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

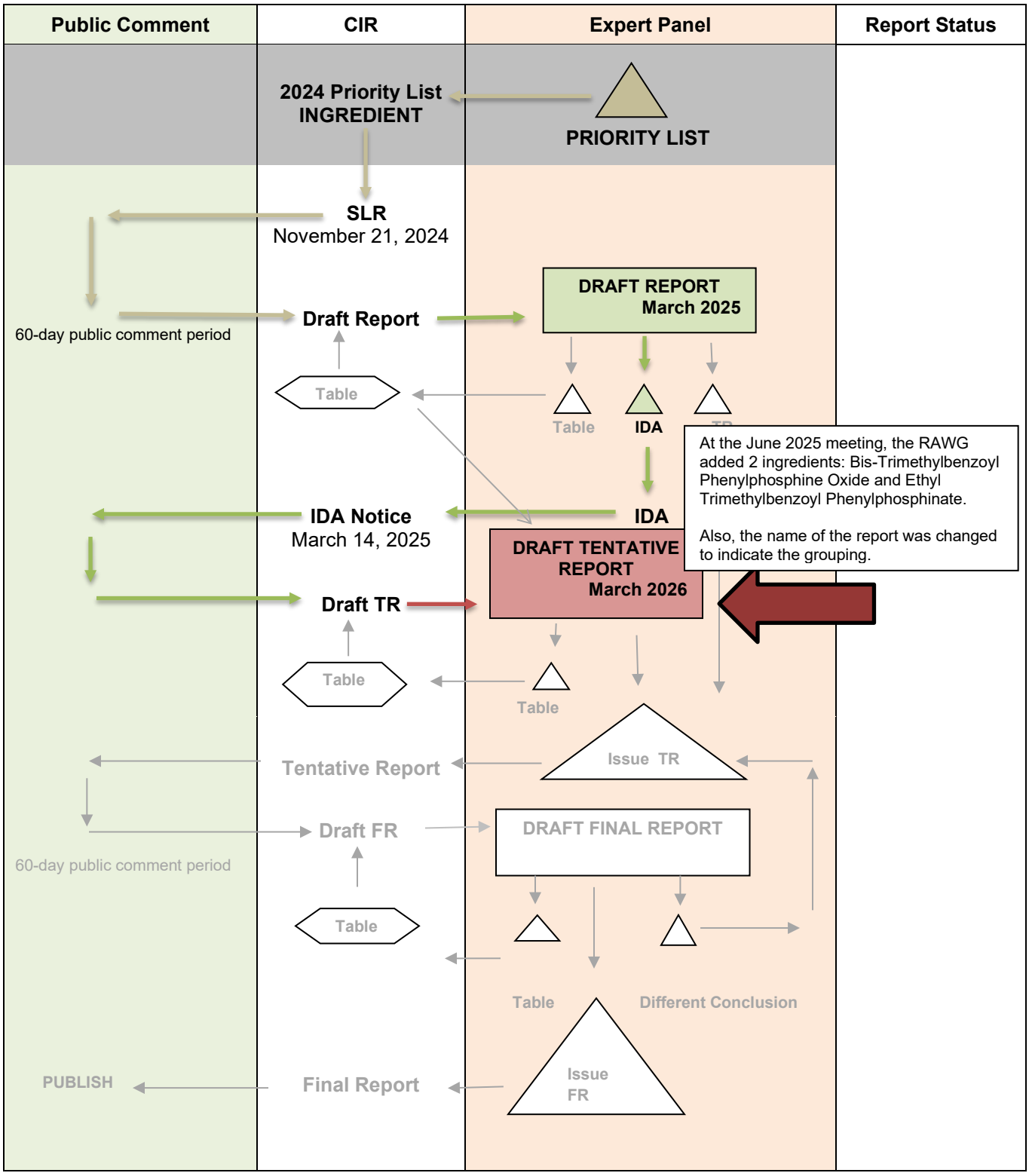
Status:	Draft Tentative Report for Panel Review
Release Date:	February 17, 2026
Panel Meeting Date:	March 12 – 13, 2026

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Samuel 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. 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., Senior Scientific Analyst/Writer, CIR.

