're going to have to go through all the data needs again, but just to get clarity on the eye from you.

DR. BELSITO: Fully reversible irritation, yeah. What did we have? Ocular irritation at concentration. So, yeah, I think we're okay with removing the ocular irritation.

DR. DAVID COHEN: All right. Don, you had a list that didn't totally harmonize with ours, but I agreed with your additions. My motion will be an Insufficient Data Conclusion on this. But do we have -- Don, are any of your requests new?

DR. BELSITO: No.

DR. DAVID COHEN: Okay. So it's an Insufficient Data Conclusion, correct?

DR. BELSITO: The only difference is that we're splitting nail from non-nail. So, insufficient in nail for photo, and for non-nail the list is larger.

DR. DAVID COHEN: Why would you split --

DR. BERGFELD: Bart wants to respond.

DR. HELDRETH: Thank you, Dr. Bergfeld. What does make it new, however, is that we have two new ingredients in there, and we're asking for what may be the same data request, but now on two new ingredients. And we haven't allowed there to be a response to those requests on those two ingredients. So, I would suggest this is a second IDA.

DR. DAVID COHEN: Okay, I'm fine with that. Don, why just the phototox for the nails and not everything? Why wouldn't the IDA just be phototox and photosensitization data?

DR. BELSITO: Well, I mean, since we're going for an IDA, I don't think we need to separate nail out at this point.

DR. DAVID COHEN: Okay. So, we're going to issue an Insufficient Data --

DR. BELSITO: But as a hint to industry, since we were told that the major use is in nails, and that's what they're concerned about, if they want to get nail approved, the thing that they should do is provide us with some photo data. Either look at the absorption spectrum and see if absorption is below Henry's law, and we can dispense with it without studies.

And in fact, I said that for photosensitization, there are no good non-animal models, and the OECD has no guidelines. But JaCVAM, the Japanese association, has accepted a negative ROS assay as indication that there'd be no photosensitization. I'd even be okay if they could do a ROS assay with these and show no activation, a negative ROS assay.

DR. DAVID COHEN: So, the IDA that we had at the last meeting was concentration of use in non-nail products, dermal irritation and sensitization at max use concentration for skin exposure. We took out ocular irritation, we asked for photosensitization, and the MOE we sort of dealt with, right? Was there anything I missed?

DR. BELSITO: I have non-nail concentration of use.

DR. DAVID COHEN: Okay.

DR. BELSITO: I have manufacturing for Bis-Trimethylbenzoyl, Ethyl Trimethylbenzoyl --

DR. DAVID COHEN: That's new, isn't it?

DR. BELSITO: No, I don't think so.

DR. DAVID COHEN: We had that in there?

DR. BELSITO: No, because these were added in, David.

DR. DAVID COHEN: Ah, ah, so -- but it is new from the last IDA?

DR. BELSITO: Yeah.

DR. DAVID COHEN: All right.

DR. BELSITO: Impurities for Bis-Trimethyl and Ethyl Trimethyl. Why the correction in the DART NOAEL to 150 milligrams? That was also done by SCCS, and I don't understand that. That's not my area of expertise, but what we have in our report was a NOAEL of 600 milligrams per kilogram per body weight per day. So I don't understand.

DR. ROSS: I can comment on that in a minute, yeah, and I'll let you get through the list.

DR. BELSITO: Okay. Irritation and use concentration -- at use concentration for Trimethylbenzoyl. Sensitization at use concentration for all three, and then the phototoxicity, photosensitization.

DR. DAVID COHEN: Okay. I think some of those continue to overlap. Okay. Priya, do you have all those?

MS. FERGUSON: I do.

DR. DAVID COHEN: Okay. That's the motion.

DR. BERGFELD: Is there a second?

DR. BELSITO: Second.

DR. BERGFELD: Okay. David Ross, you wanted to clarify something?

DR. ROSS: Well, Jinqiu did these. When I'm just looking at the data, I mean, for TPO, the Trimethyl, looks to me like the NOAEL used was 100 mg/kg from a 90-day oral tox study.

DR. BELSITO: Right. But there's a reproductive NOAEL of 60 milligrams per kilogram for body weight.

DR. ROSS: Yeah. Actually, I had that in my comments in our team. That one wasn't a typical DART study we would typically use for a NOAEL, because I think that was a one-generation study for 10- to 12-week dosing. Typically, you use days 8 through 20. But still, I proposed yesterday that given the potential reproductive concerns with some of these things -- it's CMR 1B in Europe, for example.

DR. BERGFELD: Right.

DR. ROSS: We should put in an additional line on the MOE, just like we did in one of the previous reports, saying that, for a more conservative calculation we also moved to a very conservative value of 60 mgs per kg, and did another MOE with that value. And I think it would still indicate safety by a long way. I think that should be in there as well, given the concerns with reproductive toxicity that are out there for TPO.

DR. BELSITO: Yeah, you're right, David. So, it was a one-generation repro study with Trimethylbenzoyl up to 600 milligrams. It was for 10 to 12 weeks.

DR. ROSS: Yeah. Well, 60, yeah.

DR. BELSITO: The NOAEL was 60. Yeah.

DR. ROSS: Yeah, my memory is not failing me. Yeah, okay, good.

DR. BELSITO: Yeah. Reduced fertility, testicular abnormalities that were observed.

DR. ROSS: So, Jinqiu, could we add that one in?

DR. ZHU: Yes, of course, we can recalculate it.

DR. ROSS: Great, thank you.

DR. BERGFELD: Okay. Anything else to be discussed or added to the text or Discussion right now?

DR. BELSITO: No.

DR. BERGFELD: In the Discussion, the want list will go -- or the needs list will go as well.

DR. BELSITO: Yeah.

DR. BERGFELD: All right. Going to call the question, then. All those opposed? Abstaining? Approval to go forward as insufficient with all that data that was just discussed.

Safety Assessment of Bis-Trimethylbenzoyl Phenylphosphine Oxide, Ethyl Trimethylbenzoyl Phenylphosphinate, and Trimethylbenzoyl Diphenylphosphine Oxide

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ABBREVIATIONS

AEL	acceptable exposure level
CAS	Chemical Abstracts Service
CCK-8	cell counting kit-8
CFR	Code of Federal Regulations
CIR	Cosmetic Ingredient Review
CMC	carboxymethylcellulose
CMR	carcinogenic, mutagenic, or toxic for reproduction
Council	Personal Care Products Council
CPSC	US Consumer Product Safety Commission
Dictionary	*International Cosmetic Ingredient Dictionary*
DMSO	dimethyl sulfoxide
DST	dermal sensitization threshold
EC	European Commission
EC_3	amount of chemical that is required to elicit a 3-fold increase in lymph node proliferative activity
ECHA	European Chemicals Agency
EPA	US Environmental Protection Agency
EU	European Union
FDA	US Food and Drug Administration
GD	gestation day
GPMT	guinea pig maximization test
HEK293T	human embryonic kidney 293 cells
HPLC	high-performance liquid chromatography
HRIPT	human repeated-insult patch test
HUVEC-12	human umbilical vein endothelial cells
ISO	International Organization for Standardization
K_{ow}	n-octanol/water partition coefficient
L02	human fetal hepatocyte line
LD_{50}	median lethal dose
LED	light-emitting diode
LLNA	local lymph node assay
MCF-7	Michigan Cancer Foundation-7 human breast cancer cell line
MoCRA	Modernization of Cosmetics Regulation Act of 2022
MOE	margin of exposure
MOS	margin of safety
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide
MW	molecular weight
NESIL	no-expected-sensitization-induction-level
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
NR	not reported
OECD	Organisation for Economic Co-operation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
PBS	phosphate-buffered saline
PND	post-natal day
POD	point of departure
RLD	Registration and Listing Data
SED	systemic exposure dose
SCCS	EC Scientific Committee on Consumer Safety
SIDS	screening information dataset
TG	test guideline
TI	tail intensity
US	United States
UV	ultraviolet

DRAFT ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of Bis-Trimethylbenzoyl Phenylphosphine Oxide, Ethyl Trimethylbenzoyl Phenylphosphinate, and Trimethylbenzoyl Diphenylphosphine Oxide as used in cosmetics. Bis-Trimethylbenzoyl Phenylphosphine Oxide and Ethyl Trimethylbenzoyl Phenylphosphinate are reported to function as light stabilizers in cosmetics, and Trimethylbenzoyl Diphenylphosphine Oxide is reported to function as an artificial nail builder in cosmetics. The Panel reviewed relevant data related to these ingredients and concluded…[TBD].

INTRODUCTION

This assessment reviews the safety of Bis-Trimethylbenzoyl Phenylphosphine Oxide, Ethyl Trimethylbenzoyl Phenylphosphinate, and Trimethylbenzoyl Diphenylphosphine Oxide as used in cosmetic formulations. According to the *International Cosmetic Ingredient Dictionary* (*Dictionary*), Bis-Trimethylbenzoyl Phenylphosphine Oxide and Ethyl Trimethylbenzoyl Phenylphosphinate are reported to function as light stabilizers in cosmetics, and Trimethylbenzoyl Diphenylphosphine Oxide is reported to function as an artificial nail builder in cosmetics.[1] The ingredients reviewed in this report have been grouped together as they are all acylphosphine oxide/phosphinate photoinitiators.[2]

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an extensive search of the world's literature; a search was last conducted August 2026. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Much of the data included in this safety assessment was found on the European Chemicals Agency (ECHA)[3-5] and the European Commission (EC) Scientific Committee on Consumer Safety (SCCS)[6] websites. Please note that these websites provide summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when these sources are cited.

CHEMISTRY

Definition and Structure

The definitions and structures of the ingredients included in this review are provided in Table 1. Trimethylbenzoyl Diphenylphosphine Oxide (CAS No. 75980-60-8) is an alpha-cleavage photo-initiator (Norrish type-1 photoinitiator) with low energy bonds, which after homolytic cleavage yield free radicals.[7] Type-1 photoinitiators involve absorption of light and subsequent excitation to singlet state and photochemical cleavage of carbon-phosphorous bonds, and do not require co-initiators. Trimethylbenzoyl Diphenylphosphine Oxide undergoes rapid cleavage from a triplet excited state and yields two radicals: a trimethylbenzoyl (mesitoyl) radical and a diphenylphosphinoyl radical, each of which initiate polymerization at different rates. Bis-Trimethylbenzoyl Phenylphosphine Oxide, by contrast, carries 2 mesitoyl groups bound to phosphorous, and can undergo sequential alpha-cleavages to generate multiple radicals.[2] Ethyl Trimethylbenzoyl Phenylphosphinate has the same mesitoyl chromophore plus an ethoxy substituent on phosphorous and similarly functions as an efficient Type 1 photoinitiator under recommended curing conditions.[8]

It is assumed that Trimethylbenzoyl Diphenylphosphine Oxide is quickly consumed during the polymerization process when used in nail gel products, and therefore, very little residual amounts would remain.[6] Under the unlikely event that minimal residual amounts are present, they would be trapped in the hardened polymer matrix of the formed nail coating.

Chemical Properties

Bis-Trimethylbenzoyl Phenylphosphine Oxide (molecular weight (MW) = 418.5 g/mol; n-octanol/water partition coefficient (log K_{ow}) @ 22 ºC = 5.8)), Ethyl Trimethylbenzoyl Phenylphosphinate (MW = 316.3 g/mol; log K_{ow} @ 25 ºC = 2.9), and Trimethylbenzoyl Diphenylphosphine Oxide (MW = 348.4 g/mol; log K_{ow} @ 23 ºC = 3.1) are yellow phosphine oxide-based photoinitiators.[3,5,9-11] These ingredients have low vapor pressures, limited water solubility, and moderate to high lipophilicity. All 3 photoinitators exhibit ultraviolet (UV) light absorption, with reported maxima between 230 and 400 nm.[6,12,13] Bis-Trimethylbenzoyl Phenylphosphine Oxide exhibits strong absorption within the emission range of commonly used UV/light-emitting diode (LED) nail lamps.[8] Other chemical properties of the ingredients reviewed in this report may be found in Table 2.

Method of Manufacture

The following methods of manufacturing are general to the production of these phosphine oxide and phosphinate ingredients, and it is unknown whether they are used in the manufacture of these ingredients for use in cosmetics.

Trimethylbenzoyl Diphenylphosphine Oxide

Trimethylbenzoyl Diphenylphosphine Oxide is commonly synthesized by using the Arbuzov-type reaction of 2,4,6-trimethylbenzoyl chloride with alkoxylphosphine, that is synthesized from diphenylphosphine chloride and low-boiling point

alcohol.[14] As this method is associated with several drawbacks (e.g., toxic pollutants), alternative methods of manufacture of this ingredient have been described in the literature. These methods are described below.

A Schlenk tube was charged with diphenylphosphine oxide, 2,4,6-trimethylbenzaldehyde, and toluene and stirred at room temperature for 16 h.[14] Residue was washed with ethyl acetate and recrystallization resulted in α-hydroxy(2,4,6-trimethylbenzyl)diphenylphosphine oxide. For the oxidation step, a mixture of α-hydroxy(2,4,6-trimethylbenzyl)diphenyl-phosphine oxide, dichloromethane, and manganese dioxide was stirred at room temperature for 1 h, followed by removal of manganese dioxide and the solvent. The crude product was diluted in deuterated chloroform, and Trimethylbenzoyl Diphenylphosphine Oxide was purified through a silica gel column with ethyl acetate and hexane.

Alternatively, to minimize decomposition products, a 500 ml, three-necked, round-bottomed flask was charged with triphenylphosphine oxide and dry tetrahydrofuran.[15] After ice bath cooling, sodium dispersion was added dropwise via a 50 ml syringe. The crude reaction mixture was filtered under nitrogen, the insoluble part was washed with tetrahydrofuran, and the organic layers were combined. Trimethylsilyl chloride was then dropwise added followed by removal of volatiles. Hexane was then added, and the sodium chloride precipitate was filtered under nitrogen. The solid was washed with hexane and methyl chlorothioformate and added to the hexane solution overnight (over continuous heat), and Trimethylbenzoyl Diphenylphosphine Oxide formed as a precipitate. Simple filtration yielded pure Trimethylbenzoyl Diphenylphosphine Oxide.

Impurities

Ethyl Trimethylbenzoyl Phenylphosphinate

As reported in a National Industrial Chemicals Notification and Assessment Scheme (NICNAS) safety assessment, Ethyl Trimethylbenzoyl Phenylphosphinate has reported purity as a substance used in industry.[10] The degree of purity is expected to be ≥ 95%.

Trimethylbenzoyl Diphenylphosphine Oxide

The purity of Trimethylbenzoyl Diphenylphosphine Oxide was provided in an SCCS opinion. According to specifications in that opinion, Trimethylbenzoyl Diphenylphosphine Oxide is predominantly ≥ 99% pure.[6]

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these phosphine oxides and phosphinate ingredients in cosmetics. Registration and Listing Data (RLD) obtained from the FDA report frequency of use, and responses to a survey conducted by the Personal Care Products Council (Council) indicate maximum reported concentrations of use; it is these values that define the present practices of use and concentration that are assessed by the Panel. Since 2024, as a result of the Modernization of Cosmetics Regulation Act of 2022 (MoCRA), manufacturers and processors are required to register facilities and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses (average gross annual sales in the US of cosmetic products for the previous 3-yr period is less than $1,000,000, adjusted for inflation), which are exempt from MoCRA reporting for most cosmetic product categories. Eye area products, injected products, internal use products, or products that alter appearance for more than 24 h, and the facilities that manufacture these products, are not included in this exemption.[16] Another change resulting from MoCRA is the addition of tattoo preparations (permanent tattoo inks, temporary tattoo inks, and other tattoo products) to the product categories for which companies need to list their products with FDA. However, evaluating the safety of ingredients as used in tattoo preparations is not within the purview of the Panel; accordingly, such use is not included as part of the present practices of use that are assessed by the Panel.

According to RLD obtained from the FDA in 2025, Trimethylbenzoyl Diphenylphosphine Oxide has the highest frequency of use among the ingredients reviewed in this report; it is used in 4399 total formulations (at up to 5% in nail polish and enamel; Table 3).[17-19] However, according to the results of the Council concentration of use survey, Ethyl Trimethylbenzoyl Phenylphosphinate is reported to have to the highest concentration of use; it is used at up to 6.2% in nail polish and enamel.[20]

Although the primary reported use of all 3 ingredients reviewed in this report is in nail products, these ingredients may result in eye exposure as they are used in products near the eye (e.g., Ethyl Trimethylbenzoyl Phenylphosphinate is used in a mascara formulation) and in incidental ingestion and mucous membrane exposure (e.g., Trimethylbenzoyl Diphenylphosphine Oxide is used in lipstick and lip gloss formulations). In addition, these ingredients are used in children's makeup (e.g., Ethyl Trimethylbenzoyl Phenylphosphinate is used in children's lipstick and lip glosses). However, concentrations of use are not reported for products that result in these additional exposures.

Trimethylbenzoyl Diphenylphosphine Oxide may be incidentally inhaled as it is reported to be used in perfume formulations (concentration not stated). In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be

deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.

Following the passage of MoCRA, the FDA created a number of new product categories, including "(17) Other preparations (i.e., those preparations that do not fit another category)" (Category 17). CIR and the Panel utilize these product categories to inform, in part, the weight-of-evidence (WoE) in exposure and risk analyses. However, citation of Category 17, alone, as the product use category is uninformative. When a product is co-categorized with both Category 17 and one or more common product use categories (e.g., eye makeup preparations), or other information in the RLD such as the product name are indicative of use type (e.g., "lip balm" is part of the product name), then those uses are accounted for and may be considered to be part of the "the present practices of use" for those products; as such, the Panel's safety conclusion may be inclusive thereon. Conversely, for instances wherein the use of an ingredient in a cosmetic product is only categorized as Category 17 and other information in the RLD is not indicative of use type, the present practices of use for these products remain unknown and the Panel's safety assessment conclusion, therefore, does not apply thereon.

Some products containing these ingredients may be marketed for use with airbrush delivery systems. With the advent of MoCRA and the current product categories outlined by the FDA, it is now mandatory that cosmetic products used in airbrush delivery systems be reported as such for some, but not all, product categories in the RLD. In other words, a reliable source of frequency of use data regarding the use of cosmetic ingredients in conjunction with airbrush delivery systems is now available, in some instances. Additionally, the concentration of use surveys are conducted based on product categories as stated in the RLD. None of the reported product categories for these ingredients as listed in the RLD, or those reported in the concentration of use survey results, include a designation of using airbrush application, so it is possible that these ingredients are used with airbrush delivery systems, but not reported as such. Nevertheless, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety. Without information regarding the consumer habits and practices data or product particle size data (or other relevant particle data, e.g., diameter) related to this use technology, the data profile is incomplete, and the Panel is not able to determine safety for use in airbrush formulations. Accordingly, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

According to the European Union (EU), Trimethylbenzoyl Diphenylphosphine Oxide is classified as a carcinogenic, mutagenic, or toxic for reproduction (CMR) substance of category IB (toxic for reproduction), that is prohibited in cosmetics (EC 1223/2009 Annex II).[21] Bis-Trimethylbenzoyl Phenylphosphine Oxide and Ethyl Trimethylbenzoyl Phenylphosphinate are not listed as restricted or prohibited under the EU Cosmetics Regulation and may be used subject to general safety and labeling requirements.

Cosmetic use application of Trimethylbenzoyl Diphenylphosphine Oxide

Two artificial nail systems (nail polishes and nail enhancement products) containing Trimethylbenzoyl Diphenyl-phosphine Oxide are commonly used for fingernails and toenails.[6] For polishes, nails are cleaned and prepared, a brush is wetted, dipped into the gel with initiator, applied to the nail, shaped, and cured under a UV lamp. (The application process consists of a base, middle, and top coat, with curing following each application.) The polymerization is completed in approximately 2 – 3 min (procedure may be repeated up to 2 – 3 times). Applications of nail enhancement products are typically performed every 2 – 3 wk (with refills every 1 – 2 wk). Full application uses 2 – 4 g of gel, and 1 g of gel is used for refills (for artificial nail systems), corresponding to a maximum of 200 mg Trimethylbenzoyl Diphenylphosphine Oxide in total for all nail plates (which corresponds to an amount of 10 mg/nail (considering the total fingernail and toenail area of 22 cm^2)).