555 13th Street, NW, Suite 300W, Washington, DC 20004
cirinfo@cir-safety.org

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Phosphine Oxides & Phosphinate Ingredients
MEETING March 2026



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons

From: Priya Ferguson, M.S.
Senior Scientific Analyst/Writer, CIR

Date: February 17, 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_032026*). At the June 2025 meeting, the Read-Across-Working Group (RAWG) determined that 2 additional ingredients from the 2026 draft priorities list – Bis-Trimethylbenzoyl Phenylphosphine Oxide and Ethyl Trimethylbenzoyl Phenylphosphinate – should be added to this report due to structural similarity to Trimethylbenzoyl Diphenylphosphine Oxide. Changes made since the last iteration of the report (Draft Report reviewed at the March 2025 meeting) and data relating to these 2 new ingredients have been identified in yellow highlighted text throughout the report.

When the Draft Report that was reviewed at the March 2025 meeting, Trimethylbenzoyl Diphenylphosphine Oxide was the only ingredient included in that assessment. At that meeting, the Panel issued an Insufficient Data Announcement (IDA) for the 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

Since the IDA was issued, CIR has not received any of the requested data; however, updated (2025) concentration of use data on Trimethylbenzoyl Diphenylphosphine Oxide (*data1_PhosphineOxides_032026*) have been received. These data state that this ingredient is now used at up to 5% in nail polish and enamel. Because this value aligns with that used in the SCCS MOE calculation on Trimethylbenzoyl Diphenylphosphine Oxide, the same MOE calculation was retained in the report. In addition, an MOE calculation was performed by CIR staff for Ethyl Trimethylbenzoyl Diphenylphosphine Oxide, which is used at concentrations up to **6.2%** in nail polish and enamel. In addition, 2025 RLD have been received and incorporated into the report. Compared to 2024 RLD, the frequency of use for all ingredients reviewed in this report has increased. Use categories between 2024 and 2025 RLD were similar; however, Bis-Trimethylbenzoyl Phenylphosphine Oxide is now reported to be used in non-coloring hair preparations.

Comments on the Draft Report that was presented at the March 2025 meeting were received from the Council (*PCPCcomments1_PhosphineOxides_032026*) and responses to these comments (*response-PCPCcomments1_PhosphineOxides_032026*) have been provided herein. Additional supporting documents for this report package include concentration of use data on Bis-Trimethylbenzoyl Phenylphosphine Oxide and Ethyl Trimethylbenzoyl Phenylphosphinate (*data2_PhosphineOxides_032026*), a flow chart (*flow_ PhosphineOxides_032026*), report history (*history_PhosphineOxides_032026*), a search strategy (*search_PhosphineOxides_032026*), a data profile (*dataprofile_PhosphineOxides_032026*), and transcripts from previous meetings (*transcripts_PhosphineOxides_032026*).

It is important to note that comments on the Draft Tentative Report from Council (*PCPCcomments2_PhosphineOxides_032026* (corresponding responses *(response-PCPCcomments2_PhosphineOxides_032026*)) were received after the Draft Tentative Report was submitted to Panel for the December 2025 meeting. Because that meeting was delayed and the report is now being reviewed in March 2026,

notable changes since the last version submitted to the Panel are included in this report and highlighted in blue for ease of review.

Lastly, it should be noted that, according to the EU, Trimethylbenzoyl Diphenylphosphine Oxide is classified as a carcinogenic, mutagenic, or toxic for reproduction (CMR) category 1B substance (toxic for reproduction), that is prohibited in cosmetics. Bis-Trimethylbenzoyl Phenylphosphine Oxide and Ethyl Trimethylbenzoyl Phenylphosphinate are not listed as restricted or prohibited under the EU Cosmetics Regulation and are permitted for use, subject to general safety and labeling requirements.

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, a table of insufficiencies/data requests has been provided below.

Insufficiency/Data Requests	**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

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

Phosphine Oxides and Phosphinate Ingredients Data Profile* – March 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			
Ethyl Trimethylbenzoyl Phenylphosphinate	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/

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: March 4, 2025

SUBJECT: Draft Report: Safety Assessment of Trimethylbenzoyl Diphenylphosphine Oxide as Used in Cosmetics (draft prepared for the March 13-14, 2025 meeting)

The Personal Care Products Council respectfully submits the following comments on the draft report, Safety Assessment of Trimethylbenzoyl Diphenylphosphine Oxide as Used in Cosmetics.