Cosmetic use application and exposure assumptions for Bis-Trimethylbenzoyl Phenylphosphine Oxide and Ethyl Trimethylbenzoyl Phenylphosphinate

Nail products containing Bis-Trimethylbenzoyl Phenylphosphine Oxide and Ethyl Trimethylbenzoyl Phenylphosphinate are intended for application exclusively to the nail plate. Following application, the product remains on the nails until removal, which typically occurs every 2 – 3 wk.[8] Each applied layer is light-cured; the base coat gel is applied directly to the nail plate, while subsequent color and topcoat layers are applied over previously polymerized coatings. Products containing these ingredients are formulated to undergo rapid polymerization under UV/LED curing conditions.

Use studies evaluating both professionally applied and self-applied gel polish systems were considered in establishing product application amounts for an exposure assessment.[8] A high-end application amount (95th percentile) of 0.21 g was selected. The amounts applied during each step of the manicure were not summed because UV-curable gel systems are applied and cured sequentially. Accordingly, the highest measured per-layer application amount of 0.21 g was used to represent high-end potential exposure, while avoiding overestimation from summing layers that had already undergone curing. The SCCS has conservatively used a combined fingernail and toenail surface area of approximately 22 cm^2 in exposure assessments of artificial nail systems, as described above. To account for a combined manicure and pedicure during the same treatment session, a second exposure scenario using twice the application amount (0.42 g) was also evaluated. This scenario assumes high-end application amounts for both the fingernails and toenails during the same treatment session. The 0.21- and 0.42-g application amounts were used in the margin of exposure (MOE) assessments described in the Risk Assessment section of this report.

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

The amount of Trimethylbenzoyl Diphenylphosphine Oxide per usage was evaluated via application on artificial nail tips.[6] A base coat gel was first applied to the artificial nail tip (nails made up of acrylonitrile-butadiene-styrene copolymer), followed by an intermediate color coat gel, and a topcoat gel (each gel contained 3% Trimethylbenzoyl Diphenylphosphine Oxide). Each step was followed by curing under a UV lamp. (Therefore, only the base coat was applied to the nail; other applications were to the polymerized base coat). The weight of gel samples applied to 2 nail tips was approximately 72 and 78 mg/nail (corresponding to approximately 2.16 – 2.34 mg Trimethylbenzoyl Diphenylphosphine Oxide in uncured gels). The cured polish was then immersed in an aqueous 0.1% sodium chloride solution for extraction. The extracted solution was analyzed using high-performance liquid chromatography (HPLC) with a UV detector. The extracted Trimethylbenzoyl Diphenylphosphine Oxide was nearly undetectable (0.0044 and 0.0047 mg at 22 and 50°C, respectively) due to the curing process, with the limit of detection being 0.2 ppm. This result indicates that less than 0.14 – 0.16 mg of Trimethylbenzoyl Diphenylphosphine Oxide per nail, which is less than 0.2% of the total Trimethylbenzoyl Diphenylphosphine Oxide content in the uncured gel, could have been theoretically extracted.

Non-Cosmetic

The ingredients reviewed in this report are used in several industries/products including printing inks, paints/coatings/lacquers/varnishes, adhesives/sealants, and fillers/putties/plasters.[22] These ingredients may also be used as a photoinitiator in the dental industry.[2,7]

TOXICOKINETIC STUDIES

No toxicokinetics studies were found in the published literature, and no unpublished data were submitted. However, as Ethyl Trimethylbenzoyl Phenylphosphinate has a low molecular weight (316.3 g/mol) and partition coefficient (log K_{ow} = 2.91), passive diffusion across the gastrointestinal tract and dermal absorption may occur.[10] According to an SCCS opinion, Trimethylbenzoyl Diphenylphosphine Oxide is lipophilic and sparingly soluble in water and is therefore unlikely to readily penetrate the nail plate.[6]

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Details on the acute toxicity studies summarized below can be found in Table 4.

Bis-Trimethylbenzoyl Phenylphosphine Oxide (purity not stated; tested neat), Ethyl Trimethylbenzoyl Phenylphosphinate (purity 95.7%; tested neat), and Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.5%; tested at 40%; in olive oil) showed dermal LD_{50}s of > 2000 mg/kg bw in acute toxicity assays performed in rats under semi-occlusive conditions.[3-5] An oral LD_{50} of > 2000 mg/kg bw was observed in an oral acute toxicity assay in which rats were given Bis-Trimethylbenzoyl Phenylphosphine Oxide (purity 98.4%; tested at 20% in water).[5] LD_{50}s of > 5000 mg/kg were determined in acute oral toxicity assays performed in rats using Ethyl Trimethylbenzoyl Phenylphosphinate (purity > 97%; tested at up to 50%; in 0.5% aqueous carboxymethylcellulose (CMC) or arachis oil) and Trimethylbenzoyl Diphenylphosphine Oxide (99% purity; tested at up to 50%). No abnormalities or deaths were observed in an acute inhalation toxicity assay in which rats were exposed whole-body to 0.000027 mg/l Ethyl Trimethylbenzoyl Phenylphosphinate (purity > 97%) for 7 h.

Short-Term and Subchronic Toxicity Studies

Details on the repeated-dose oral toxicity studies summarized below can be found in Table 5.

Bis-Trimethylbenzoyl Phenylphosphine Oxide (purity 98.2 – 98.4% pure; in 1% aqueous methylcellulose or 1% aqueous CMC) had a no-observed-adverse-effect-level (NOAEL) of 1000 mg/kg bw/d in 7- and 28-d studies in rats, and a no-observed-effect-level (NOEL) of 300 mg/kg bw/d in a 3-mo study due to abnormal blood chemistry and duodenal thickening at higher doses.[5] In a 7-d study, 500 mg/kg bw/d Ethyl Trimethylbenzoyl Phenylphosphinate (purity and vehicle not stated) resulted in increased liver weights and decreased relative spleen weights.[24] In a 14-d study, Ethyl Trimethyl-benzoyl Phenylphosphinate (purity and vehicle not stated) at 1000 mg/kg bw/d resulted in moribundity, body weight loss, and changes in organ weights (increased liver, kidney, and adrenal weights and decreased spleen weights). Increased liver weights were also observed in a 20-d assay in which rats were treated with Ethyl Trimethylbenzoyl Phenylphosphinate (purity 96.9% vehicle not stated) at doses as low as 150 mg/kg bw/d and in a 28-d study in which rats were treated with Ethyl Trimethylbenzoyl Phenylphosphinate (purity 95.7% in 1% aqueous CMC) at 500 mg/kg bw/d.[4] In a 13-wk study, administration of Ethyl Trimethylbenzoyl Phenylphosphinate (purity 96.9%; in 1% aqueous CMC) at 500 mg/kg bw/d resulted in adverse effects (hematological alterations, organ weight increases (liver and kidney)). The NOAEL in this study was determined to be 100 mg/kg bw/d. Trimethylbenzoyl Diphenylphosphine Oxide (purity 94.8 – 99.3%; in arachis oil or 0.5 – 1% aqueous CMC) resulted in NOAELs ranging from 50 – 100 mg/kg bw/d in 28- and 90-d studies in rats, with higher doses causing body weight reduction, organ weight increases (liver and kidney), clinical chemistry changes, and testicular atrophy.[3,6,25] However, no signs of toxicity were observed in a 28-d assay in which rats were given 1000 mg/kg bw Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.3%; in 0.5% aqueous CMC. All short-term and subchronic toxicity assays were performed in rats, and test substances were administered via gavage.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Details on the oral developmental and reproductive toxicity studies summarized below can be found in Table 6.

No maternal or fetal toxicity was observed when Bis-Trimethylbenzoyl Phenylphosphine Oxide (purity not stated) was administered to rats at up to 1000 mg/kg bw/d in 1% aqueous CMC during gestation days (GD) 6 – 19, establishing an NOAEL of 1000 mg/kg bw/d.[5] Ethyl Trimethylbenzoyl Phenylphosphinate (purity 96.8 – 97.8%; by gavage on GD 6 - 19) in 0.5% sodium CMC resulted in an NOAEL and NOEL for prenatal developmental toxicity of 300 and 100 mg/kg bw/d, respectively.[4] Trimethylbenzoyl Diphenylphosphine Oxide (purity not stated) in 1% aqueous CMC produced maternal and developmental effects (reduced maternal weight gain, fetal skeletal variations) at 500 mg/kg bw/d in rats (treatment on days post-coitum 6 – 20), establishing an NOAEL of 150 mg/kg bw/d.[3] In a one-generation reproductive toxicity study in rats, Trimethylbenzoyl Diphenylphosphine Oxide (99.3% purity; up to 600 mg/kg bw/d in 1% aqueous CMC; 10 – 12-wk administration) gave an overall reproductive NOAEL of 60 mg/kg bw/d, with reduced fertility and testicular abnormalities observed at higher doses. In rabbits, administration of Trimethylbenzoyl Diphenylphosphine Oxide (99.3% purity; up to 100 mg/kg bw/d in 1% aqueous CMC; treatment on days 6 – 28 post-coitum) showed no maternal or dose-dependent fetal toxicity; a slight increase in misaligned vertebrae in fetuses at 100 mg/kg bw/d was within historical control limits. All developmental and reproductive toxicity studies were performed via gavage.

GENOTOXICITY STUDIES

Details regarding the in vitro genotoxicity studies summarized below can be found in Table 7.

In gene mutation assays, Bis-Trimethylbenzoyl Phenylphosphine Oxide (in DMSO; purity not stated) was negative in an Ames assay using *Salmonella typhimurium* and *Escherichia coli* at up to 5000 µg/plate and in a mammalian cell gene mutation assay using mouse lymphoma L5178Y cells at up to 80 µg/ml, with and without metabolic activation.[5] Ethyl Trimethylbenzoyl Phenylphosphinate (purity 95.7 – 100%) was negative in Ames assays using *S. typhimurium* and *E. coli* at up to 2500 – 5000 µg/plate and in a mammalian cell gene mutation assay using Chinese hamster lung fibroblasts (V79) at up to 3300 µg/ml, with and without metabolic activation.[4] Trimethylbenzoyl Diphenylphosphine Oxide was negative in Ames assays using *S. typhimurium* (purity > 98%; up to 2500 µg/plate in ethanol) and *S. typhimurium* and *E. coli* (purity 99%; up to 5000 µg/plate in ethanol), and was non-mutagenic in a mammalian cell gene mutation assay using Chinese hamster lung fibroblasts (purity 99.5%; in ethanol; up to 40.5 µg/ml), with and without metabolic activation.[3,6] In assays evaluating chromosomal damage, Bis-Trimethylbenzoyl Phenylphosphine Oxide (in dimethyl sulfoxide (DMSO); purity not stated) was negative in a chromosomal aberration assay using stimulated cultured human lymphocytes at up to 100 µg/ml, with and without metabolic activation. Ethyl Trimethylbenzoyl Phenylphosphinate (purity 95.7 – 100%) was evaluated in micronucleus and chromosomal aberration assays using human lymphocytes and V79 cells at concentrations ranging from 6.25 – 255 µg/ml, with and without metabolic activation. The substance was non-clastogenic in V79 micronucleus assays; in human lymphocyte micronucleus and chromosomal aberration assays (purity 100%; in DMSO), statistically significant increases were observed primarily at high or cytotoxic concentrations and were generally within historical control ranges or limited to individual replicates, with no consistent dose-dependent effects and no clear evidence of genotoxicity in the presence of metabolic activation. Trimethylbenzoyl Diphenylphosphine Oxide (purity 99%; in DMSO) was non-clastogenic in a chromosomal aberration assay using Chinese hamster lung cells at up to 30 µg/ml, with and without metabolic activation. In a comet assay, Trimethylbenzoyl Diphenylphosphine Oxide (purity > 99.8%; in ethanol) resulted in statistically significant increases in tail intensity in fetal lung fibroblasts at ≥ 0.04 µg/ml (tail intensity not increased at 0.008 µg/ml).[26]

CARCINOGENICITY STUDIES

No relevant carcinogenicity studies on the ingredients reviewed in this report were found in the published literature, and unpublished data were not submitted.

OTHER RELEVANT STUDIES

Cytotoxicity

Bis-Trimethylbenzoyl Phenylphosphine Oxide, Ethyl Trimethylbenzoyl Phenylphosphinate and Trimethylbenzoyl Diphenylphosphine Oxide

The cytotoxic potential of Bis-Trimethylbenzoyl Phenylphosphine Oxide, Ethyl Trimethylbenzoyl Phenylphosphinate and Trimethylbenzoyl Diphenylphosphine Oxide (1 – 50 µM; vehicle: 0.2% ethanol) was evaluated in various mammalian cell lines (human embryonic kidney cells (HEK293T), human umbilical vein endothelial cells (HUVEC-12), human fetal hepatocyte line (L02), and primary lymphocyte cells; 24 h incubation).[27] Cells were treated with 0.2% ethanol as the negative control. HEK293T cells were exposed to the test substance with and without irradiation (irradiation with 455 nm blue light for 5 min). Cytotoxicity was evaluated via an MTT assay and a cell counting kit-8 (CCK-8) assay (for lymphocyte cells only). Bis-Trimethylbenzoyl Phenylphosphine Oxide exhibited the highest cytotoxicity among the evaluated photoinitiators. Dose-dependent decreases in cell viability were observed in all cell types under both irradiated and non-irradiated conditions. At 50 µm, cell viability was approximately 40 - 45% in all cell types, under non-irradiated conditions, and around 35% in irradiated HEK293T cells. Conversely, without irradiation, Ethyl Trimethylbenzoyl Phenylphosphinate did not induce cytotoxicity in any cell type (cell viability in treated groups were comparable to controls (approximately

100%). After irradiation, viability in HEK293T cells exposed to Ethyl Trimethylbenzoyl Phenylphosphinate was approximately 80%. Exposure to Trimethylbenzoyl Diphenylphosphine Oxide with and without irradiation led to a clear dose-dependent decrease in viability in all evaluated cell types. At 50 µm, cell viability was approximately 80% in all cell types, under non-irradiated conditions, and around 65% in irradiated HEK293T cells.

Trimethylbenzoyl Diphenylphosphine Oxide

The cytotoxicity of Trimethylbenzoyl Diphenylphosphine Oxide (1 – 50 µM; vehicle: 1% dimethyl sulfoxide) was also evaluated in a different assay using L-929 fibroblasts (performed according to International Organization for Standardization (ISO) standard 10993-5:2009).[28] MTT assays were performed to evaluate cytotoxicity after a 24 h incubation period. Cell viability was approximately 93.35, 92.01, 85.14, 76.80, and 61.84% when tested at 1, 5, 10, 25, and 50 µM, respectively. Cell viability of the positive and negative controls was 7.58 and 95.8%, respectively (substances used for positive and negative controls not stated).

The cytotoxic effect of Trimethylbenzoyl Diphenylphosphine Oxide with and without irradiation was evaluated in breast cancer cells (human Michigan Cancer Foundation-7 (MCF-7) and mouse 4T1 cells).[29] Cells were plated and incubated overnight with Trimethylbenzoyl Diphenylphosphine Oxide at concentrations of 5, 10, 20, 40, and 80 µM. Cells were cultured in two different types of environments (dark for up to 24 h or exposed to irradiation (405 nm) for different irradiation times (0, 1, 5, 10, and 15 min)). 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assays were performed to evaluate cell viability after exposure to the test substance. A statistically significant decrease of cell viability in 4T1 and MCF-7 cells was observed in the dark group at concentrations of 40 µM and higher, compared to the control group ($p < 0.05$). Irradiation use resulted in further decreased cell viability in both 4T1 cells and MCF-7 cells. Further testing of the apoptotic effect of Trimethylbenzoyl Diphenylphosphine Oxide (0, 5 or 20 µM) in MCF-7 and 4T1 cells was evaluated via fluorescence microscopy with and without 15 min of irradiation (405 nm). Apoptosis was not observed in non-irradiated cells in a statistically significant manner; however, significant cell death was observed in irradiated cells in a concentration-dependent manner (effect was statistically significant at both tested concentrations in 4T1 cells and at a concentration of 20 µM in MCF-7 cells).

Sensitization Studies in Nails

Trimethylbenzoyl Diphenylphosphine Oxide

Sensitization assays were performed using a nail gel color containing a 2.6% Trimethylbenzoyl Diphenylphosphine Oxide (n = 51) and a nail gel sealer containing Trimethylbenzoyl Diphenylphosphine Oxide at an unknown concentration (n = 50).[6] These substances were applied to the nails 3x/wk for a total of 9 induction applications, followed by a challenge application 2 wk after the last induction application. Each application consisted of a single coat applied using a brush, left on for 10 min, and wiped off. The test substances were considered to be non-irritating and non-sensitizing to the nail and cuticle. It should be noted that these products would typically be used prior to polymerization, and polymerization was not performed in these assays.

Tolerability of UV/LED Gel Nail System

A 6-wk use study was performed in 32 adult female subjects to evaluate the skin and nail tolerability of a UV/LED-curable gel nail system consisting of a base coat containing 2.19% Ethyl Trimethylbenzoyl Phenylphosphinate, 2 color coats containing either up to 5.29% Ethyl Trimethylbenzoyl Phenylphosphinate or up to 0.33% Bis-Trimethylbenzoyl Phenylphosphine Oxide, and a top coat containing 1.98% Ethyl Trimethylbenzoyl Phenylphosphinate.[30] Products were applied and removed by trained nail technicians according to intended-use instructions, with 2 complete application and removal cycles performed during the study. Skin and nail assessments were conducted at baseline and after 3 and 6 wk of use. Occasional dryness, tension, or tickling was reported by a small number of subjects and was generally very slight in severity. Small increases in nail roughness and grooving were observed in some subjects, but remained very slight; nail discoloration was minimal and infrequent. The investigators concluded that the evaluated UV/LED gel nail regimens demonstrated good to very good skin and nail tolerability under the conditions of use. Results of the dermal irritation evaluations performed in this study are described in the Dermal Irritation section.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Details on the dermal irritation and sensitization studies summarized below can be found in Table 8.

Bis-Trimethylbenzoyl Phenylphosphine Oxide (purity not stated; applied moistened with water; 4-h application) did not result in irritation when evaluated in rabbits under semi-occlusive conditions.[5] Similarly, no irritation was observed when Ethyl Trimethylbenzoyl Phenylphosphinate (purity not stated; applied neat) was applied to the skin of rabbits for 4 h under occlusive conditions.[4] Local skin irritation was observed following application of 40% Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.5%; in olive oil; semi-occlusive application) to the skin of rats for 24 h.[3,6] (Results regarding systemic toxicity endpoints evaluated in this study can be found in the Acute Toxicity section of this report.) A 50% aqueous formulation of Trimethylbenzoyl Diphenylphosphine Oxide (purity > 98%) was slightly irritating in an assay performed in rabbits in which the test substance was applied to intact and abraded skin (use of occlusion and exposure duration not stated; however, it can be assumed to be 24 h as this was the first observation point). No signs of irritation were observed (e.g.,

erythema, itching) in a use assay in which a gel nail system consisting of a base coat containing 2.19% Ethyl Trimethylbenzoyl Phenylphosphinate, 2 color coats containing either up to 5.29% Ethyl Trimethylbenzoyl Phenylphosphinate or up to 0.33% Bis-Trimethylbenzoyl Phenylphosphine Oxide, and a top coat containing 1.98% Ethyl Trimethylbenzoyl Phenylphosphinate was used in 32 subjects.[30] Similarly, no irritation was observed in a use assay in which subjects (n = 34) applied, removed, and re-applied nail products containing Trimethylbenzoyl Diphenylphosphine Oxide (base coat, gel nail color, and top coat containing 0.25, 3.65, and 1.5%, respectively; curing in between each coat) 3 times over a 6-wk period.[31]

Bis-Trimethylbenzoyl Phenylphosphine Oxide (purity 95 – 98.4%; intradermal induction concentrations: 0.5 – 1%; epicutaneous induction concentrations: 50 – 70%; challenge concentrations of 10 – 70% in petrolatum or acetone) was sensitizing in guinea pig maximization tests (GPMT).[5] Similarly, Ethyl Trimethylbenzoyl Phenylphosphinate (purity 95.7%; up to 50% in acetone and olive oil) was positive in a local lymph node assay (LLNA) performed in mice.[4] In an LLNA using mice, Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.5%) applied at up to 50% was considered sensitizing.[3,6]

OCULAR IRRITATION STUDIES

Details on the ocular irritation studies summarized below may be found in Table 9.

Bis-Trimethylbenzoyl Phenylphosphine Oxide (purity 98.4%) was applied to the eyes of rabbits and resulted in fully reversible eye irritation, including diffuse conjunctival redness and slight swelling.[5] Ethyl Trimethylbenzoyl Phenylphosphinate (purity not stated) was applied to the eyes of rabbits and produced no significant eye irritation; all observed effects were reversible.[4] Trimethylbenzoyl Diphenylphosphine Oxide (purity > 98%) applied to rabbit eyes induced reversible conjunctival redness in all animals and corneal opacity in 2 animals; scores differed depending on ECHA or SCCS reporting.[3,6]

RISK ASSESSMENT

Systemic Exposure and MOE Assessment

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

Two approaches for estimating systemic exposure and calculating MOEs are presented below: an SCCS-based approach[6] and a refined approach provided in an industry submission.[8] The approaches differ in their product application amounts, treatment of application frequency, absorption assumptions, and adjustments to the oral PODs.

SCCS-Based Exposure Assessment

The SCCS-based calculations below used a gel application amount of 4 g, corresponding to the upper end of the reported range (2 – 4 g) for a full application of nail enhancement products.[6] It was assumed that 1% of the initial amount of each ingredient remained following polymerization and that 100% of this residual amount was absorbed through the nail plate.[6] Exposure of the periungual skin was not estimated separately, and the SED was calculated without averaging exposure over the interval between applications. For each ingredient, the oral POD was multiplied by 0.5 to account for the assumed 50% oral bioavailability. Details regarding the parameters used in the SCCS-based calculations are provided in Table 10.

Trimethylbenzoyl Diphenylphosphine Oxide

The SCCS calculated an MOE of 1515 at a maximum concentration of 5%, using an NOAEL of 100 mg/kg bw/d and a bioavailability-adjusted POD of 50 mg/kg bw/d.[6] Because an NOAEL of 60 mg/kg bw/d was identified in a one-generation reproductive toxicity study,[3] CIR staff calculated an additional, more conservative MOE using this value as the POD and otherwise retaining the assumptions used in the SCCS assessment. Following adjustment for 50% bioavailability, the resulting POD was 30 mg/kg bw/d and the calculated MOE was 909.

Ethyl Trimethylbenzoyl Phenylphosphinate

Using the same conservative SCCS approach, CIR staff calculated an MOE for Ethyl Trimethylbenzoyl Phenylphosphinate using the maximum reported concentration of use of 6.2%.[32] An NOAEL of 100 mg/kg bw/d from a 90-d repeated dose oral toxicity study[4] was selected as the POD. Of note, a NOEL of 100 mg/kg bw/d was also identified in a prenatal developmental toxicity study [4], providing the same POD based on a developmental toxicity endpoint. Following adjustments for 50% oral bioavailability, the resulting POD was 50 mg/kg bw/d, and the calculated MOE was approximately 1211.

Refined Exposure Assessment

The refined assessment submitted by industry incorporated product-use data and application frequency and estimated systemic exposure through the nail plate and periungual skin separately.[8] The submitted calculations did not apply the 50% oral bioavailability adjustment used in the SCCS-based calculations.

The submission selected a product application amount of 0.21 g, reported as the 95th-percentile amount per layer based on use studies evaluating professionally applied and self-applied gel polish systems.[8] The selected per-layer amount was used without summing the amounts across all layers. Because UV-curable gel systems are applied and cured sequentially, application amounts across layers were not summed; instead, the highest measured per-layer was used to represent high-end exposure without including product from layers that had already undergone curing. An additional conservative scenario was evaluated for the systemic exposure and MOE assessment using twice this amount (0.42 g) to represent combined manicure and pedicure use during the same treatment session. For both scenarios, an application frequency of once every 2 wk was assumed, exposure was averaged over this interval, and a default body weight of 60 kg was used.

The nail plate penetration adjustment factors were derived based on a published framework that assigns categorical adjustment factors for molecular weight, vapor pressure, log P, water solubility, keratin binding, and polymerization-induced trapping within the cured coating .[23] Multiplication of these factors resulted in overall penetration adjustment factors of 0.00025 and 0.0004 for Bis-Trimethylbenzoyl Phenylphosphine Oxide and Ethyl Trimethylbenzoyl Phenylphosphinate, respectively.

Based on reported nail plate and nail wall surface areas, 82% of the applied product was assigned to the nail plate, and 18% to the periungual skin.[33] The model-derived nail plate permeation adjustment factors described above were further applied to the nail plate portion, while 50% dermal absorption was assumed for the periungual skin portion. The nail plate and periungual skin contributions were summed to obtain the total SED.

Bis-Trimethylbenzoyl Phenylphosphine Oxide

For Bis-Trimethylbenzoyl Phenylphosphine Oxide, the submitted assessment selected an NOAEL of 300 mg/kg bw/d from a 90-d repeated-dose oral toxicity study.[5] This value was adjusted by a factor of 2 to account for extrapolation from subchronic to potential chronic exposure, resulting in a POD of 150 mg/kg bw/d. Using an overall nail plate penetration adjustment factor of 0.00025 and a concentration of 0.69%, the total SED for the 0.21-g application scenario was 0.000156 mg/kg bw/d, resulting in an MOE of 963,988. For the combined manicure and pedicure application scenario (0.42 g), the MOE was 481,994. It should be noted that the source of the 0.69% concentration used in the submitted assessment was not identified, while no concentration-of-use data for this ingredient were reported in the Council's 2025 survey.

Ethyl Trimethylbenzoyl Phenylphosphinate

For Ethyl Trimethylbenzoyl Phenylphosphinate, the submitted assessment selected an NOAEL of 100 mg/kg bw/d from the 90-d repeated-dose oral toxicity study[4] as the POD (no additional adjustment to this POD was reported). Using an overall nail plate penetration adjustment factor of 0.0004 and a concentration of 5.6%, the total SED for the 0.21-g application scenario was 0.00126 mg/kg bw/d, resulting in an MOE of 79,077. For the combined manicure and pedicure application scenario (0.42 g), the MOE was 39,538. The source of the 5.6% concentration used in the submitted assessment was not identified.

CIR staff recalculated the SED and MOE using the maximum concentration of use of 6.2% reported in the Council's 2025 survey, while retaining the PODs and other exposure assumptions used in the submitted assessment. For the 0.21-g scenario, the SED was approximately 0.0014 mg/kg bw/d, resulting in an MOE of 71,400. For the combined manicure and pedicure scenario (0.42 g), the MOE was approximately 35,700.

Skin Sensitization Risk Assessment

A skin sensitization risk assessment was performed for Bis-Trimethylbenzoyl Phenylphosphine Oxide and Ethyl Trimethylbenzoyl Phenylphosphinate.[8] Potential sensitization exposure was evaluated for 2 scenarios: inadvertent periungual skin contact with uncured product during application and incidental skin contact with the cured nail coating during wear. For the wet-application scenario, 18% of the applied product was assumed to contact 3.3 cm^2 of periungual skin, and a retention factor of 0.1 was applied to account for the limited duration of contact with uncured product.

Bis-Trimethylbenzoyl Phenylphosphine Oxide

For Bis-Trimethylbenzoyl Phenylphosphine Oxide, an LLNA-derived EC_3 was not available; therefore, a WoE approach was used to characterize sensitization potency. Structural alert analysis identified Schiff-base-forming reactivity; however, the ingredient did not meet the criteria for classification as a high-potency contact allergen. Accordingly, a dermal sensitization threshold (DST) of 73 µg/cm² for reactive, non-high-potency sensitizers was used in the assessment. For the wet-application scenario, the calculated consumer exposure level (CEL) was 7.90 µg/cm².

Residual Bis-Trimethylbenzoyl Phenylphosphine Oxide was not analytically determined; therefore, the Ethyl Trimethylbenzoyl Phenylphosphinate extractable loading was used as a conservative upper-bound surrogate for Bis-Trimethylbenzoyl Phenylphosphine Oxide. The estimated CELs for the wet-application and post-cure scenarios were below the corresponding DST.

Ethyl Trimethylbenzoyl Phenylphosphinate

For Ethyl Trimethylbenzoyl Phenylphosphinate, an EC_3 value of 16.4% from an LLNA[4] was used to derive a no-expected-sensitization-induction level (NESIL) of 4100 µg/cm². Application of a safety assessment factor of 10 to account for interindividual variability resulted in an acceptable exposure level (AEL) of 410 µg/cm². For the wet-application scenario, the calculated CEL was 63.92 µg/cm².

For the post-cure exposure scenario, residual Ethyl Trimethylbenzoyl Phenylphosphinate was quantified in a film representing a complete salon-applied gel nail system consisting of a basecoat, 2 color coats, and a topcoat. Following sequential application and curing, film samples were extracted for 20 h at 37°C and analyzed by HPLC. The amount extracted from the cured film was 39,280 µg/g, corresponding to 456 µg/cm². Because the extraction procedure was designed to maximize recovery of residual photoinitiator from the cured polymer matrix, this value was considered a conservative estimate of the amount potentially available following curing. The extractable amount was time-averaged over the 2-wk wear period, resulting in a CEL of 32.57 µg/cm². The estimated CELs for the wet-application and post-cure scenarios were below the AEL of 410 µg/cm².

SUMMARY

The safety of Bis-Trimethylbenzoyl Phenylphosphine Oxide, Ethyl Trimethylbenzoyl Phenylphosphinate, and Trimethylbenzoyl Diphenylphosphine Oxide as used in cosmetics is reviewed in this report. Bis-Trimethylbenzoyl Phenylphosphine Oxide and Ethyl Trimethylbenzoyl Phenylphosphinate are reported to function as light stabilizers in cosmetics, and Trimethylbenzoyl Diphenylphosphine Oxide is reported to function as an artificial nail builder in cosmetics.

According to RLD submitted by the FDA in 2025, Trimethylbenzoyl Diphenylphosphine Oxide has the highest frequency of use among the ingredients reviewed in this report (it is used in 4399 total formulations). However, Ethyl Trimethylbenzoyl Phenylphosphinate is reported to have the highest concentration of use (it is used at up to 6.2% in nail polish and enamel). The primary use of all 3 ingredients reviewed in this report are in nail products.

Trimethylbenzoyl Diphenylphosphine Oxide is used as a photoinitiator in nail products and is therefore used in gel products (nail enhancement products and gel nail polishes) requiring light curing. Full application of nail enhancement products typically results in a maximum exposure of 200 mg Trimethylbenzoyl Diphenylphosphine Oxide for all nail plates. Nail products containing Bis-Trimethylbenzoyl Phenylphosphine Oxide and Ethyl Trimethylbenzoyl Phenylphosphinate are also applied to the nail plate in sequentially cured layers and typically remain on the nails for 2 – 3 wk. The amount of Trimethylbenzoyl Diphenylphosphine Oxide extracted was lower than the limit of detection (0.2 ppm) after curing in an assay in which the amount of Trimethylbenzoyl Diphenylphosphine Oxide was quantified in artificial nails painted with gel polishes (base, intermediate, and topcoat) containing 3% Trimethylbenzoyl Diphenylphosphine Oxide.

Bis-Trimethylbenzoyl Phenylphosphine Oxide (tested neat), Ethyl Trimethylbenzoyl Phenylphosphinate (tested neat), and Trimethylbenzoyl Diphenylphosphine Oxide (tested at 40%) resulted in dermal LD_{50}s > 2000 mg/kg bw in rats in acute studies performed under semi-occlusive conditions. An oral LD_{50} of > 2000 mg/kg bw was observed in an oral acute toxicity assay in which rats were given Bis-Trimethylbenzoyl Phenylphosphine Oxide (tested at 20%). LD_{50}s of > 5000 mg/kg were determined in acute oral toxicity assays performed in rats using Ethyl Trimethylbenzoyl Phenylphosphinate (tested at up to 50%) and Trimethylbenzoyl Diphenylphosphine Oxide (tested at up to 50%). No abnormalities or deaths were observed in an acute inhalation toxicity assay in which rats were exposed whole-body to 0.000027 mg/l Ethyl Trimethylbenzoyl Phenylphosphinate for 7 h.

Bis-Trimethylbenzoyl Phenylphosphine Oxide showed an NOAEL of 1000 mg/kg bw/d in 7- and 28-d studies and an NOEL of 300 mg/kg bw/d in a 3-mo study. Ethyl Trimethylbenzoyl Phenylphosphinate produced adverse effects at ≥ 150 – 500 mg/kg bw/d, including increased liver, kidney, and adrenal weights, decreased spleen weights, and hematological changes (assays ranged from 7 d to 13 wk). Trimethylbenzoyl Diphenylphosphine Oxide showed NOAELs of 50 – 100 mg/kg bw/d in 28- and 90-d studies, with higher doses resulting in reduced body weight, organ weight increases, and testicular atrophy. All short-term and subchronic toxicity assays were performed in rats via gavage.

No maternal or fetal toxicity was observed when Bis-Trimethylbenzoyl Phenylphosphine Oxide (up to 1000 mg/kg bw/d; purity not stated) was administered to rats on GD 6 – 19. Ethyl Trimethylbenzoyl Phenylphosphinate (purity 96.8–97.8%; by gavage on GD 6 - 29) resulted in a prenatal developmental toxicity NOAEL of 300 mg/kg bw/d. Trimethylbenzoyl Diphenylphosphine Oxide (purity not stated) in produced maternal and developmental effects (reduced maternal weight gain, fetal skeletal variations) at 500 mg/kg bw/d in rats (treatment on days post-coitum 6 – 20). In a one-generation reproductive toxicity study in rats, Trimethylbenzoyl Diphenylphosphine Oxide (99.3% purity; up to 600 mg/kg bw/d; 10 – 12-wk administration) gave an overall reproductive NOAEL of 60 mg/kg bw/d. In rabbits, administration of Trimethylbenzoyl Diphenylphosphine Oxide (99.3% purity; up to 100 mg/kg bw/d; treatment on days 6 – 28 post-coitum) showed no maternal or dose-dependent fetal toxicity. All developmental and reproductive toxicity studies were performed via gavage.

In gene mutation assays, Bis-Trimethylbenzoyl Phenylphosphine Oxide (purity not stated), Ethyl Trimethylbenzoyl Phenylphosphinate (purity 95.7 – 100%), and Trimethylbenzoyl Diphenylphosphine Oxide (purity 99 – 99.8%) were non-

genotoxic in Ames assays at up to 2500 – 5000 µg/plate and mammalian cell gene mutation assays at up to 80, 3300, and 40.5 µg/ml, respectively, with and without metabolic activation. In assays evaluating chromosomal damage, Bis-Trimethylbenzoyl Phenylphosphine Oxide was negative in a chromosomal aberration assay at up to 100 µg/ml, and Trimethylbenzoyl Diphenylphosphine Oxide was non-clastogenic in a chromosomal aberration assay at up to 30 µg/ml. Ethyl Trimethylbenzoyl Phenylphosphinate was non-clastogenic in V79 micronucleus assays; in human lymphocyte micronucleus and chromosomal aberration assays, statistically significant increases were observed primarily at high or cytotoxic concentrations, with no consistent dose-dependent effects. In a comet assay, Trimethylbenzoyl Diphenylphosphine Oxide resulted in significant increases in tail intensity in fetal lung fibroblasts at ≥ 0.04 µg/ml.

The cytotoxic potential of Bis-Trimethylbenzoyl Phenylphosphine Oxide, Ethyl Trimethylbenzoyl Phenylphosphinate, and Trimethylbenzoyl Diphenylphosphine Oxide (1 – 50 µM) was evaluated in various mammalian cell lines. Bis-Trimethylbenzoyl Phenylphosphine Oxide produced the greatest cytotoxicity, with dose-dependent decreases in cell viability under both irradiated and non-irradiated conditions. Ethyl Trimethylbenzoyl Phenylphosphinate was largely non-cytotoxic without irradiation and only slightly reduced viability following irradiation. Trimethylbenzoyl Diphenylphosphine Oxide caused moderate, dose-dependent cytotoxicity, which increased with irradiation. The cytotoxicity of Trimethylbenzoyl Diphenylphosphine Oxide (1 – 50 µM; vehicle: 1% dimethyl sulfoxide) was also evaluated in a different assay using L-929 fibroblasts. Cell viability was approximately 93.35, 92.01, 85.14, 76.80, and 61.84 % when tested at 1, 5, 10, 25, and 50 µM, respectively. The cytotoxic potential of Trimethylbenzoyl Diphenylphosphine Oxide (5 – 80 µM) with and without irradiation was evaluated in breast cancer cells (MCF-7 and 4T1 cells). A statistically significant decrease of cell viability in 4T1 and MCF-7 cells was observed in the dark group at concentrations of 40 um and higher, compared to the control group ($p < 0.05$). Irradiation resulted in further decreased cell viability in both 4T1 cells and MCF-7 cells.

No irritation or sensitization were observed in studies performed using a nail gel color containing a 2.6% Trimethylbenzoyl Diphenylphosphine Oxide (n = 51) and a nail gel sealer containing Trimethylbenzoyl Diphenylphosphine Oxide at an unknown concentration (n = 50); applications performed directly on the nails. It should be noted that these products would typically be used prior to polymerization, and polymerization was not performed in these assays.

In a 6-wk use study of a UV/LED-curable gel nail system containing Ethyl Trimethylbenzoyl Phenylphosphinate (up to 5.29%) or Bis-Trimethylbenzoyl Phenylphosphine Oxide (up to 0.33%), no treatment-related adverse reactions were observed. The tested gel nail regimens demonstrated good to very good skin and nail tolerability under the conditions of use.

Bis-Trimethylbenzoyl Phenylphosphine Oxide (purity not stated; moistened with water; 4-h semi-occlusive) and Ethyl Trimethylbenzoyl Phenylphosphinate (purity not stated; neat; 4-h occlusive) were non-irritating in rabbits. Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.5%; 40% in olive oil, 24-h semi-occlusive) caused local irritation in rats, while a 50% aqueous formulation (purity > 98%) was slightly irritating in rabbits (use of occlusion and exposure duration not stated). No signs of irritation were observed in a 6-wk use study of a gel nail system containing up to 5.29% Ethyl Trimethylbenzoyl Phenylphosphinate and up to 0.33% Bis-Trimethylbenzoyl Phenylphosphine Oxide in 32 subjects. Similarly, no irritation occurred in a 6-wk human use study (n = 34) with nail products containing up to 3.65% Trimethylbenzoyl Diphenylphosphine Oxide. Bis-Trimethylbenzoyl Phenylphosphine Oxide (purity 95 – 98.4%; challenge concentration: 10–70%) was sensitizing in GPMTs, and Ethyl Trimethylbenzoyl Phenylphosphinate (purity 95.7%; up to 50%) and Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.5%; up to 50%) were sensitizing in LLNAs.

Bis-Trimethylbenzoyl Phenylphosphine Oxide (98.4%) and Trimethylbenzoyl Diphenylphosphine Oxide (>98%) caused reversible eye irritation in rabbits. Ethyl Trimethylbenzoyl Phenylphosphinate (purity not stated) caused no significant irritation.

In an SCCS assessment of Trimethylbenzoyl Diphenylphosphine Oxide at 5%, an MOE of 1515 was calculated; use of the more conservative reproductive toxicity POD of 60 mg/kg bw/d resulted in an MOE of 909. Using the same conservative approach, an MOE of 1211 was calculated for Ethyl Trimethylbenzoyl Phenylphosphinate at the maximum reported concentration of use of 6.2%. Using a refined exposure model provided in an industry submission, MOEs of approximately 71,400 and 963,988 were calculated for Ethyl Trimethylbenzoyl Phenylphosphinate at 6.2% and Bis-Trimethylbenzoyl Phenylphosphine Oxide at the submitted concentration of 0.69% respectively; under a combined manicure/pedicure scenario, the corresponding MOEs were approximately 35,700 and 481,994, respectively. In skin sensitization risk assessments, wet-application CELs were 63.92 and 7.90 µg/cm² for Ethyl Trimethylbenzoyl Phenylphosphinate and Bis-Trimethylbenzoyl Phenylphosphine Oxide, respectively, and the post-cure CEL was 32.57 µg/cm² for Ethyl Trimethylbenzoyl Phenylphosphinate; all estimated exposures were below the respective AEL or DST.