Key Issue

Cosmetic Use – Although the description of MoCRA in the Cosmetic Use section is better, it is still not very clear. The report currently states: "As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was terminated in 2023, and as of 2024, manufacturers and processors have been mandated to register and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses, which are exempt from MoCRA reporting for most cosmetic product categories. However, to utilize the exemption, the small business must not sell eye area products, injected products, internal use products, or products that alter appearance for more than 24 h."

We suggest the following changes (shown in red): "As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was ~~terminated~~ discontinued in 2023, and as of 2024, manufacturers and processors ~~have been mandated~~ 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-year period is less than $1,000,000, adjusted for inflation), which are exempt from MoCRA reporting for most cosmetic product categories. ~~However, to utilize the exemption, the small business must not sell~~ 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."

Additional Considerations

Abbreviations – With MCF-7, it would be helpful to note that this is a human breast cancer cell line.

Cosmetic Use; Summary – Since it is a new category, please be more specific and say eyelash and eyebrow adhesives rather than the general category eye makeup preparations. If use of Trimethylbenzoyl Diphenylphosphine Oxide was reported in more than one type of eye makeup product, the general category would be appropriate. Since it was reported in only one specific category, which is new, please use the specific category.
.
Genotoxicity; Summary – In the study in human fetal lung fibroblast cells, please also state the concentration at which tail intensity was not increased (0.008 µg/ml).

Dermal Irritation and Sensitization – The number of subjects completing the use study (reference 19) was 34, not 30 as stated in the CIR report. The objective was to have 30 subjects. They included 34 subjects and all completed the study.

Summary – The sensitization studies on nails are correctly not being called HRIPTs earlier in the report. These studies should not be called HRIPTs in the Summary.

Summary – It would be helpful to state the EC_3 value for the LLNA (27%) in the Summary.

Phosphine Oxides and Phosphinate Ingredients – March 2026 – Priya Ferguson	
Comment Submitter: Personal Care Products Council **Date of Submission: March 4, 2025**	
Comment	**Response/Action**
Cosmetic Use – Although the description of MoCRA in the Cosmetic Use section is better, it is still not very clear. The report currently states: "As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was terminated in 2023, and as of 2024, manufacturers and processors have been mandated to register and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses, which are exempt from MoCRA reporting for most cosmetic product categories. However, to utilize the exemption, the small business must not sell eye area products, injected products, internal use products, or products that alter appearance for more than 24 h."	boilerplate updated
We suggest the following changes (shown in red): "As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was terminated discontinued in 2023, and as of 2024, manufacturers and processors have been mandated 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-year period is less than $1,000,000, adjusted for inflation), which are exempt from MoCRA reporting for most cosmetic product categories. ~~However, to utilize the exemption, the small business must not sell~~ 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.	boilerplate updated
Abbreviations – With MCF-7, it would be helpful to note that this is a human breast cancer cell line	addressed
Cosmetic Use; Summary – Since it is a new category, please be more specific and say eyelash and eyebrow adhesives rather than the general category eye makeup preparations. If use of Trimethylbenzoyl Diphenylphosphine Oxide was reported in more than one type of eye makeup product, the general category would be appropriate. Since it was reported in only one specific category, which is new, please use the specific category	addressed
Genotoxicity; Summary – In the study in human fetal lung fibroblast cells, please also state the concentration at which tail intensity was not increased (0.008 µg/ml).	addressed
Dermal Irritation and Sensitization – The number of subjects completing the use study (reference 19) was 34, not 30 as stated in the CIR report. The objective was to have 30 subjects. They included 34 subjects and all completed the study	addressed
Summary – The sensitization studies on nails are correctly not being called HRIPTs earlier in the report. These studies should not be called HRIPTs in the Summary.	addressed
Summary – It would be helpful to state the EC3 value for the LLNA (27%) in the Summary	details found in table

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Jaap Venema, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: November 26, 2025