DRAFT DISCUSSION

[Note: This Discussion is in the draft form, and changes will be made following the Panel meeting.]

This assessment reviews the safety of Bis-Trimethylbenzoyl Phenylphosphine Oxide, Ethyl Trimethylbenzoyl Phenylphosphinate, and Trimethylbenzoyl Diphenylphosphine Oxide as used in cosmetic formulations, in accordance with the product categories and concentration of use identified in the Use section and Use table. The Panel considered the available data and concluded …[TBD].

The Panel discussed the issue of incidental inhalation exposure resulting from these ingredients (e.g., Trimethylbenzoyl Diphenylphosphine Oxide is used in perfumes (concentration not stated)). Inhalation toxicity data were not available. However, the Panel noted that the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the low concentrations at which these ingredients are used (or expected to be used) in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

At least 1 use for the ingredients assessed in this assessment is reported in the RLD under Category 17, "other preparations." For instances wherein the use of an ingredient in a cosmetic product is only categorized as Category 17, and other information in the RLD is not indicative of use type, the present practices of use for such products remain unknown and the Panel's safety assessment conclusion, therefore, does not apply thereon.

The Panel's respiratory exposure resource document (see link above) notes that airbrush technology presents a potential safety concern. Although frequency and concentration of use data are now available (and in some cases mandated) for ingredients marketed for use with airbrush delivery systems in certain product categories, no data are available for consumer habits and practices thereof, product particle size, or other relevant particle data (e.g., diameter). As a result of deficiencies in these critical data needs, the data profile is incomplete, and the safety of cosmetic ingredients applied by airbrush delivery systems cannot be determined by the Panel. Accordingly, the Panel has concluded the data are insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

CONCLUSION

To be determined.

TABLES

Table 1. Definitions, idealized structures, and reported functions[1, CIR Staff]

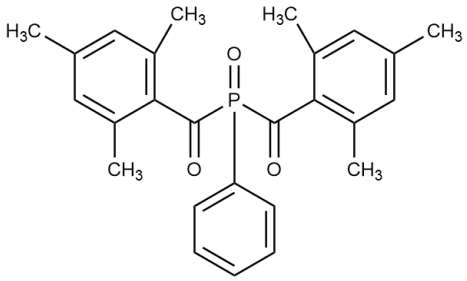
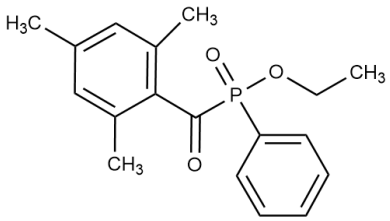
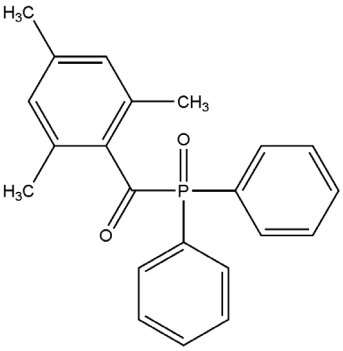
Ingredient/CAS No.	Definition	Function(s)
Bis-Trimethylbenzoyl Phenylphosphine Oxide (162881-26-7)	Bis-Trimethylbenzoyl Phenylphosphine Oxide is the organic compound that conforms to the structure: 	light stabilizer
Ethyl Trimethylbenzoyl Phenylphosphinate (84434-11-7)	Ethyl Trimethylbenzoyl Phenylphosphinate is the organic compound that conforms to the structure: 	light stabilizer
Trimethylbenzoyl Diphenylphosphine Oxide (75980-60-8)	Trimethylbenzoyl Diphenylphosphine Oxide is the organic compound that conforms to the structure: 	artificial nail builder

Table 2. Chemical properties

Property	Value	Reference
Bis-Trimethylbenzoyl Phenylphosphine Oxide		
Physical Form	liquid, pellets, or large crystals	[11]
Color	yellow	[5]
Molecular Weight (g/mol)	418.5	[11]
Density (kg/m^3 at 21 ºC)	1190	[5]
Vapor Pressure (Pa @ 20 ºC)	0.0000002	[5]
Melting Point (ºC)	131.4	[5]
Water Solubility (g/l @ 20 ºC)	< 0.0001	[5]
log K_{ow} (@ 22 ºC)	5.8	[5]
UV Absorption (λ_{max}; nm)	370, 400	[13]
Particle Size Distribution (mean mass median diameter; µm)	25.5	[5]
Ethyl Trimethylbenzoyl Phenylphosphinate		
Physical Form	liquid	[10]
Color	yellow	[10]
Molecular Weight (g/mol)	316.3	[10]
Vapor Pressure (Pa @ 20 ºC)	0.00021	[10]
Boiling Point (ºC)	257.4	[10]
Water Solubility (mg/l @ 20 ºC)	35	[10]
log K_{ow} (@ 25 ºC)	2.9	[10]
UV Absorption (λ_{max}; nm)	230, 275, 370	[12]
Trimethylbenzoyl Diphenylphosphine Oxide		
Physical Form	liquid, pellets, large crystals, or dry powder	[3,9]
Color	yellow	[3]
Molecular Weight (g/mol)	348.4	[9]
Specific Gravity (@ 20 ºC)	1.218	[3]
Vapor Pressure (Pa @ 25ºC)	0.00000305	[6]
Melting Point (ºC)	93	[3]
Boiling Point (ºC)	> 300	[6]
Water Solubility (mg/l @ 20 ºC & pH of 6.9)	3.4	[3]
log K_{ow} (@ 23 ºC & pH of 6.4)	3.1	[3]
UV Absorption (λ_{max};) nm)	235, 290, 385	[6]
Particle Size Distribution (mean mass median diameter; µm)	172.6	[3]

Table 3. Frequency and concentration of use according to likely duration and exposure and by product category[17-20]

	Bis-Trimethylbenzoyl Phenylphosphine Oxide		Ethyl Trimethylbenzoyl Phenylphosphinate		Trimethylbenzoyl Diphenylphosphine Oxide	
	# of Uses	Max Conc of Use	# of Uses	Max Conc of Use	# of Uses	Max Conc of Use
	RLD (2025)	% (2025)	RLD (2025)	% (2025)	RLD (2025)	% (2025)
Totals*	**505**	**NR**	**3436**	**0.25 – 6.2**	**4399**	**0.25 – 5%**
summarized by likely duration and exposure**						
Duration of Use						
Leave-On	*550*	*NR*	*3938*	*0.25 – 6.2*	*5150*	*0.25 – 5%*
Rinse-Off	*21*	*NR*	*2179*	*NR*	*71*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Permanent Tattoo Ink	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Unknown	*8*	*NR*	*28*	*NR*	*30*	*NR*
Exposure Type						
Baby Products	NR	NR	NR	NR	NR	NR
Children's Makeup	NR	NR	5	NR	2	NR
Eye Area	14	NR	2	NR	5	NR
Incidental Ingestion	1	NR	14	NR	8	NR
Mucous Membrane	NR	NR	14	NR	8	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	68	NR
Incidental Inhalation-Airbrush	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	20	NR	12	NR	97	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	16	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	540	NR	3958	0.25 – 6.2	5138	0.25 - 5
Tattoo Preparations	NR	NR	NR	NR	NR	NR
Other Preparations (Unknown Exposure Type)	8	NR	28	NR	30	NR
as reported by product category						
Eye Makeup Preparations (not children's)						
Mascara			1	NR		
Eyelash and Eyebrow Adhesives/Glues/Sealants	14	NR			5	NR
Eyelash Cleansers			1	NR		
Fragrance Preparations						
Perfumes					68	NR
Hair Preparations (non-coloring)						
Rinses (non-coloring)	8	NR				
Other Hair Preparations	8 (l.o.)	NR				
Makeup Preparations (not eye or children's)						
Lipsticks and Lip Glosses	1	NR	12	NR	8	NR
Makeup Preparations for Children (not eye)						
Children's Foundations					1	NR
Children's Lipsticks and Lip Glosses			2	NR		
Other Children's Makeup			3	NR	1	NR
Manicuring Preparations						
Basecoats and Undercoats	35	NR	306	NR	255	0.25 – 0.7
Cuticle Softeners	6	NR	8	NR	22	NR
Nail Creams and Lotions	7	NR	48	NR	52	NR
Nail Extenders	14	NR	342	NR	468	NR
Nail Polish and Enamel	432	NR	2170	4 – 6.2	3299	3 – 5
Nail Polish and Enamel Removers	7	NR	30	NR	49	NR

Table 3. Frequency and concentration of use according to likely duration and exposure and by product category[17-20]

	Bis-Trimethylbenzoyl Phenylphosphine Oxide		Ethyl Trimethylbenzoyl Phenylphosphinate		Trimethylbenzoyl Diphenylphosphine Oxide	
	# of Uses	Max Conc of Use	# of Uses	Max Conc of Use	# of Uses	Max Conc of Use
	RLD (2025)	% (2025)	RLD (2025)	% (2025)	RLD (2025)	% (2025)
Other Manicuring Preparations	39	NR	1054	0.25	993	1.5
Other Preparations (i.e., those that do not fit another category)	8	NR	28	NR	30	NR

NR – not reported

*The sum of the counts given for duration of use and by exposure type, and the sum of the frequency reported by product category, may not equal the sum of total uses because each ingredient may be used in cosmetic formulations that are reported under more than one product category.

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

Table 4. Acute toxicity studies

Test Article	Vehicle	Animals/Group	Concentration/Dose	Protocol	LD_{50}/LC_{50}/Results	Reference
DERMAL						
Bis-Trimethylbenzoyl Phenylphosphine Oxide (purity not stated)	none	Sprague-Dawley rats (5/sex)	100% (corresponding to 2000 mg/kg bw)	OECD TG 402; test substance applied to clipped skin; semi-occlusive conditions; 24-h exposure; sites evaluated for 14 d	$LD_{50} \geq 2000$ mg/kg bw	5
Ethyl Trimethylbenzoyl Phenylphosphinate (purity: 95.7%)	none	Wistar rats (5/sex)	100% (corresponding to 2000 mg/kg bw)	OECD TG 402; test substance applied to clipped skin; semi-occlusive conditions; 24-h exposure; sites evaluated for 14 d	$LD_{50} \geq 2000$ mg/kg bw	4
Trimethylbenzoyl Diphenylphosphine Oxide (purity: 99.5%)	olive oil	Wistar rats (5/sex)	40% (corresponding to 2000 mg/kg bw)	OECD TG 402; test substance applied to clipped skin; semi-occlusive conditions; 24-h exposure; sites evaluated for 14 d	$LD_{50} \geq 2000$ mg/kg bw	3
ORAL						
Bis-Trimethylbenzoyl Phenylphosphine Oxide (purity: 98.4%)	water	Sprague-Dawley rats (5/sex)	20% (corresponding to 2000 mg/kg bw)	OECD TG 401; gavage administration; observation for 14 d	$LD_{50} \geq 2000$ mg/kg bw	5
Ethyl Trimethylbenzoyl Phenylphosphinate (purity: > 97%)	0.5% aqueous CMC	Wistar rats (5/sex/group)	26.1, 38.3, and 50% (corresponding 2610, 3830, and 5000 mg/kg)	OECD TG 401; gavage administration; observation for 14 d	$LD_{50} \geq 5000$ mg/kg bw (mortality occurred at all dose levels in females; mortality occurred in one male rat in the high-dose group)	4
Trimethylbenzoyl Diphenylphosphine Oxide (purity not stated)	0.5% aqueous CMC	Sprague-Dawley rats (5/sex/group)	10 and 50% (corresponding to 1000 and 5000 mg/kg bw)	OECD TG 401; gavage administration; observation for 14 d	$LD_{50} \geq 5000$ mg/kg bw	3
Trimethylbenzoyl Diphenylphosphine Oxide (purity: 99%)	arachis oil	Sprague-Dawley rats (5/sex)	50% (corresponding to 5000 mg/kg bw)	OECD TG 401; gavage administration; observation for 14 d	$LD_{50} \geq 5000$ mg/kg bw	3
INHALATION						
Ethyl Trimethylbenzoyl Phenylphosphinate (purity: > 97%)		Sprague-Dawley rats (3/sex)	0.000027 mg/l	OECD TG 403; whole-body inhalation exposure; exposure for 7 h; observation for 14 d	No abnormalities or deaths observed.	4,10

CMC = carboxymethylcellulose; LD_{50} = median lethal dose; OECD = Organisation for Economic Co-operation and Development; TG = test guideline

Table 5. Repeated-dose oral toxicity studies

Test Article	Vehicle	Animals/ Group	Study Duration	Dose/ Concentration	Protocol	Results	Reference
Bis-Trimethylbenzoyl Phenylphosphine Oxide (purity: 98.4%)	1% aqueous methylcellulose	Sprague-Dawley rats (3/sex/group)	7 d	0, 500, 750, or 1000 mg/kg bw/d	Dose-range finding study; animals given test substance via gavage; controls untreated; clinical chemistry, body weight, food and water consumption, mortality evaluated	No mortality or clinical signs of toxicity were observed. High-dosed females showed lower body weight gain (83% of control). Food and water consumption were mostly unaffected. Necropsy revealed no gross abnormalities. The NOAEL was determined to be 1000 mg/kg bw/d.	[5]
Bis-Trimethylbenzoyl Phenylphosphine Oxide (purity: 98.4%)	1% aqueous methylcellulose	Sprague-Dawley rats (5-10/sex/group)	28 d	0, 15, 150, and 1000 mg/kg bw/d	OECD TG 407; animals given test substance via gavage; controls untreated; mortality, body weight, food and water consumption, hematological analyses, urinalysis, organ weight assessment, and histopathological assessments were performed; following a 4-wk treatment period, 5 animals/sex from each group were retained for a 2-wk post-treatment recovery observation period	Doses up to 1000 mg/kg bw/d caused no mortality or treatment-related clinical signs, and body weight, food, and water intake were unaffected. After the treatment period, statistically significant changes (compared to controls) included increased neutrophil counts in males at 1000 mg/kg bw/d, elevated mean corpuscular hemoglobin in males at 15, 150, and 1000 mg/kg bw/d, decreased serum glutamic-oxaloacetic transaminase in females at 150 and 1000 mg/kg bw/d, decreased gamma-glutamyltransferase and alkaline phosphatase in males at 1000 mg/kg bw/d, reduced urinary volume and increased urinary protein in males at 15, 150, and 1000 mg/kg bw/d. There were no statistically significant differences in control and treated groups regarding hematological parameters, biochemical parameters, or urinalysis at the end of the recovery period. However, at the end of the recovery period, group mean spleen weight was statistically significantly higher in males in the highest dose group compared to controls (caused by a particularly high value for one animal; effect not seen after treatment period). All changes were considered incidental and not toxicologically relevant. The NOAEL was 1000 mg/kg bw/d.	[5]
Bis-Trimethylbenzoyl Phenylphosphine Oxide (purity: > 98.2%)	1% aqueous CMC	Crl:WI (Han) rats (10/sex/group)	92 d (male); 93 d (female)	0, 100, 300, or 1000 mg/kg bw/d	OECD TG 408; animals given test substance via gavage; control animals given vehicle only; mortality, body weight, food and water consumption, hematological analyses, organ weight assessment, and histopathological assessments were performed	No treatment-related effects were observed with 100 or 300 mg/kg bw/d. At the highest dose, increased hemoglobin, hematocrit, and red blood cell counts were observed in both sexes (statistically significant compared to controls). At this dose, reduced total protein and albumin was observed in males (statistically significant compared to controls). Duodenal thickening was observed in 6/10 males and 2/10 females in the highest dose group (this effect was not seen in controls or at lower doses). The NOEL was determined to be 300 mg/kg bw/d.	[5]
Ethyl Trimethylbenzoyl Phenylphosphinate (purity not stated)	NR	Wistar rats (4/group/sex)	7 d	0 or 500 mg/kg bw/d	dose-range finding assay; animals treated via gavage	Erosions/ulcerations in the glandular stomach were observed in 1 animal. Absolute liver weights were increased (+27%) compared to controls. Relative spleen weight was decreased (-21%) compared to controls.	[24]
Ethyl Trimethylbenzoyl Phenylphosphinate (purity not stated)	NR	Wistar rats (4/group/sex)	14 d	0 or 1000 mg/kg bw/d	dose-range finding assay; animals treated via gavage; blood samples taken at end of test period followed by necropsy	After treatment with test substance, 2 females in moribund condition were killed. All animals treated animals showed piloerection and salivation. Other observed effects in treated animals include apathy and hunched posture. Body weight was decreased up to 19% in males and 87% in females. Food consumption dropped by 36% in males and 35% in females. Significant organ changes included absolute liver weight increases in (+84% in males and +133% in females) and absolute kidney weight increases (+11% in males and +40% in females). Absolute adrenal gland weight was increased in males (+66%) and females (+23%). Spleen weights were decreased in males (-56%). Organ weight changes were compared to controls.	[24]

Table 5. Repeated-dose oral toxicity studies

Test Article	Vehicle	Animals/ Group	Study Duration	Dose/ Concentration	Protocol	Results	Reference
Ethyl Trimethylbenzoyl Phenylphosphinate (96.9% purity)	NR	female Wistar rats (7/group)	20 d	0, 150, or 500 mg/kg bw/d	dose-range finding assay; animals given test substance via gavage for 20 d; control animals used but details regarding treatment not stated; parameters evaluated: mortality, food/water consumption, clinical observations, adrenal gland, kidney, liver, and spleen weight, and clinical pathology	All animals survived. Treatment-related clinical signs in the high-dose group included salivation, abnormal activity, and piloerection. High-dose animals exhibited statistically significant reduction in body weight gain and food consumption compared to controls. Statistically significant increases in water consumption were observed at 150 and 500 mg/kg bw/d, compared to controls. Hematological and clinical chemistry analyses revealed dose-related, statistically significant abnormalities in the high-dose groups (e.g., increased white blood cell count and triglycerides). Organ weight analysis showed statistically significant increases in absolute and relative kidney, liver, and spleen weights at 500 mg/kg bw/d, with relative liver weights also statistically significantly increased at 150 mg/kg bw/d (compared to controls). Gross pathology findings included liver discoloration in 6/7 high-dose females and kidney pelvic dilation in 1 high-dose female.	[4]
Ethyl Trimethylbenzoyl Phenylphosphinate (purity: 95.7%)	1% aqueous CMC	Wistar rats (5/sex/group)	28 d	0, 50, 150, 500 mg/kg bw/d	OECD TG 407; animals given test substance via gavage; controls given vehicle; mortality, body weight, food and water consumption, hematological analyses, organ weight assessment, and histopathological assessments were performed	No mortality occurred at any dose. Salivation was observed at 500 mg/kg bw/d and sporadically at 150 mg/kg bw/d. Body weight, weight gain, food, and water consumption were unaffected, except a transient lower body weight change in females at 150 mg/kg bw/d on day 7 (not significant). Hematology and clinical chemistry changes (mean corpuscular volume, reticulocytes, monocytes, inorganic phosphate, creatinine, cholesterol, triglycerides) were observed in some groups but were either within historical ranges or non-adverse; cholesterol decrease in males and triglyceride increase in females at 500 mg/kg bw/d were treatment-related but not adverse. Urobilinogen increased at 500 mg/kg bw/d; non-adverse. Liver and kidney absolute and relative weights were statistically significantly increased at 500 mg/kg bw/d (compared to controls). The increase in liver weight correlated with slight centrilobular hepatocellular hypertrophy, with no signs of clinical chemistry or histopathological signs of toxicity indicating liver damage. The centrilobular liver hypertrophy was considered adaptive and non-adverse. The increase in kidney weight had no histopathological correlation and was interpreted as an adaptive response. The NOAEL was determined to be 500 mg/kg bw/d.	[4]

Table 5. Repeated-dose oral toxicity studies

Test Article	Vehicle	Animals/ Group	Study Duration	Dose/ Concentration	Protocol	Results	Reference
Ethyl Trimethylbenzoyl Phenylphosphinate (purity: 96.9%)	1% aqueous CMC	Wistar rats (10/sex/group)	13 wk	0, 20, 100, or 500 mg/kg bw/d	OECD TG 408; animals given test substance via gavage; controls given vehicle; mortality, body weight, food and water consumption, urinalysis, hematological analyses, behavioral assessment, organ weight assessment, and histopathological assessments were performed	One male in the 100 mg/kg group died, no further animals died prematurely. At 500 mg/kg, male rats exhibited statistically significant reductions in body weight and body weight gain. Hematological changes at this dose included significant decreases in hemoglobin, hematocrit, mean corpuscular volume, and mean corpuscular hemoglobin in both sexes. Males also showed significant increases in reticulocytes, while females had significant increases in total white blood cells and lymphocytes, along with significant decreases in relative neutrophils. Clinical chemistry revealed statistically significant elevations in alanine aminotransferase and cholesterol in both males and females. Additionally, in this dose group, males had significant increases in alkaline phosphatase, urea, bilirubin, potassium, phosphate, and calcium, and significant decreases in glucose and chloride. Females showed significant reductions in albumin and increases in triglycerides. Organ weight analysis indicated statistically significant increases in liver and kidney weights in both sexes of the high-dose group. Other male organ weight changes were secondary to decreased body weight and considered non-adverse. Urinalysis showed statistically significant elevations in urobilinogen in both sexes at the mid- and high-dose levels. At 500 mg/kg bw/d, females had significant increases in urine bilirubin and urine volume and significant decreases in urine specific gravity, while males had statistically significant increases in ketones and renal epithelial cells, and statistically significant decreases in urine pH. No treatment-related effects were observed in behavior, food consumption, or functional observational tests. All reported effects were reported relative to controls. The NOAEL was established at 100 mg/kg bw/d.	[4]
Trimethylbenzoyl Diphenylphosphine Oxide (purity 99%)	arachis oil	Sprague-Dawley rats (5/sex/group)	28 d	0, 50, 250, or 750 mg/kg bw/d	Animals given test substance via gavage; control animals were given the vehicle only; recovery groups were treated with the same test substance at 750 mg/kg bw/d or the vehicle alone for 28 consecutive days and then were maintained without treatment for a further 14-d period; mortality, hematological analyses, urinalysis, organ weight assessment, and histopathological assessments were performed.	One female from the recovery high-dose group and one female from the recovery control group died during the study period (study authors claimed this was not treatment-related). Hunched posture, increased salivation, lethargy, and piloerection were observed in animals treated with 250 and 750 mg/kg bw/d. Decreased body weight gain, decreased food efficiency, increased liver and kidney weights, and small testes were also observed in these groups. Blood chemistry (increased bilirubin, triglycerides, cholesterol, gamma glutamyl transpeptidase, alkaline phosphatase, creatinine, and urea in plasma) and urine abnormalities (ketones in urine) indicative of hepatic and renal injury were observed in mid- and high-dosed groups. These abnormalities (aside from slight increase in cholesterol in females and calcium in males) were considered to be reversible as they were not seen in the treated recovery animals. Periportal hepatocyte vacuolization and basophilia were observed in the high-dose group but were not observed in the recovery groups (treated and untreated). Testicular atrophy was observed in the high-dose group as well as in the treated recovery group. The NOAEL was determined to be 50 mg/kg bw/d.	[3,6]

Table 5. Repeated-dose oral toxicity studies

Test Article	Vehicle	Animals/ Group	Study Duration	Dose/ Concentration	Protocol	Results	Reference
Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.3%)	0.5% aqueous CMC	Male Wistar rats (number of animals in test group not stated; 3 control animal)	28 d	0 or 1000 mg/kg bw/d	Animals given test substance via gavage; control animals given vehicle only; analyses on mortality, clinical parameters, body weight, and organ weights were performed	No signs of toxicity observed.	[6]
Trimethylbenzoyl Diphenylphosphine Oxide (purity 94.8%)	0.5% aqueous CMC	Wistar rats (10/sex/group)	90 d	0, 100, 300, or 1000 mg/kg bw/d	OECD TG 408; Animals given test substance via gavage; control animals given vehicle only; clinical signs, body weight, food consumption, blood chemistry, neurotoxicity, and histopathological parameters were evaluated	Two females of the high-dose group died during the study. Increased food consumption was observed in female rats of the high-dose group. A significant reduction in body weight in male rats of the 300 (12% reduction) and 1000 mg/kg bw/d (26% reduction) groups was observed compared to controls. High-dose animals displayed hairless extremities and reddening/scale formation on the ears. Abnormalities in clinical chemistry were observed in high-dose females (decreased erythrocytes, hemoglobin, hematocrit, thromboplastin time, gamma-glutamyltransferase, total protein, globulins, and cholesterol; increased leucocytes, alkaline phosphatase; platelets, eosinophilic granulocytes, neutrophilic polymorphonuclears, and triglycerides). Abnormalities (increased alkaline phosphatase, gamma-glutamyltransferase, alanine aminotransferase; decreased triglycerides) were also observed in high-dose males. Hematocrit and hemoglobin values were decreased, and leucocytes, eosinophilic granulocytes, neutrophilic polymorphonuclears, and calcium values were increased in females treated with 300 mg/kg bw/d. Relative kidney and liver weights (40 - 60% above control values) were observed in high-dose females, and similar effects were noted in mid- and high-dose males. Relative brain weights and adrenal gland weights were also significantly increased in mid- and high-dosed males compared to controls (this effect was not observed in females). Absolute testes weights in animals treated with 0, 100, 300, and 1000 mg/kg bw/d were reported to be 3.56, 3.68, 1.69, and 1.69 g, respectively. Marked diffuse atrophy of the testicular parenchyma and slight moderate interstitial edema was observed all males of the mid- and high-dose groups. No signs of neurotoxicity were observed. The NOAEL was determined to be 100 mg/kg bw/d.	[3,6,25]
Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.3%)	0.5% CMC	Male Wistar rats (10/group)	90 d	0 or 1000 mg/kg bw/d	Animals given test substance via gavage; control animals received vehicle only; Body weight and histopathological assessments were performed	Absolute mean body weights were 10% lower in the treated group compared to controls after 3 mo of treatment. Absolute mean testes weights were determined to be 3.29 and 2.1 g in the control and treated groups, respectively. Treated animals also revealed a slight to severe diffuse atrophy of the seminiferous tubules of the testes. In 4 treated animals, edemas and minimal to slight hyperplasia of the Leydig cells were observed. Reduced testes size was correlated with an oligozoospermia up to grade 5.	[3,6]

CMC = carboxymethylcellulose; NOAEL = no-observed-adverse-effect-level; NOEL = no-observed-effect-level; NR = not reported; OECD = Organisation for Economic Co-operation and Development; TG = test guideline

Table 6. Oral developmental and reproductive toxicity studies

Test Article	Vehicle	Animals/Group	Dose/Concentration	Procedure	Results	References
Bis-Trimethylbenzoyl Phenylphosphine Oxide (purity not stated)	1% aqueous CMC	female Crl:WI (Han) rats (25/group)	0, 100, 300, and 1000 mg/kg bw/d	OECD TG 414; animals treated via gavage on GD 6 – 19; animals killed for examination on GD 20; controls given vehicle; maternal (body weight, food consumption, uterus weights, conception rate, mean number corpora lutea, number of implantation sites, number of viable fetuses) and fetal examinations (sex distribution, fetal weights, external malformations) performed	Results were similar in control and treated groups for dams and fetuses. The NOAEL for maternal and developmental toxicity was determined to be ≥ 1000 mg/kg bw/d.	[5]
Ethyl Trimethylbenzoyl Phenylphosphinate (purity 96.8 – 97.8%)	0.5% sodium CMC	female Wistar rats (25/group)	0, 30, 100, and 300 mg/kg bw/d	OECD TG 414; animals treated via gavage on GD 6 – 19; animals killed for examination on GD 20; controls given vehicle; maternal (body weight, water/food consumption, uterus weights, conception rate, mean number corpora lutea, number of implantation sites, number of viable fetuses) and fetal examinations (sex distribution, fetal weights, external malformations) performed	Food consumption and body weight were similar among control and treated groups. Nearly all animals in the high-dose group and 1 animal in the mid-dose group showed transient salivation post-dosing. Mean water consumption was statistically significantly increased in the 300 mg/kg bw/d group compared to controls. A slight but significant increase in absolute and relative liver weights of animals in the high-dose group was observed compared to controls. No differences of toxicological relevance between control and treated animals were observed for any reproductive parameters evaluated. Similarly, no influence of the test substance on fetal weight or sex ratio was observed at any dose. Skeletal malformations (incomplete ossification of skull, unossified sternebrae, and wavy ribs) occurred in the high-dose group. No unusual pattern of ossification was otherwise observed in treated fetuses, and the observed skeletal variations did not influence the overall rate of fetal variations; and therefore, these skeletal variations were assessed as treatment-related but non-adverse. The NOAEL for prenatal developmental toxicity was determined to be 300 mg/kg bw/d, while the NOEL was determined to be 100 mg/kg bw/d.	[4]

Table 6. Oral developmental and reproductive toxicity studies

Test Article	Vehicle	Animals/Group	Dose/Concentration	Procedure	Results	References
Trimethylbenzoyl Diphenylphosphine Oxide (purity not stated)	1% aqueous CMC	female Wistar rats (22 rats/group)	0, 50, 150, and 500 mg/kg bw/d	OECD TG 414; animals treated via gavage from days 6 – 20 post-coitum, inclusive; control animals given vehicle only; animals killed for examination on day 21 post-coitum (or within 24 h of abortion or early delivery); maternal (clinical observation, body weight, conception rate, number of viable fetuses, mean number corpora lutea, number of implantation sites, pre- and post-implantation loss) and fetal (fetal weight, sex ratio, litter size, skeletal malformations) evaluations performed	Six total animals delivered early (1 control animal, 1 low-dose animal, 2 mid-dose animals, and 2 high-dose animals); increased salivation was observed in dams in a dose-dependent manner (since no correlated findings were noted, researchers attributed this to the taste of the test substance); piloerection (in 7/22 dams) and hunched posture (in 4/22 dams) was observed in animals treated with the highest dose; mean body weight gain was significantly reduced in the highest dose group compared to controls from day 9 post-coitum onwards (mean body weight on day 21 post-coitum was 285 g in 500 mg/kg bw/d treated group compared to 305 g in controls); no effects were observed on the number of pregnant females, corpora lutea, implantations sites, or pre- or post-implantation loss; 4 animals were found not pregnant (effect was not dose-dependent) At 500 mg/kg bw/d, female fetal weights were slightly but significantly lower compared to the control group (4.8 g versus 5.1 g in controls); a similar effect was observed in fetal males of the high-dose group, however, this was not statistically significant; the male:female ratio was unaffected by treatment; litter size was unaffected by treatment; no treatment-related external malformations were observed (tail malformations were observed in 2 pups of the high-dose group; however, this was not considered to be related to treatment); a statistically significant increase in the number of fetuses with bent limb bones were observed in the high-dose group compared to controls; this group also had a statistically increased incidence of reduced ossification of the skull and unossified metatarsals and metacarpals compared to controls; no visceral malformations were observed The NOAEL for maternal and developmental toxicity was determined to be 150 mg/kg bw/d	[3]
Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.3%)	1% aqueous CMC	Wistar Han rats (5/sex/group)	0, 60, 200, and 600 mg/kg bw/d	OECD TG 421; one-generation reproductive toxicity study; test item was administered via gavage 7 d/wk for a minimum of 12 wk; males treated for 85-92 d up to and including the day before scheduled necropsy (including a minimum of 10 wk prior to mating) and during mating; females that delivered were treated for 10 wk prior to mating, during the variable time to conception, during pregnancy, and at least 20 d after delivery; females that failed to deliver or had total litter loss were treated for 99-117 d; control animals treated with vehicle only; evaluated parameters include clinical and reproductive performance of P0, clinical evaluation of F1 pups, live birth indices, mortality, pup body weight, pup gross pathological evaluation	One female of the control group and one female of the 600 mg/kg died during the premating period. Extended diestrus cycles during the mating period was observed was observed in 1 female treated with 60 mg/kg and 3 females treated with 600 mg/kg. Mating indices were 67% at 600 mg/kg and 100% for all other groups. Precoital time was considered not to be affected by treatment up to 600 mg/kg for all mated females. At 600 mg/kg, all mated females presented with 0 implantation sites (and 0 corpora lutea). At 60 and 200 mg/kg, the mean number of implantation sites remained in the same range of controls. Fertility indices were 100%, 90%, 100% and 0% for the control, 60, 200, and 600 mg/kg groups, respectively. Gestation indices were 100%, 100%, and 90% for the control, 60 and 200 mg/kg groups, respectively. Average live litter sizes were 10.6, 10.8, and 10.4 living fetuses/litter for the control, 60 and 200 mg/kg groups, respectively. One female at 200 mg/kg had only 1 living pup. Tubular atrophy was present in all males treated with the highest dose (correlating with decreased testes weight/reduced testes size). Atypical residual bodies and multinucleated giant cells were present in all males treated at 200 mg/kg at a slight to moderate degree. Atypical residual bodies were present in all males treated at 200 mg/kg at a slight to moderate degree. Multinucleated giant cells were present in a single male treated at 200 mg/kg and in a single male treated at 600 mg/kg at a moderate degree.	[3]

Table 6. Oral developmental and reproductive toxicity studies

Test Article	Vehicle	Animals/Group	Dose/Concentration	Procedure	Results	References
					Degeneration and depletion of germ cells were present in a single male treated at 200 mg/kg at moderate degree. Cell debris was present in the epididymis of a single male treated at 200 mg/kg to a moderate degree and in most males treated at 600 mg/kg up to moderate degree. Reduced sperm was present in a single male treated at 200 mg/kg to a slight degree and in all males treated at 600 mg/kg at a high degree. A minimal increase in hypertrophy of the follicular epithelium of the thyroid glands was noted in males at 200 and 600 mg/kg and in females at 600 mg/kg (considered non-adverse at current severity and in absence of any other pathological finding). No treatment-related clinical signs or adverse gross pathological findings were observed in pups. Live birth indices (number of live offspring on PND 1 as percentage of total number of offspring born) were 97% for the control and 99% for the 60 and 200 mg/kg groups. Parental toxicity NOAEL: 200 mg/kg bw/d**.** Developmental toxicity NOAEL: 200 mg/kg bw/d. Overall reproductive toxicity NOAEL: 60 mg/kg bw/d.	
Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.3%)	1% aqueous CMC	New Zealand White rabbits (22 females/group)	0, 10, 30, or 100 mg/kg bw/d	OECD TG 414; animals treated with test substance via gavage on day 6-28 post-coitum, inclusive; control animals were treated with the vehicle only; maternal (body weight, food consumption, uterus weights, conception rate, mean number corpora lutea, number of implantation sites, number of viable fetuses) and fetal examinations (sex distribution, fetal weights, external malformations) performed	No clinical signs of toxicity, treatment-related mortality, body weight changes, or gross pathological abnormalities were observed in dams. The number of pregnant females, corpora lutea, implantation sites, and pre- and post-implantation loss were similar in control and treated groups. Slightly decreased fetal weight was observed in the 100 mg/kg dose group compared to controls. No abnormalities regarding the female:male ratio or litter size/weight were observed. External malformations were observed in 2, 3, and 1 fetus(es) of the control, 10, and 30 mg/kg groups, respectively (effect not seen in the high-dose group). A statistically significant increase in the incidence of misaligned vertebrae was observed in fetuses of the high-dose group compared to controls (9.2% versus 3.8% in controls; however, the value remained within the maximum value of the available historical control data (10.2% per litter). Visceral malformations occurred in 2, 3, 2, and 1 fetus(es) I the control, 10, 30, and 100 mg/kg groups, respectively. The maternal and developmental NOAEL was determined to be >100 mg/kg bw/d	[3]

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

Table 7. In vitro genotoxicity studies

Test Article	Vehicle	Concentration/Dose	Test System	Procedure	Results	References
			Gene Mutation			
Bis-Trimethylbenzoyl Phenylphosphine Oxide (purity not stated)	DMSO	312.5, 625, 1250, 2500, and 5000 µg/plate	*S. typhimurium* strains TA102, TA100, TA 98, TA 1537, and TA 1535 and *E. coli* strain WP2 uvrA	Bacterial reverse mutation assay; OECD TG 471; performed with and without metabolic activation; negative control: DMSO; positive controls: 2-aminoanthracene, cyclophosphamide, sodium azide; 4-nitroquinoline, mitomycin C, 2-nitrofluorene, 9-aminoacridine	Non-genotoxic	[5]
Bis-Trimethylbenzoyl Phenylphosphine Oxide (purity not stated)	DMSO	Experiment 1: 2.5, 5, 10, 20, 40, 60, and 80 µg/ml Experiment 2: 5, 10, 20, 40, 60, and 80 µg/ml	mouse lymphoma L5178Y cells	2-part in vitro mammalian cell gene mutation assay; OECD TG 476; performed with and without metabolic activation; negative control: DMSO; positive controls: methylmethanesulfonate and cyclophosphamide	Non-genotoxic	[5]
Ethyl Trimethylbenzoyl Phenylphosphinate (purity 96.4%)	acetone	study did not clearly list all applied concentrations; however, the maximum concentration can be inferred to be 2500 µg/plate	*S. typhimurium* strains TA1535, TA 1537, TA98, TA100 and *E. coli* strain WP2	Ames assay; OECD TG 471; performed with and without metabolic activation; negative controls: untreated and vehicle; positive controls: positive controls: methyl-N-nitro-N-nitrosoguanidine, 4-nitro-*o*-phenylenediamine, 9-aminoacridine, 4-nitroquinolone N-oxide	Non-genotoxic	[4]
Ethyl Trimethylbenzoyl Phenylphosphinate (purity 100%)	DMSO	study did not clearly list all applied concentrations; however, the maximum concentration can be inferred to be 5000 µg/plate)	*S. typhimurium* strains TA1535, TA1537, TA98, TA100 and TA102	Ames assay; OECD TG 471; performed with and without metabolic activation; negative controls: untreated and vehicle; positive controls: 9-aminoacridine, 2-nitrofluorine, sodium azide, glutaraldehyde, benzo(a)pyrene, 2-aminoanthracene	Non-genotoxic	[4]
Ethyl Trimethylbenzoyl Phenylphosphinate (purity 95.7%)	DMSO	study did not clearly list all applied concentrations; however, the maximum concentration can be inferred to be 3300 µg/ml)	Chinese hamster lung fibroblasts (V79)	In vitro mammalian cell gene mutation assay; OECD TG 476; performed with and without metabolic activation; negative control: DMSO; positive controls: 7,12-dimethylbenzanthracene and ethylmethanesulfonate	Non-mutagenic	[4]
Trimethylbenzoyl Diphenylphosphine Oxide (purity > 98%)	methanol	0, 500, and 2500 µg/plate	*S. typhimurium* strains TA1535, TA1537, TA98, and TA 100	Ames assay; OECD TG 471; performed with and without metabolic activation; negative controls: untreated and vehicle; positive controls: cyclophosphamide, methyl-N-nitro-N-nitrosoguanidine, 2-aminoanthracene	Non-genotoxic; cytotoxicity was observed at 2500 µg/plate in the presence of metabolic activation in all strains, and without S9 in TA1535, but no increase in the number of his-positive revertants could be detected under all conditions tested; controls gave expected results.	[3,6]
Trimethylbenzoyl Diphenylphosphine Oxide (purity 99%)	ethanol	Experiment 1: 0, 8, 40, 200, 1000, and 5000 µg/plate Experiment 2: 0, 312.5, 625, 1250, 2500 and 5000 µg/plate	*S. typhimurium* strains TA1535, TA 1537, TA98, TA100 and *E. coli* strain WP2	2-part Ames assay; OECD TG 471; performed with and without metabolic activation; negative controls: untreated and vehicle; positive controls: methyl-N-nitro-N-nitrosoguanidine, 4-nitro-*o*-phenylenediamine, 9-aminoacridine, 4-nitroquinolone N-oxide, 2-aminoanthracene	Non-genotoxic; controls gave expected results	[3,6]