SUBJECT: Draft Tentative Report: Safety Assessment of Bis-Trimethylbenzoyl Phenylphosphine Oxide, Ethyl Trimethylbenzoyl Phenylphosphinate, and Trimethylbenzoyl Diphenylphosphine Oxide (December 2025 meeting draft)

The Personal Care Products Council respectfully submits the following comments on the draft tentative report, Safety Assessment of Bis-Trimethylbenzoyl Phenylphosphine Oxide, Ethyl Trimethylbenzoyl Phenylphosphinate, and Trimethylbenzoyl Diphenylphosphine Oxide

Key Issues

Cosmetic Use; Summary – It should be made clear that all three ingredients are primarily used in nail products. Based on Table 3, Bis-Trimethylbenzoyl Phenylphosphine Oxide has 432 nail product uses vs 3 uses in other products; Ethyl Trimethylbenzoyl Phenylphosphinate has 1792 nail product uses vs 37 uses in other products; and Trimethylbenzoyl Diphenylphosphine Oxide has 2330 nail product uses vs 46 uses in other products.

Cosmetic Use – Trimethylbenzoyl Diphenylphosphine Oxide was moved to EU Annex II of the cosmetic regulations in EU 2025/877 which was published on May 12, 2025. This prohibition went into effect on September 1, 2025. Therefore, it is not correct to state that "this ingredient is to be moved to European Commission 1223/2009 Annex II". This has already happened.

Additional Considerations

Impurities – Rather than stating, "According to the National Industrial Notification and Assessment Scheme (NICNAS), it would be more accurate to state: "As reported in a NICNAS assessment" as it is likely industry not NICAS that reported the purity information.

Cosmetic Use – When discussing the use of these ingredients, please revise "and mouth" (generally, CIR reports discuss mucous membrane exposure for lipstick products).

Only Ethyl Trimethylbenzoyl Phenylphosphinate was reported in children's makeup products.

Stating “these ingredients are used in children’s makeup” implies that all three ingredients were reported to be used in children’s makeup products. Please make it clear that this use was reported for one ingredient.

Short-Term and Subchronic – Rather than stating “organ weight increases”, please identify the organs for which the weight was increased. Please state which “clinical chemistry” endpoints were changed, and the direction of change.

Genotoxicity; Summary – Please do not use “mixed results” when describing the results of genotoxicity studies. Based on Table 7, the results in one human lymphocyte study of Ethyl Trimethylbenzoyl Phenylphosphinate were equivocal (although significant increases were observed, they were still in the range of historical controls). In a second human lymphocyte study of Ethyl Trimethylbenzoyl Phenylphosphinate, a small increase in structural chromosomal aberrations were observed without metabolic activation, but no increases were observed with metabolic activation.

Carcinogenicity – The lack of carcinogenicity studies for the two additional ingredients should also be mentioned in this section.

Dermal Irritation and Sensitization – Please correct: “skin or rabbits” (should be “skin of rabbits”)

The induction concentrations used in the sensitization studies should also be stated.

Summary – Please add “dermal” to describe the “LD_{50s} >2000 mg/kg bw in rats”

Please indicate that Ethyl Trimethylbenzoyl Phenylphosphinate was sensitizing in an GPMT and an LLNA, and that Trimethylbenzoyl Diphenylphosphine Oxide was sensitizing in an LLNA (it was not tested in guinea pigs).