Table 7. In vitro genotoxicity studies

Test Article	Vehicle	Concentration/Dose	Test System	Procedure	Results	References
Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.5%)	ethanol	Experiment 1: 4-h treatment without S9 mix: 1.3, 2.5, 5.0, 10, 20, 30,* 40*µg/ml 4-h treatment with S9 mix: 3.4, 6.8, 13.5, 27, 40.5, 54 µg/ml Experiment 2: 24-h treatment without S9 mix: 5, 10, 15, 20, 25, 30, 35, 40* µg/ml 4-h treatment with S9 mix: 0, 20, 30, 40,* 45,* 50,* 55,* 60* µg/ml	Chinese hamster lung fibroblasts (V79)	2-part mammalian cell gene mutation test (*hprt* locus); OECD TG 476; in experiment 1, test substance was added to cultures for 4 h, with and without S9 mix; in experiment 2, test substance was added to cultures for 24 h without S9 mix and 4 h with S9 mix; negative control: ethanol; positive controls: ethyl methanesulfonate, 7,12-dimethyl-benz(a)anthracene	Non-mutagenic; cytotoxicity observed in all experiment parts at concentrations ≥ 10 µg/ml (without S9 mix) and ≥40 µg/ml (with S9 mix); no reproducible increase in mutant frequency observed up to maximum concentrations of 30 µg/ml (without S9 mix) and 40.5 µg/ml (with S9 mix); controls gave expected results	[3,6]
			Chromosomal Damage			
Bis-Trimethylbenzoyl Phenylphosphine Oxide (purity not stated)	DMSO	Experiment 1 (without metabolic activation): 0, 1, 3, 5.6, 10, 13, 18, 24, 33, 42, 56, 75, and 100 µg/ml Experiment 1 (with metabolic activation): 0, 10, 33, and 100 µg/ml Experiment 2 (without metabolic activation): 0, 10, 18, and 24 µg/ml Experiment 2 (with metabolic activation): 0, 10, 33, and 100 µg/ml	stimulated cultured human lymphocytes	2-part in vitro mammalian chromosomal aberration assay; OECD TG 473; performed with and without metabolic activation; negative control: DMSO; positive control: mitomycin C and cyclophosphamide	Non-genotoxic	[5]
Ethyl Trimethylbenzoyl Phenylphosphinate (purity 98.7%)	DMSO	Experiment 1 and 2 : 0, 6.25, 12.5, 25, 50, 75, and 100 µg/ml Experiment 2: 0, 6.25, 12.5, 250, 50, 75, and 100 µg/ml Experiment 3: 0, 80, 100, 120, 140, and 160 µg/ml Experiment 4: 0, 60, 70, 80, 90, and 100 µg/ml	Chinese hamster lung fibroblasts (V79)	4-part in vitro mammalian cell micronucleus assay; OECD TG 487; performed with and without metabolic activation; negative control: DMSO; positive controls: cyclophosphamide and ethylmethanesulfonate	Non-clastogenic	[4]

Table 7. In vitro genotoxicity studies

Test Article	Vehicle	Concentration/Dose	Test System	Procedure	Results	References
Ethyl Trimethylbenzoyl Phenylphosphinate (purity 100%)	DMSO	Experiment 1 (without metabolic activation; 3-h treatment): 96.17, 113.1, 133.1 µg/ml Experiment 1 (with metabolic activation; 3-h treatment): 81.75, 113.1, 156.6 µg/ml Experiment 1 (20-h treatment): 26.21, 30.83, 36.27 µg/ml Experiment 2: 113.1, 216.8, and 255 µg/ml Experiment 3: 113.1, 156.6, and 184.2 µg/ml	human lymphocytes	3-part in vitro mammalian cell micronucleus assay; OECD TG 487; experiment 1 performed with and without metabolic activation; experiments 2 and 3 performed with metabolic activation only; negative control: DMSO; positive controls: 4-nitroquinoline-N-oxide and cyclophosphamide; 3- and 20-h exposures; 3- and 20-h treatment in experiment 1; 3-h treatment in experiment 2 and 3	The test substance produced equivocal results for micronucleus induction in the presence of metabolic activation. In Experiment 1, a 3-h exposure caused statistically significant increases in micronuclei at 113.1 and 156.6 µg/ml, but values were within historical control ranges except for one culture at the highest dose, and a 20-h exposure led to significant increases at 30.83 and 36.27 µg/ml that were not dose-dependent and generally within historical ranges. In Experiment 2, a significant increase was observed at the highest concentration tested (255 µg/ml), but only one replicate exceeded the historical solvent control range. Similarly, in Experiment 3, the highest concentration analyzed (184.2 µg/ml) showed a significant increase, yet only two replicates exceeded historical control limits,	[4]
Ethyl Trimethylbenzoyl Phenylphosphinate (purity 100%)	DMSO	Experiment 1 (without metabolic activation): 80.53, 125.8, and 196.6 µg/ml Experiment 1 (with metabolic activation): 80.53, 125.8, 196.6, 245.8 µg/ml Experiment 2 (without metabolic activation): 50.20, 59.06, 81.75, 113.1 µg/ml Experiment 2 (with metabolic activation): 139.5, 191.3, and 236.2 µg/ml	human lymphocytes	2-part; in vitro mammalian chromosomal aberration assay; OECD TG 473; performed with and without metabolic activation; negative control: DMSO; positive control: 4-nitroquinoline-N-oxide and cyclophosphamide; 3-h treatment in experiment 1 and 20-h treatment in experiment 2	Small but statistically significant increases in structural chromosome aberrations were observed after 20-h exposure in the absence of metabolic activation at 113.1 µg/ml, a concentration that also caused clear cytotoxicity. No increases in structural aberrations were observed in the presence of metabolic activation. Short (3-h) treatments, both with and without metabolic activation, led to increased numerical aberrations attributable to polyploidy, whereas continuous exposure in the absence of metabolic activation did not induce numerical aberrations.	[4]
Trimethylbenzoyl Diphenylphosphine Oxide (purity 99%)	DMSO	6-h treatment without S9 mix: 0, 15, 20, 23.3, and 25 µg/ml 6-h treatment with S9 mix: 0, 20, 23.3, 26.6, and 30 µg/ml 24-h treatment without S9 mix: 0, 5, 10, 15, and 20 µg/ml 48-h treatment without S9 mix: 0, 2.5, 5, 10, and 20 µg/ml	Chinese hamster lung cells	Chromosomal aberration assay; OECD TG 473; cells incubated without S9 mix for either 6, 24, or 48 h or with S9 mix for 6 h; negative control: vehicle; positive controls: mitomycin C, cyclophosphamide A preliminary test was performed to determine levels at which precipitation would occur. Maximum levels of 20 µg/ml (without S9 mix) and 30 µg/ml (with S9 mix) were determined for this assay.	Non-clastogenic; controls gave expected results	[3,6]
				Other		
Trimethylbenzoyl Diphenylphosphine Oxide (purity ≥ 99.8%)	ethanol	0.008, 0.04, 0.20 and 1.0 µg/ml	Human fetal lung fibroblasts (MRC-5)	Comet assay; cells exposed to test substance for 24 h; positive control: 4-nitroquinolone-1-oxide: negative control: untreated; solvent control: ethanol; TIs scored as reflection of DNA damage	Genotoxic; TIs were statistically significantly higher in cells treated with the test substance at 0.04 µg/ml and higher ($p < 0.05$); solvent control gave negative results; positive and untreated controls gave expected results	[26]

*precipitation observed

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

Table 8. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
IRRITATION						
ANIMAL						
Bis-Trimethylbenzoyl Phenylphosphine Oxide (purity not stated)	The study did not specify a vehicle; however, it is likely that the test material was applied neat.	The applied test concentration was not specified; however, given the study design, it is presumed that the substance was tested neat; 0.5 mg	3 New Zealand white rabbits (sex not stated)	OECD TG 404; test substance moistened with water and applied to clipped skin under semi-occlusive conditions for 4 h; observation 24, 48, and 72 h after patch removal	No indication of skin irritation was observed. Mean erythema and edema scores were 0 across all observation periods.	[5]
Ethyl Trimethylbenzoyl Phenylphosphinate (purity not stated)	none	neat; 0.5 ml	Vienna white rabbits (1 male and 2 females)	OECD TG 404; test substance applied to clipped skin for 4 h under occlusive conditions; application area: 2.5 cm^2; observation 24, 48, 72 h, and 9 d after patch removal	No indication of skin irritation was observed. Mean erythema and edema scores were 0 across all observation periods.	[4]
Trimethylbenzoyl Diphenylphosphine Oxide (99.5% purity)	olive oil	40%; 2000 mg/kg bw	Wistar rats (5/sex)	Test substance applied to clipped skin of rats under semi-occlusive conditions for 24 h; 14-d observation; application area approximately 40 cm^2; sites were observed 30 – 60 min after patch removal, and at regular intervals until the last day of observation	Local skin irritation (erythema, incrustation, scaling) was observed in 1 male and all females throughout the study.	[3,6]
Trimethylbenzoyl Diphenylphosphine Oxide (purity > 98%)	water	50%; 500 mg	Vienna white rabbits (2 males, 4 females)	Test substance applied to intact and abraded skin; application area of 2.5 cm^2; use of occlusion and exposure duration not stated (however, it can be assumed to be 24 h as this was the first observation point); animals were evaluated for skin irritation 24, 48, and 72 h and 8 d after application	The mean primary irritation index was determined to be 1.33 (fully reversible by day 8; unknown if this average includes both abraded and intact skin; mean of results observed at 24, 48, and 72 h; potential maximum value not provided). Mean erythema and edema scores for intact skin were 0.6/4 and 0.3/4, respectively. Mean erythema and edema scores for abraded skin were 0.9/4 and 0.4/4. The test substance was considered slightly irritating.	[3,6]
HUMAN						
Base coat containing 2.19% Ethyl Trimethylbenzoyl Phenylphosphinate Color coat containing up to 5.29% Ethyl Trimethylbenzoyl Phenylphosphinate Color coat containing up to 0.33% Bis-Trimethylbenzoyl Phenylphosphine Oxide Top coat containing 1.98% Ethyl Trimethylbenzoyl Phenylphosphinate	none	neat	32 female subjects	Use study; UV/LED-curable gel nail system; curing in between layers in following order; base coat, 2 color coats; top coat; products applied and removed by trained nail technicians according to intended use instructions; 2 complete application and removal cycles performed during study; assessments conducted at baseline and after 3 and 6 wk of use	No treatment-related erythema, scaling, fissures, papules, pustules, edema, vesicles, or weeping were observed, and no itching or burning was reported. Results of the nail tolerability evaluations performed in this study are described in the Tolerability of UV/LED Gel Nail System section.	[30]

Table 8. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
Base coat containing 0.25% Trimethylbenzoyl Diphenylphosphine Oxide Gel nail color containing 3.65% Trimethylbenzoyl Diphenylphosphine Oxide Top coat containing 1.5% Trimethylbenzoyl Diphenylphosphine Oxide	none	neat	34 female subjects	Use study; subjects applied gel manicure (1 layer of base coat, 2 layers of gel nail color, and top coat (gel curing in between each layer with LED lamp)), kept manicure on for 2 wk, then removed with polish remover; after previous polish was removed, gel manicure was re-applied for another 2 wk (this process was repeated for a total of 3 applications over a 6-wk period); erythema, dryness, and splitting/cracking of the skin was evaluated at baseline and at the end of the study period	Non-irritating; no signs of dermal irritation (erythema, dryness, splitting/cracking) were observed	[31]
SENSITIZATION						
ANIMAL						
Bis-Trimethylbenzoyl Phenylphosphine Oxide (purity > 95%)	intradermal induction: peanut oil and adjuvant/saline; epicutaneous induction and challenge: petrolatum	intradermal induction: 0.5% epicutaneous induction: 50% challenge: 10%	Pirbright-Hartley guinea pigs (5-10/sex/group)	GPMT; OECD TG 406; animals induced with intradermal injections and a topical application (occlusive), followed by a 14-d rest period; on day 22, animals were challenged with a topical application of the test material under occlusion; controls treated with vehicles only; evaluations at 24- and 48-h after patch removal	Sensitizing; challenge with the test substance resulted in positive reactions in 18/20 animals at 24 h and 16/20 animals at 48 h. No positive reactions were observed in control animals.	[5]
Bis-Trimethylbenzoyl Phenylphosphine Oxide (purity 98.4%)	intradermal induction: acetone, adjuvant, and coconut oil derivative; epicutaneous induction and challenge: acetone	intradermal injection: 1% epicutaneous induction: 70% challenge: 35 and 70%	Male Dunkin-Hartley guinea pigs (5 -10 group)	GPMT; OECD TG 406; animals induced with intradermal injections and a topical application (occlusive), followed by a 14-d rest period; animals were then challenged with a topical application of the test material under occlusion; controls treated with vehicles only; positive controls treated with known sensitizers; evaluations at 24-, 48-h, and 72-h after patch removal	Sensitizing; challenge with the test substance at 70% showed 3 positive reactions, 4 inconclusive reactions, and 3 negative reactions. At 35%, 2 animals were positive, 4 were inconclusive, and 4 were negative. The positive control group showed 6 – 10 positive responses out of 10 animals. No reactions were observed in the negative control group.	[5]
Ethyl Trimethylbenzoyl Phenylphosphinate (95.7%)	acetone and olive oil	0, 10, 25, and 50%	Female CBA mice (5/group)	LLNA; OECD TG 429; test substance applied to the dorsal surface of both ears for 3 consecutive days; controls treated with vehicle alone (negative control) or alpha hexyl cinnamaldehyde (positive control); on day 6 animals were injected with 20.1 µCi of radiolabeled [3H]-thymidine in PBS and killed 5 h later; lymph nodes were obtained and used for stimulation index calculations (values of 3 or more are considered positive) and EC_3 values required to elicit a stimulation index value of 3	Sensitizing; stimulation index values for the test substance at 10, 25, and 50% were determined to be 1.5, 5, and 6.7, respectively, indicating an EC_3 value of 16.4%. Mid- and high-dose groups exhibited a statistically significant increase in lymph node weight and cell count compared to the vehicle control, exceeding the positive response cutoff (1.55) with indices of 2.0 and 2.2. Although ear weights increased slightly in all test groups (indices 1.08, 1.13, 1.16), they remained below the excessive irritation threshold of 1.25.	[4]
Trimethylbenzoyl Diphenylphosphine Oxide (purity 99.5%)	acetone and olive oil	0, 10, 25, and 50%	Female CBA/CaOlaHsd mice (5/group)	LLNA; OECD TG 429; performed as described above	Sensitizing; stimulation index results for the test substance at 10, 25, and 50% were determined to be 2.22, 2.96, and 3.46, indicating an EC_3 value of 27%. The stimulation index value was determined to be 1.00 for the negative control group (results not reported for positive control group).	[3,6]

EC_3 = amount of chemical that is required to elicit a 3-fold increase in lymph node proliferative activity; GPMT = guinea pig maximization test; LED = light-emitting diode; LLNA = local lymph node assay; NR = not reported; OECD = Organisation for Economic Co-operation and Development; PBS - phosphate-buffered saline; TG = test guideline; UV = ultraviolet

Table 9. Ocular irritation studies

Test Article	Vehicle	Concentration/ Dose	Test Population	Protocol	Results	Reference
Bis-Trimethylbenzoyl Phenylphosphine Oxide (purity 98.4%)	none	neat; 73 mg	3 New Zealand white rabbits (sex not stated)	OECD TG 405; test substance placed in 1 eye; examinations after 1, 24, 48, and 72-h; irritation parameters evaluated: corneal ulceration, corneal opacity, conjunctivae score, chemosis	Mild, fully reversible indications of eye irritation were seen in all test animals over the duration of the assay. Grade 1 iridial inflammation was seen in one animal at 24 h. A diffuse crimson coloration of the conjunctivae with slight swelling was seen in all animals within 1 h of treatment; these reactions generally ameliorated within 3 or 4 d. Indications of eye irritation did not meet criteria for consideration of the test material as an eye irritant under the criteria under the EU Classification, Labeling, and Packaging regulations.	[3,5]
Ethyl Trimethylbenzoyl Phenylphosphinate (purity not stated)	none	neat; 0.1 ml	Vienna white rabbits (3/sex/)	OECD 405; test substance placed in 1 eye; evaluation 1, 24, 48, and 72 h, and 8 d after instillation; irritation parameters evaluated: corneal opacity, iris score, conjunctivae score, and chemosis; evaluated via Draize system	No significant eye irritation was observed. Mean corneal opacity, iris, conjunctivae (in animal 1-5), conjunctivae (in animal 6), and chemosis scores were 0.05/4, 0/2, 0.3 – 1.3/3, 2/3, and 0.1/4, respectively. All effects were reversible.	[3,4]
Trimethylbenzoyl Diphenylphosphine Oxide (purity > 98%)	none	neat; 56 mg	Vienna white rabbits (2 males, 4 females)	Test substance placed in left eye and evaluated 24, 48, 72 h, and 5 d after instillation; irritation parameters evaluated: corneal opacity, iris score, conjunctivae score, conjunctiva discharge, chemosis; evaluated via Draize system	This study was summarized in both an ECHA dossier and in an SCCS opinion; results differed by source. According to ECHA,mean corneal opacity scores, iris scores, conjunctivae scores (in 4/6 animals), chemosis, and conjunctival discharge scores were 0/4, 0/2, 0.3/3, 0/4, and 0/3, respectively (results were the same for time points 24/48/72 h). According to the SCCS opinion, no effects on the iris were noted; however, at 24 h, conjunctival redness was observed in all animals, and persisted up until the 48-h reading. In 2 animals, corneal opacity was observed by the 72-h reading.	[3,6]

Table 10. Margin of safety calculation[6]

Parameter	Value	Details
MOE Calculation Parameters for Trimethylbenzoyl Diphenylphosphine Oxide		
MOE calculated using 90-d oral tox NOAEL		
Amount of gel applied	4 g	Full artificial nail systems are typically applied every 2 – 3 wk, with a refill application after 1 - 2 wk; full application of artificial nail systems range between 2 – 4 g of gel; refills consist of approximately 1 g of gel
Concentration in gel product	5%	Maximum concentration of use according to PCPC 2025 survey
Total amount applied	200mg	The use of 4 g of gel containing 5% Trimethylbenzoyl Diphenylphosphine Oxide will result in a total application of 200 mg Trimethylbenzoyl Diphenylphosphine Oxide/human (corresponds to 10 mg/nail; considering total fingernail and toenail area of 22 cm^2)
Human body weight	60 kg	Default human body weight
Amount applied/kg human bw	3.33 mg/kg bw	200 mg Trimethylbenzoyl Diphenylphosphine Oxide/60 kg = 3.33 mg/kg bw
Assumed residue	1%*	Worst-case assumption
Assumed absorption through the nail plate	100%	Worst-case assumption
SED	0.033 mg/kg bw/d	3.33 mg/kg bw x 0.01 = 0.033 mg/kg bw/d
NOAEL (90-d oral tox)	100 mg kg/bw/d**	Based on a 90-d oral toxicity study performed in rats (can be found in the Short-Term and Subchronic Toxicity Studies section of this report)[3,6,25]
Corrected NOAEL for 50% bioavailability	50 mg/kg bw/d	Standard procedure according to SCCS's Notes of Guidance for the testing of cosmetic ingredients and their safety evaluation
SCCS MOE (Trimethylbenzoyl Diphenylphosphine Oxide)	**1515**	50 mg/kg bw/d / 0.033 mg/kg bw/d = 1515
MOE calculated using reproductive NOAEL		
NOAEL (reproductive tox)	60 mg/kg bw/d	Based on NOAEL from one-generation reproductive toxicity assay[3] (can be found in the Developmental and Reproductive Toxicity section of this report)
Corrected NOAEL for 50% bioavailability	30 mg/kg bw/d	Standard procedure according to SCCS's Notes of Guidance for the testing of cosmetic ingredients and their safety evaluation
MOE using reproductive POD	**909**	30 mg/kg bw/d / 0.033 mg/kg bw/d = 909
MOE Calculation Parameters for Ethyl Trimethylbenzoyl Phenylphosphinate		
Amount of gel applied	4 g	Full artificial nail systems are typically applied every 2 – 3 wk, with a refill application after 1 - 2 wk; full application of artificial nail systems range between 2 – 4 g of gel; refills consist of approximately 1 g of gel
Concentration in gel product	6.2%	Maximum concentration of use according to PCPC 2025 survey
Total amount applied	248 mg	The use of 4 g of gel containing 6.2% Ethyl Trimethylbenzoyl Phenylphosphinate will result in a total application of 248 mg Ethyl Trimethylbenzoyl Phenylphosphinate/human (corresponds to 12.4 mg/nail; considering total fingernail and toenail area of 22 cm^2)
Human body weight	60 kg	Default human body weight
Amount applied/kg human bw	4.13 mg/kg bw	248 mg Ethyl Trimethylbenzoyl Phenylphosphinate/60 kg = 4.13 mg/kg bw
Assumed residue	1%*	Worst-case assumption
Assumed absorption through the nail plate	100%	Worst-case assumption
SED	0.0413 mg/kg bw/d	4.13 mg/kg bw x 0.01 = 0.0413 mg/kg bw/d
NOAEL (90-d oral tox)	100 mg/kg bw/d	Based on a 90-d repeated dose oral toxicity study (can be found in the Short-Term and Subchronic Toxicity Studies section of this report)[4]
Corrected NOAEL for 50% bioavailability	50 mg/kg bw/d	
MOE (Ethyl Trimethylbenzoyl Phenylphosphinate)	**1211**	50 mg/kg bw/d / 0.0413 mg/kg bw/d = 1211

NOAEL = no-observed-adverse-effect-level; POD = point of departure; SCCS = EU Scientific Committee on Consumer Safety; SED = systemic exposure dose

* These ingredients are used as chemical photoinitiators in curable gel systems for artificial nails, where they rapidly splits into free radicals that integrate into the polymer chain ends and is mostly consumed during polymerization. Any residual amounts, under a worst-case scenario assuming 1%, gets trapped in the hardened polymer matrix of the nail coating.[6]

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

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Personal Care Products Council

Memorandum

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

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

DATE: July 30, 2026

SUBJECT: Bis-Trimethylbenzoyl Phenylphosphine Oxide (BAPO) and Ethyl Trimethylbenzoyl Phenylphosphinate (TPO-L)

Anonymous. 2026. Safety assessment summary for Bis-Trimethylbenzoyl Phenylphosphine Oxide (BAPO) (CAS 162881-26-7) and Ethyl Trimethylbenzoyl Phenylphosphinate (TPO-L) (CAS 84434-11-7).

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DATE: 7/2026

Safety assessment summary for Bis-Trimethylbenzoyl Phenylphosphine Oxide (BAPO) (CAS 162881-26-7) and Ethyl Trimethylbenzoyl Phenylphosphinate (TPO-L) (CAS 84434-11-7)

I. Systemic exposure assessment

A. Product description

UV/LED-curable nail products are polymerizing systems intended exclusively for application to the nail plate. Following application, the product remains on the nails until removal, which typically occurs once every 2–3 weeks. Each applied layer of curable formulation is followed by light curing according to the manufacturer's protocol. Only the base coat gel is applied directly to the nail, while subsequent color and topcoat layers are applied onto previously cured polymerized coatings. UV-curable gel nail systems containing BAPO and TPO-L are designed to undergo rapid polymerization under UV/LED curing conditions (Ref 14, & Confidential Supplier documentation). BAPO exhibits strong absorption within the emission range of commonly used UV/LED nail lamps, while TPO-L similarly functions as an efficient Type 1 photoinitiator under recommended curing conditions (Ref 15, & Confidential Supplier documentation). UV/LED curable gels achieve high polymerization efficiency when formulations are cured according to the product instructions.

B. Product usage amount

The amount of product (g) used for the exposure assessments was derived from experimentally measured application data across salon-use studies evaluating both professionally applied and self-applied gel polish systems. These datasets capture realistic use conditions across different application settings and provide a basis for estimating high-end usage (P95 value) per individual layer (Ref 13, 16, 23). For the exposure assessments, the P95 application amount of 0.21 g was selected as the representative product amount. The total product applied across all manicure steps was not summed because UV-curable gel systems are applied and cured sequentially. The use of the highest measured per-layer application amount of 0.21 g therefore represents a conservative estimate of potential exposure while avoiding overestimation that could result from summation of all cured layers.

C. Pedicure considerations

The mean total surface area of fingernails is approximately 10.4 cm^2, whereas the corresponding surface area for toenails is approximately 7.6 cm^2, demonstrating that toenail exposure is slightly lower but of the same order of magnitude as fingernail exposure (Ref 7). The SCCS has conservatively applied a combined fingernail and toenail surface area of approximately 22 cm^2 in exposure assessments for artificial nail systems (Ref 6).

Because product-specific pedicure application data were not available, the primary exposure assessment was based on the application amount of 0.21 g. To evaluate the potential impact of combined manicure and pedicure use during the same treatment

session, a sensitivity analysis was performed using a doubled application amount of 0.42 g (See Supplemental Table 1 and Table 2). This sensitivity analysis is considered conservative because it assumes high end application amounts for both fingernails and toenails during the same treatment session. Both scenarios are presented to demonstrate that the systemic safety conclusions are robust under measured high end use conditions and a conservative combined manicure/pedicure assumption.

D. Post cure residual photoinitiator extraction study

The extraction study was designed to exhaustively recover residual TPO-L from the cured film therefore the resulting values represent a worst-case estimate of residual photoinitiator remaining after curing. To obtain the maximum amount of extracted initiator, the extraction is typically conducted with pure organic solvents such as acetonitrile, isopropanol, or hexane, depending on the solubility of the analyte. Solvent entry into the polymer network causes the polymer structure to expand, thereby facilitating the extraction of unreacted initiator. The actual consumer exposure during normal wear is expected to be substantially lower than the amount recovered by the extraction procedure. Therefore, the extraction data were used as input to derive the conservative upper-bound Consumer Exposure Level (CEL) for the post-cure skin sensitization assessment.

A film representing the complete salon-applied system was prepared by sequentially applying the basecoat, two color coats, and the topcoat. The gel film was using the published methodology London et al., 2024 (Ref 25). Prior to the drawdown process, the polyethylene film was outlined to match the finger guide on the manufacturer's hand piece (Figure 1). The wet thickness of the film replicated the thickness of a brush application on fingernails. The product-coated film was then placed on a cardboard stand to simulate the average height of a hand. Each coated film was irradiated following the nail curing lamp protocol.

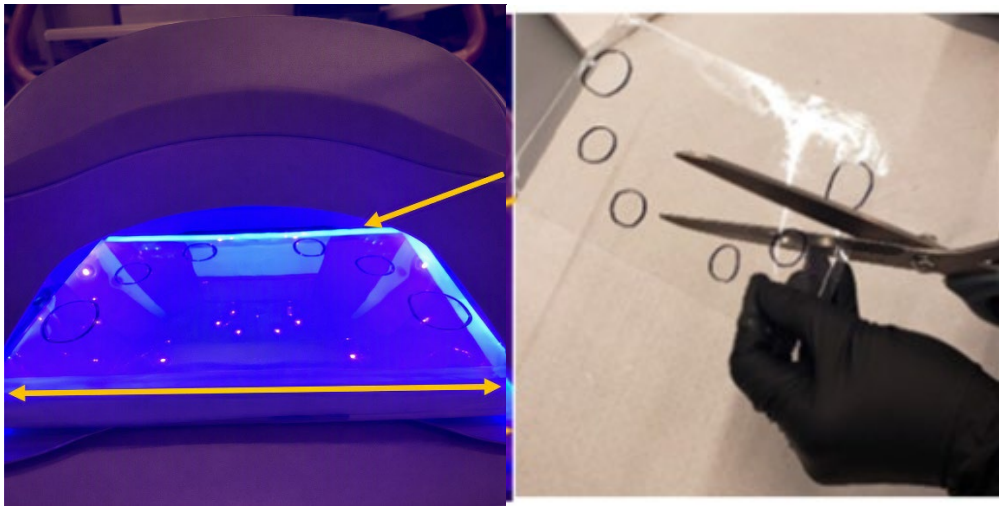


Figure 1. Cardboard stand with polyester substrate outlined to duplicate the finger guide of the manufacturer's lamp.

Duplicate film sections representing the typical thumb, middle, and index finger positions in the UV nail lamp were cut and prepared as described in London et al., 2024 (Ref 25). Samples were then agitated at 37 °C for 20 hours prior to collection and analysis following the published procedure (Ref 25). HPLC analysis was conducted to determine the TPO-L concentration in the films using an internally developed analytical method (Ref 26 - Unpublished data). The amount of T-POL extracted from the film was 39,280 µg/g, corresponding to a consumer exposure level of 456 µg/cm^2.

E. Ungual (nail plate) permeation

The healthy nail plate is highly keratinized and recognized as an effective barrier to chemical penetration. Available evidence indicates that penetration through the healthy nail plate is generally limited and substantially lower than dermal penetration (Ref 8, 9, 11,12). This is attributable to the dense keratinized structure of the nail plate, its hydrogel-like properties, and the low permeability of many ingredients used in nail cosmetic products.

To refine the estimation of systemic exposure via the nail plate, an ungual permeation adjustment factor was derived for BAPO and TPO-L using the framework described by Yin et al. (2024) (Ref 8). This framework considers the physicochemical properties known to influence nail penetration, including molecular weight, vapor pressure, log Kow, water solubility, keratin binding, and polymerization-induced trapping within the cured product matrix to calculate individual permeation adjustment factors ($AF_{att\text{-}ing}$). The individual permeation factors are then combined to derive an overall permeation adjustment factor AF_{ove} which represents an estimated fraction of ingredient available for penetration through the nail plate. Physicochemical property data for BAPO and TPO-L were obtained from the corresponding REACH registration dossiers (Ref 2 and 22) and are summarized in Table 1.

The application of the Yin et al. framework resulted in overall ungual permeation adjustment factors (AF_{ove}) of 0.00025 for BAPO and 0.0004 for TPO-L (Table 2). These low values are primarily driven by the combination of high molecular weight, low water solubility, and polymerization-induced trapping of the photoinitiators within the cured gel matrix.

Table 1: Physicochemical data

Ingredient	**BAPO**	**TPO-L**
Molecular weight (Da)	418,5	316,3
Vapor pressure (kPa)	0,002	0,00000021
LogP	5,78	2,91
Water solubility (mg/mL)	0,001	0,035

Table 2: Ungual Permeation Adjustment Factors (AF)

Attribute	**AF_{att}**	**Threshold**	**AF_{thr}**	**BAPO**	**TPO-L**
				$AF_{att\text{-}ing}$	**$AF_{att\text{-}ing}$**
Molecular weight (Da)	0.1 - 1	≤ 240 or ND	1		
		> 240-500	0,5	0,5	0,5
		> 500	0,1		

Vapor pressure (kPa)	0.1 - 1	≤ 0.01 or ND	1	1	1
		> 0.01 - 1	0,7		
		>1 - 10	0,4		
		> 10	0,1		
LogP	0.5 - 1	≤ 0.5 or ND	1		
		> 0.5 - 3	0,8		0,8
		> 3 - 5	0,6		
		>5	0,5	0,5	
Water solubility (mg/mL)	0.1-1	>33 or ND	1		
		1-33	0,5		
		<1	0,1	0,1	0,1
Keratin binding	0.5 or 1	Yes	0,5		
		No or ND	1	1	1
Polymerization/Trapping	0.01 or 1	Yes	0,01	0,01	0,01
		No	1		
AFove				**0,00025**	**0,0004**

AF: Adjustment factor; AF_{att}: AF for attribute; AF_{thr}: AF for the threshold; AF_{ove}: Overall AF for ingredient = Product of $AF_{att-ing}$ for the ingredient; ND: No data (Default AF = 1).

F. Point of Departure (POD):

BAPO

Toxicological endpoints for BAPO are available in the corresponding ECHA dossier (Ref 2). The point of departure (POD) selected for systemic exposure risk assessment is based on a 90-day repeated-dose oral rat study (OECD TG 408). A NOAEL of 300 mg/kg bw/day was identified. To account for the use of a subchronic study for assessment of potential chronic consumer exposure, an assessment factor of 2 was applied in accordance with ECHA Guidance R.8, resulting in an adjusted POD of 150 mg/kg bw/day (Ref 24).

TPO-L

Toxicological data for TPO-L are available in the corresponding ECHA registration dossier (Ref 22). The POD selected for systemic risk assessment is based on a 90-day repeated-dose oral toxicity study in which a NOAEL of 100 mg/kg bw/day was identified.

G. Systemic Exposure Dose (SED; mg/kg bw/day) and Margin of Safety (MOS)

Contact with the surrounding skin is minimized under intended conditions of use, however, inadvertent periungual skin contact may occur during application of nail cosmetic products (Ref 7). Such exposure is expected to be minimal and transient, as excess product is removed from the skin in accordance with usage instructions. In a probabilistic assessment of self-applied nail lacquer, Ficheux et al. (2014) reported P95 nail polish application surface

area values of 14.8 cm^2 for the nail plate and 3.3 cm^2 for the nail wall across all 10 fingers in adults and adolescents (Ref 7). Based on these data, approximately 82% of the exposed surface area is associated with the nail plate and 18% with the adjacent periungual skin. These values were used to characterize high-end exposure scenario so likely overestimates the amount of gel contacting periungual skin during foreseeable uses. Product specific observations from internal salon evaluation indicated that consumers did not exhibit significant deposition of gel on the periungual skin during self-application, however the amount and surface area of incidental skin contact were not quantified. For this exposure assessment, the Ficheux surface area proportions were applied as deposition fractions to partition the total product application amount (210 mg) between nail plate (82%) and periungual skin (18%).

The product amount associated with each exposure compartment (nail plate versus skin) was calculated as:

Equation 1a

Product Amount $_{skin}$ (mg) = Total product amount per application (mg) × Deposition fraction (0.18)

Equation 1b

Product Amount $_{nail}$ (mg) = Total product amount per application (mg) × Deposition fraction (0.82)

Systemic exposure was estimated separately for the nail plate and periungual skin since these tissues differ substantially in their barrier properties. Exposure via the nail plate was adjusted using the ungual permeation framework described in Section E. Exposure via periungual skin was estimated assuming 50% dermal absorption in accordance with SCCS notes of Guidance in the absence of substance-specific dermal absorption data (Ref 3). Relative Daily Exposure of the product was calculated as using the adjusted product amount, application frequency (2 weeks), and a default body weight 60 kg.

Equation 2

$$\text{Product Relative Daily Exposure } \left(\frac{\text{mg}}{\text{kg bw/day}}\right) = \frac{Adjusted\ product\ amount\ (mg)\ \times Frequency}{60\ kg}$$

Equation 3

Ingredient specific SED was then calculated as:

$$\text{Ingredient SED } \left(\frac{\text{mg}}{\text{kg bw/day}}\right) = Relative\ daily\ exposure\ \left(\frac{mg}{kg\ bw/\ day}\right) \times Permeation\ or\ Dermal\ abs\ Factor \times Ingredient\ \%$$

The total SED was obtained by summing the nail plate and periungual skin contributions. Margin of Safety (MOS) values were then calculated by dividing the selected PODs by the corresponding SEDs (Table 3 & 4).

$$\text{MOS} = \frac{POD}{SED}$$

H. Calculations

Table 3. TPO-L

	Total product amount per application (mg)	Adjusted product amount (mg)	Frequency	Bodyweight (kg)	Product relative daily exposure mg/kg bw/day	TPO-L%	Permeation or dermal absorption factor	TPO-L SED (mg/kg bw/day)
NAIL PLATE (deposition fraction 82%)	210	172,2	0,071	60	0,205	5,6	0,0004	0,000005
NAIL WALL (deposition fraction 18%)	210	37,8	0,071	60	0,045	5,6	0,5	0,00126
* Ficheux et al., 2014								
SUM TPO-L SED mg/kg bw/day	0,00126							
NOAEL (mg/kg bw/day)	100							
MOS	79077							

Table 4. BAPO

	Total product amount per application (mg)	Adjusted product amount (mg)	Frequency	bw (kg)	Product relative daily exposure mg/kg bw/day	BAPO %	Permeation or dermal absorption factor	BAPO SED (mg/kg bw/day)
NAIL PLATE (weighted fraction 82%)	210	172,2	0,071	60	0,205	0,69	0,00025	0,000000
NAIL WALL (weighted fraction 18%)	210	37,8	0,071	60	0,045	0,69	0,5	0,00015525
* Ficheux et al., 2014								
SUM BAPO SED mg/kg bw/day	0,000156							
NOAEL (mg/kg bw/day)	150							
MOS	963988							

II. Skin sensitization risk assessment

A. Skin sensitization hazard

BAPO

BAPO is classified as a skin sensitizer based on available data. A Guinea Pig Maximization Tests (OECD TG 406) demonstrated positive sensitization responses with >60% of animals responding at intradermal induction concentrations ≤1% (ECHA Dossier; Ref 2). The study was assigned a Klimisch reliability score of 2 (reliable with restrictions) (Ref 1). Because the study predates LLNA (OECD 429), an EC3 value is not available. ECHA concluded that no additional LLNA testing is considered to be scientifically justified based upon animal welfare grounds. Based on the available weight of evidence, BAPO carries a Skin Sens. 1A classification under harmonized CLP (Ref 2).

TPO-L

TPO-L is classified as a skin sensitizer (Skin Sens. 1B) under the EU CLP Regulation (ECHA Dossier; Ref 22). This classification is supported by Local Lymph Node Assay (LLNA; OECD 429) data, with an EC3 16.4%. A NESIL value of 4100 ug/cm^2 can be derived.

B. BAPO dermal sensitization threshold (DST) classification

In the absence of an LLNA-derived EC3 value for BAPO, a weight-of-evidence approach was applied to distinguish intrinsic sensitization hazard from estimated consumer exposure under intended conditions of use. Structural alert analysis using the OECD QSAR Toolbox identified Schiff-base-forming reactivity. However, application of the decision framework of Aptula and Roberts (2006) and Roberts et al. (2015) indicate that BAPO does not meet the criteria for classification as a high-potency contact allergen (HPC) (Ref 4, 5, 17; Table 5).

Because BAPO did not meet the criteria for classification as an HPC, the risk characterization was refined using the DST of 73 µg/cm^2 established for reactive non-HPC sensitizers. This threshold is considered representative of the expected sensitization potency of BAPO based on its profile and classification outcome within the Aptula and Roberts, 2006 and Roberts et al., 2015 framework (See Table 5). The application of the DST is consistent with Next Generation Risk Assessment (NGRA) principles, in which estimated CEL is compared with an acceptable exposure level derived from the sensitization potency information and appropriate sensitization assessment factors (SAFs), with transparent documentation of assumptions (Refs 10, 18-21).

Table 5. Decision tree to determine BAPO DST category

Determine if chemical is categorized as Reactive -reaction mechanistic domains (Aptula and Roberts, 2006)

Step 1. OECD tool box to find the structural alerts. If any of these are found, then the chemical is categorized as Reactive.

	Michael Acceptors	
	SNAr electrophiles	
	SN2 electrophiles	
	Schiff base formers	**Yes**
	Acylating agents	

Next step: rule out HPC

Determine if chemical is an HPC according to Roberts et al., 2015

	Rule 1: Used as protein derivatization agents	**No**	
	Rule 2: A direct acting Michael acceptor?	**No**	**If no, stop here and not considered an HPC**
If Michael acceptor continue to rule 2a and 2b	Rule 2a: Classified as Quinones, di-imines and quinone-imines Rule 2b: electronegative substituents on the double bond, such as halogen, alkoxide –OR, thio –S–, increase reactivity of such compounds with CHO, –COR, –CO2R, –CONR2 activating groups. Or general structure C=C–X, where X is a stronger activating group than carbonyl (e.g. NO, –NO2, SO2R, SOR, SO3R, 2,4-dinitrophenyl…) Compounds that can be formally regarded as hydrogen halide adducts of Michael acceptors, i.e. with the sub-structure X–C–CH–M where X is halogen (or pseudohalogen) and M is a strong Michael activating group should be treated as HPC Rule 2c. Michael acceptors with more than one activating group on the double bond		

Overall classification = Reactive non HPC sensitizer

C. Safety Adjustment Factors (SAF)

BAPO: For BAPO, no additional sensitization assessment factor was applied because risk characterization was conducted using the DST approach for reactive non-HPC sensitizers.

TPO-L: Safety adjustment factor =10.
Interindividual variability: An inter-individual variability factor of 10 was applied (Ref 18, 19).
Vehicle Matrix: A factor of 1 was applied for both post cure and direct wet application scenario (Ref 18, 19). This factor is highly conservative for post cure film given the cross-linked nature of the film. The application of adjustment factor 10 yields an Adverse Exposure Level (AEL) of 410 µg/cm^2.

D. Exposure modeling for skin sensitization

Two potential sources of sensitizer exposure were considered:

1) Wet application skin contact, representing inadvertent periungual skin contact with uncured product during application prior to product wiping/removal or curing.
2) Post-cure skin contact: representing potential incidental dermal exposure resulting from repeated contact between cured nail coatings and other areas of the skin during normal product wear (e.g., touching the face, hands, or other skin surfaces). This scenario considers the maximum quantity of photoinitiator fully extracted from the cured film as a very conservative surrogate for photoinitiator that could become available through repeated skin contact over 2-week wear period.

Wet Application scenario: incidental skin contact
To calculate the consumer exposure level (CEL) under the wet application scenario, the total product application amount was first adjusted using the estimated fraction of the product associated with the periungual skin (18%) **Equation 1a**. The resulting product amount was divided by the potentially exposed skin surface area (3.3 cm^2) and then adjusted for the maximum photoinitiator concentration. A retention fraction of 0.1 was applied to account for the limited duration for which uncured product would be expected to remain on the skin under intended conditions of use (Equation 4) (Ref 10).

Equation 1a
Product Amount $_{skin}$ (mg) = Total product amount per application (mg) × Deposition fraction (0.18)

Equation 4

$$\text{Consumer exposure level } \left(\frac{\mu g}{cm2}\right) = \frac{Product\ Amount\ skin\ (mg) \times 1000\ \mu g/mg \times Max\ concentration\ in\ formula\ \% \times Retention\ Fraction}{Surface\ Area\ (cm2) \times 100}$$

Post cure scenario: incidental skin contact

For the post-cure scenario, total extractable photoinitiator concentrations derived from the cured coating analytical study described in Section D were used to estimate a conservative upper-bound exposure level to represent incidental skin contact during normal wear (unpublished data). Because the values were derived from an aggressive extraction method instead of dermal migration measurements, they are not considered representative of actual consumer exposure. Instead, the extraction data were used as a conservative surrogate for the maximum amount of residual photoinitiator potentially available following curing. To provide context for typical consumer use the total extractable loading was expressed as a time-averaged extractable loading over a 2-week wear period by assuming uniform release of the extractable reservoir throughout the wear period. Instead of assuming immediate availability of the entire extractable amount, this approach provides a more realistic representation of exposure. The resulting time-averaged extractable loading was therefore used as the CEL for comparison with the AEL.

Equation 5. Estimating consumer exposure level

$$\text{Time averaged extractable loading } \left(\frac{\mu g}{cm2}\right) = Total\ extractable\ photoinitiator\ \left(\frac{\mu g}{cm2}\right) \times Application\ Frequency$$

E. Skin sensitization risk calculations

Scenario 1: Wet Application scenario: inadvertent skin contact

TPO-L

Total product amount per application (mg)	210
Fraction of product deposited on periugnual skin*	0,18
Product Amount $_{skin}$ (mg)	37,8
Application area(cm^2)*	3,3
Product loading per unit skin area (µg/cm^2)	11454,55
Max conc. in formula (%)	5,58
Retention Factor	0,1
Consumer Exposure Level **(CEL)** (µg/cm^2)	63,92
EC3 %	16,4
NESIL (µg/cm^2)	4100
SAF	10
AEL (µg/cm^2)	410
AEL/CEL	6
* Ficheux et al., 2014	

BAPO

Product application amount/day (mg/day)	210
18% on periungual skin*	37,8
Application area(cm^2)*	3,3
Product amount applied (µg/cm^2)	11454,55
Max conc. in formula (%)	0,69
Retention Factor	0,1
Consumer Exposure Level **(CEL)** (µg/cm^2)	7,90
DST (µg/cm^2)	73
DST/CEL	9
* Ficheux et al., 2014	

The calculated Consumer Exposure Levels (CELs) for inadvertent periungual skin contact to uncured formulation at max use levels were 63.92 µg/cm^2 for TPO-L and 7.90 µg/cm^2 for BAPO.

Scenario 2: Post cure scenario: incidental skin contact

TPO-L

	TPO-L
Total extractable TPO-L loading per surface area (µg/cm^2)	456
Frequency	0,07
Time averaged extractable loading over 14 day **representing consumer exposure level** (µg/cm^2)	32,57
EC3 %	16,4
NESIL (µg/cm^2)	4100
SAF	10
AEL (µg/cm^2)	410
AEL/CEL	13

The calculated CEL for skin contact to cured film at max use levels was 32.57 µg/cm^2 for TPO-L.

BAPO

Residual extractable concentrations of BAPO were not analytically determined. Therefore, a conservative read-across approach was applied using the experimentally determined TPO-L data. TPO-L represents a conservative surrogate because it is present at substantially higher maximum concentrations in the formulations (5.6% w/w) compared to BAPO (0.69%). Consequently, the extractable loading of BAPO is expected to be no greater than that experimentally determined for TPO-L

Therefore, the TPO-L time averaged extractable loading was used as a conservative upper

bound surrogate exposure estimate for BAPO.

	Bis-Trimethylbenzoyl Phenylphosphine Oxide
Surrogate time averaged extractable loading as CEL µg/cm^2	32,57
DST (ug/cm2)	73
DST/CEL	2

Under both the wet application and post-cure exposure scenarios, estimated consumer exposure levels to the photoinitiators remained below the corresponding DST or AEL. Based on the data, these photoinitiators do not present an unacceptable skin sensitization risk under intended conditions of use in UV/LED-cured nail systems.

Conclusion

BAPO and TPO-L are recognized skin sensitizers and have been evaluated using exposure-based risk assessment approaches that consider their intended use in UV/LED-curable gel nail systems. The exposure assessment incorporated multiple conservative assumptions, including high-end (P95) product application amounts, inadvertent skin exposure scenarios, conservative dermal absorption assumptions, ingredient-specific nail plate permeation adjustment factors, and experimentally determined post-cure extractable photoinitiator concentrations. These assumptions were deliberately selected to avoid underestimation of consumer exposure.

Based on the available toxicological data, conservative exposure assumptions, and the calculated margins of safety for systemic toxicity and skin sensitization, the evaluated UV/LED curable nail products containing BAPO and TPO-L do not indicate an unacceptable risk to consumers under intended conditions of use. This conclusion is contingent upon use according to the recommended application and curing instructions and confirmation that the final marketed formulations do not exceed the assessed maximum use concentrations.

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Supplemental

Pedicure +Manicure (SED and MOS)

TPO-L

TPO-L

	Total product amount per application (mg)	Adjusted product amount (mg)	Frequency	Bodyweight (kg)	Product relative daily exposure mg/kg bw/day	TPO-L%	Permeation or dermal absorption factor	TPO-L SED (mg/kg bw/day)
NAIL PLATE (deposition fraction 82%)	420	344,4	0,071	60	0,41	5,6	0,0004	0,000009
NAIL WALL (deposition fraction 18%)	420	75,6	0,071	60	0,09	5,6	0,5	0,00252
* Fischeux et al., 2014								
SUM TPO-L SED mg/kg bw/day	0,00253							
NOAEL (mg/kg bw/day)	100							
MOS	39538							

BAPO

BAPO

	Total product amount per application (mg)	Adjusted product amount (mg)	Frequency	bw (kg)	Product relative daily exposure mg/kg bw/day	BAPO %	Permeation or dermal absorption factor	BAPO SED (mg/kg bw/day)
NAIL PLATE (weighted fraction 82%)	420	344,4	0,071	60	0,41	0,69	0,00025	0,000001
NAIL WALL (weighted fraction 18%)	420	75,6	0,071	60	0,09	0,69	0,5	0,0003105
* Fischeux et al., 2014								
SUM BAPO SED mg/kg bw/day	0,000311							
NOAEL (mg/kg bw/day)	150							
MOS	481994							

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Dermatological Tolerability Evaluation of UV/LED Gel Nail System

Gel polish formulas tested: TPO-L up to 5.29% in color, TPO-L 2.19% base coat, TPO-L 1.98% topcoat, BAPO up to 0.33% color.
Study Date: November 2023

A 6-week use study was conducted in 32 adult female subjects (30 evaluable) to assess the skin and nail tolerability of a UV/LED-curable gel nail system consisting of a base coat, two color coats, and a top coat. Products were applied and removed by trained nail technicians according to the intended use instructions, with two complete application/removal cycles performed during the study period. Assessments were conducted at baseline and after 3 and 6 weeks of use. No adverse reactions were reported or observed during the study.

1. Objective Dermatological Evaluation (Periungual Skin)
Objective evaluations of the skin surrounding the nails were performed by a trained grader at baseline and after 3 and 6 weeks of use. The study data are provided in the below tables. Overall, no treatment-related erythema, scaling, fissures, papules, pustules, edema, vesicles, or weeping were observed. Occasional observations of very slight dryness were noted but remained minimal in severity throughout the study.

2. Subjective Dermatological Assessment
Subjects evaluated sensations including itching, burning, tension, tickling, and dryness throughout the study. No cases of itching or burning were reported during the study. Minor reports of dryness, tension, or tickling were observed in a small number of subjects; however, these findings remained very slight in severity and were not associated with adverse reaction. Data not shown.

3. Nail Status Evaluation
Nail assessments were conducted following product removal and included evaluation of nail roughness, nail grooves, and nail discoloration. Small increases in nail roughness and nail grooves were observed in some subjects over the course of the study; however, all findings remained within the "very slight" severity category. Nail discoloration was minimal and infrequent. Overall, no clinically significant findings related to nail condition were identified.

Conclusion
The study concluded that the evaluated UV/LED gel nail regimens demonstrated very good to good skin and nail tolerability following repeated application and removal under intended use conditions

4.5 Results of objective dermatological evaluations

4.5.1 Skin status evaluation

For all fingers, the skin status around the nails was assessed by a trained grader before the application of the test products on day 1 of the study (baseline), as well as 3 and 6 weeks after the application of the test products, before their removal.

Tables 1a to 3a present the mean severity scores of the assessed objective parameters at each assessment time, for each of the test products. In Tables 1b to 3b, the mean scores over all fingers and treatments (A+B+C) are presented.

Table 1a: Objective dermatological evaluation – Descriptive statistics for mean severity scores by trained grader over all fingers at baseline

Parameter	Code	n	Mean ± SD	Median	Min	Max
Erythema	A	8	0.0 ± 0.0	0.0	0.0	0.0
	B	11	0.0 ± 0.1	0.0	0.0	0.5
	C	11	0.0 ± 0.0	0.0	0.0	0.0
Dryness	A	8	0.0 ± 0.0	0.0	0.0	0.0
	B	11	0.2 ± 0.3	0.0	0.0	0.5
	C	11	0.0 ± 0.2	0.0	0.0	0.5
Scaling	A	8	0.0 ± 0.0	0.0	0.0	0.0
	B	11	0.0 ± 0.0	0.0	0.0	0.0
	C	11	0.0 ± 0.0	0.0	0.0	0.0
Fissures	A	8	0.0 ± 0.0	0.0	0.0	0.0
	B	11	0.0 ± 0.0	0.0	0.0	0.0
	C	11	0.0 ± 0.0	0.0	0.0	0.0
Papules	A	8	0.0 ± 0.0	0.0	0.0	0.0
	B	11	0.0 ± 0.0	0.0	0.0	0.0
	C	11	0.0 ± 0.0	0.0	0.0	0.0

Parameter	Code	n	Mean ± SD	Median	Min	Max
Pustules	A	8	0.0 ± 0.0	0.0	0.0	0.0
	B	11	0.0 ± 0.0	0.0	0.0	0.0
	C	11	0.0 ± 0.0	0.0	0.0	0.0
Edema	A	8	0.0 ± 0.0	0.0	0.0	0.0
	B	11	0.0 ± 0.0	0.0	0.0	0.0
	C	11	0.0 ± 0.0	0.0	0.0	0.0
Vesicles	A	8	0.0 ± 0.0	0.0	0.0	0.0
	B	11	0.0 ± 0.0	0.0	0.0	0.0
	C	11	0.0 ± 0.0	0.0	0.0	0.0
Weeping	A	8	0.0 ± 0.0	0.0	0.0	0.0
	B	11	0.0 ± 0.0	0.0	0.0	0.0
	C	11	0.0 ± 0.0	0.0	0.0	0.0

Score: 0 = None; 0.5 = Very slight; 1 = Slight; 2 = Moderate; 3 = Strong

Table 1b: Objective dermatological evaluation – Mean scores by trained grader over all fingers at baseline

Parameter	Code	n	Mean scores ± SD	Min	Max
Erythema	A+B+C	30	0.0 ± 0.1	0.0	0.5
Dryness	A+B+C	30	0.1 ± 0.2	0.0	0.5
Scaling	A+B+C	30	0.0 ± 0.0	0.0	0.0
Fissures	A+B+C	30	0.0 ± 0.0	0.0	0.0
Papules	A+B+C	30	0.0 ± 0.0	0.0	0.0
Pustules	A+B+C	30	0.0 ± 0.0	0.0	0.0
Edema	A+B+C	30	0.0 ± 0.0	0.0	0.0
Vesicles	A+B+C	30	0.0 ± 0.0	0.0	0.0
Weeping	A+B+C	30	0.0 ± 0.0	0.0	0.0

Score: 0 = None; 0.5 = Very slight; 1 = Slight; 2 = Moderate; 3 = Strong

Table 2a: Objective dermatological evaluation – Descriptive statistics for mean severity scores by trained grader over all fingers on day 22

Parameter	Code	n	Mean ± SD	Median	Min	Max
Erythema	A	8	0.0 ± 0.0	0.0	0.0	0.0
	B	11	0.0 ± 0.0	0.0	0.0	0.0
	C	11	0.0 ± 0.0	0.0	0.0	0.0
Dryness	A	8	0.2 ± 0.3	0.0	0.0	0.5
	B	11	0.1 ± 0.2	0.0	0.0	0.5
	C	11	0.2 ± 0.3	0.0	0.0	0.5
Scaling	A	8	0.0 ± 0.0	0.0	0.0	0.0
	B	11	0.0 ± 0.0	0.0	0.0	0.0
	C	11	0.0 ± 0.0	0.0	0.0	0.0
Fissures	A	8	0.0 ± 0.0	0.0	0.0	0.0
	B	11	0.0 ± 0.0	0.0	0.0	0.0
	C	11	0.0 ± 0.0	0.0	0.0	0.0
Papules	A	8	0.0 ± 0.0	0.0	0.0	0.0
	B	11	0.0 ± 0.0	0.0	0.0	0.0
	C	11	0.0 ± 0.0	0.0	0.0	0.0
Pustules	A	8	0.0 ± 0.0	0.0	0.0	0.0
	B	11	0.0 ± 0.0	0.0	0.0	0.0
	C	11	0.0 ± 0.0	0.0	0.0	0.0
Edema	A	8	0.0 ± 0.0	0.0	0.0	0.0
	B	11	0.0 ± 0.0	0.0	0.0	0.0
	C	11	0.0 ± 0.0	0.0	0.0	0.0

Parameter	Code	n	Mean ± SD	Median	Min	Max
Vesicles	A	8	0.0 ± 0.0	0.0	0.0	0.0
	B	11	0.0 ± 0.0	0.0	0.0	0.0
	C	11	0.0 ± 0.0	0.0	0.0	0.0
Weeping	A	8	0.0 ± 0.0	0.0	0.0	0.0
	B	11	0.0 ± 0.0	0.0	0.0	0.0
	C	11	0.0 ± 0.0	0.0	0.0	0.0

Table 2b: Objective dermatological evaluation – Mean scores by trained grader over all fingers on day 22

Parameter	Code	n	Mean scores ± SD	Min	Max
Erythema	A+B+C	30	0.0 ± 0.0	0.0	0.0
Dryness	A+B+C	30	0.2 ± 0.2	0.0	0.5
Scaling	A+B+C	30	0.0 ± 0.0	0.0	0.0
Fissures	A+B+C	30	0.0 ± 0.0	0.0	0.0
Papules	A+B+C	30	0.0 ± 0.0	0.0	0.0
Pustules	A+B+C	30	0.0 ± 0.0	0.0	0.0
Edema	A+B+C	30	0.0 ± 0.0	0.0	0.0
Vesicles	A+B+C	30	0.0 ± 0.0	0.0	0.0
Weeping	A+B+C	30	0.0 ± 0.0	0.0	0.0

Score: 0 = None; 0.5 = Very slight; 1 = Slight; 2 = Moderate; 3 = Strong

Table 3a: Objective dermatological evaluation – Descriptive statistics for mean severity scores by trained grader over all fingers on day 43

Parameter	Code	n	Mean ± SD	Median	Min	Max
Erythema	A	8	0.0 ± 0.0	0.0	0.0	0.0
	B	11	0.0 ± 0.0	0.0	0.0	0.0
	C	11	0.0 ± 0.0	0.0	0.0	0.0
Dryness	A	8	0.3 ± 0.3	0.3	0.0	0.5
	B	11	0.1 ± 0.2	0.0	0.0	0.5
	C	11	0.0 ± 0.2	0.0	0.0	0.5
Scaling	A	8	0.0 ± 0.0	0.0	0.0	0.0
	B	11	0.0 ± 0.0	0.0	0.0	0.0
	C	11	0.0 ± 0.0	0.0	0.0	0.0
Fissures	A	8	0.0 ± 0.0	0.0	0.0	0.0
	B	11	0.0 ± 0.0	0.0	0.0	0.0
	C	11	0.0 ± 0.0	0.0	0.0	0.0
Papules	A	8	0.0 ± 0.0	0.0	0.0	0.0
	B	11	0.0 ± 0.0	0.0	0.0	0.0
	C	11	0.0 ± 0.0	0.0	0.0	0.0
Pustules	A	8	0.0 ± 0.0	0.0	0.0	0.0
	B	11	0.0 ± 0.0	0.0	0.0	0.0
	C	11	0.0 ± 0.0	0.0	0.0	0.0
Edema	A	8	0.0 ± 0.0	0.0	0.0	0.0
	B	11	0.0 ± 0.0	0.0	0.0	0.0
	C	11	0.0 ± 0.0	0.0	0.0	0.0

Parameter	Code	n	Mean ± SD	Median	Min	Max
Vesicles	A	8	0.0 ± 0.0	0.0	0.0	0.0
	B	11	0.0 ± 0.0	0.0	0.0	0.0
	C	11	0.0 ± 0.0	0.0	0.0	0.0
Weeping	A	8	0.0 ± 0.0	0.0	0.0	0.0
	B	11	0.0 ± 0.0	0.0	0.0	0.0
	C	11	0.0 ± 0.0	0.0	0.0	0.0

Table 3b: Objective dermatological evaluation – Mean scores by trained grader over all fingers on day 43

Parameter	Code	n	Mean scores ± SD	Min	Max
Erythema	A+B+C	30	0.0 ± 0.0	0.0	0.0
Dryness	A+B+C	30	0.1 ± 0.2	0.0	0.5
Scaling	A+B+C	30	0.0 ± 0.0	0.0	0.0
Fissures	A+B+C	30	0.0 ± 0.0	0.0	0.0
Papules	A+B+C	30	0.0 ± 0.0	0.0	0.0
Pustules	A+B+C	30	0.0 ± 0.0	0.0	0.0
Edema	A+B+C	30	0.0 ± 0.0	0.0	0.0
Vesicles	A+B+C	30	0.0 ± 0.0	0.0	0.0
Weeping	A+B+C	30	0.0 ± 0.0	0.0	0.0

Score: 0 = None; 0.5 = Very slight; 1 = Slight; 2 = Moderate; 3 = Strong

No signs of scaling, fissures, papules, pustules, edema, vesicles or weeping were observed on the skin around the nails at any assessment time for any of the treatment codes.

Very slight erythema was observed only for code B at baseline. Very slight dryness was observed for code B and C at baseline, for all treatment codes on day 22, and on day 43.