Phosphine Oxides – March 2026 – Priya Ferguson	
Comment Submitter: Personal Care Products Council **Date of Submission: November 26, 2025**	
Comment	**Response/Action**
Cosmetic Use; Summary – It should be made clear that all three ingredients are primarily used in nail products. Based on Table 3, Bis-Trimethylbenzoyl Phenylphosphine Oxide has 432 nail product uses vs 3 uses in other products; Ethyl Trimethylbenzoyl Phenylphosphinate has 1792 nail product uses vs 37 uses in other products; and Trimethylbenzoyl Diphenylphosphine Oxide has 2330 nail product uses vs 46 uses in other products	Addressed
Cosmetic Use – Trimethylbenzoyl Diphenylphosphine Oxide was moved to EU Annex II of the cosmetic regulations in EU 2025/877 which was published on May 12, 2025. This prohibition went into effect on September 1, 2025. Therefore, it is not correct to state that "this ingredient is to be moved to European Commission 1223/2009 Annex II". This has already happened	Addressed
Impurities – Rather than stating, "According to the National Industrial Notification and Assessment Scheme (NICNAS), it would be more accurate to state: "As reported in a NICNAS assessment" as it is likely industry not NICAS that reported the purity information.	Addressed
Cosmetic Use – When discussing the use of these ingredients, please revise "and mouth" (generally, CIR reports discuss mucous membrane exposure for lipstick products).	Addressed
Only Ethyl Trimethylbenzoyl Phenylphosphinate was reported in children's makeup products. Stating "these ingredients are used in children's makeup" implies that all three ingredients were reported to be used in children's makeup products. Please make it clear that this use was reported for one ingredient	2025 RLD indicate that Trimethylbenzoyl Diphenylphosphine Oxide is used in children's makeup products as well as Ethyl Trimethylbenzoyl Phenylphosphinate
Short-Term and Subchronic – Rather than stating "organ weight increases", please identify the organs for which the weight was increased. Please state which "clinical chemistry" endpoints were changed, and the direction of change.	Addressed
Genotoxicity; Summary – Please do not use "mixed results" when describing the results of genotoxicity studies. Based on Table 7, the results in one human lymphocyte study of Ethyl Trimethylbenzoyl Phenylphosphinate were equivocal (although significant increases were observed, they were still in the range of historical controls). In a second human lymphocyte study of Ethyl Trimethylbenzoyl Phenylphosphinate, a small increase in structural chromosomal aberrations were observed without metabolic activation, but no increases were observed with metabolic activation	Addressed
Carcinogenicity – The lack of carcinogenicity studies for the two additional ingredients should also be mentioned in this section	Addressed
Dermal Irritation and Sensitization – Please correct: "skin or rabbits" (should be "skin of rabbits")	Addressed
The induction concentrations used in the sensitization studies should also be stated	Addressed

Phosphine Oxides – March 2026 – Priya Ferguson	
Comment Submitter: Personal Care Products Council **Date of Submission: November 26, 2025**	
Comment	**Response/Action**
Summary – Please add "dermal" to describe the "LD50s >2000 mg/kg bw in rats"	Addressed
Please indicate that Ethyl Trimethylbenzoyl Phenylphosphinate was sensitizing in an GPMT and an LLNA, and that Trimethylbenzoyl Diphenylphosphine Oxide was sensitizing in an LLNA (it was not tested in guinea pigs)	Addressed

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. Where'd Don go? We lost Don.

MS. FIUME: Did he turn his video off?

DR. SNYDER: Don, are you still there?

MS. FIUME: Does that show Mute on the bottom like he had to step away? Yeah. Because he could see us because we're here.

DR. SNYDER: Oh, just wait. Give him a minute to come back?

DR. RETTIE: Did he say hold on?

DR. SNYDER: Did he say hold on? I missed it if he did.

MS. FIUME: I don't think he said it.

DR. SNYDER: I didn't think he did.

DR. BELSITO: I'm sorry, Paul, I had to step out. Where are we?

DR. SNYDER: That's okay. That's okay. Okay. Did you hear my overview of the Trimethylbenzoyl Diphenylphosphine Oxide? It's a draft report.

DR. BELSITO: Yeah. I heard that.

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.

MS. 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.

MS. EISENMANN: Right.

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

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

DR. DAVID COHEN: Right.

MS. 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.

MS. 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.

MS. 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.

MS. 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.

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.; David E. Cohen, M.D.; Samuel 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. 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., Senior Scientific Analyst/Writer, CIR.

555 13th Street, NW, Suite 300W, Washington, DC 20004
cirinfo@cir-safety.org

ABBREVIATIONS

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 reprotoxic
Council	Personal Care Products Council
CPSC	Consumer Product Safety Commission
Dictionary	*International Cosmetic Ingredient Dictionary and Handbook*
DMSO	dimethyl sulfoxide
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	Environmental Protection Agency
EU	European Union
FDA	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
MoCRA	Modernization of Cosmetics Regulation Act
MCF-7	Michigan Cancer Foundation-7 human breast cancer cell line
MOE	margin of exposure
MOS	margin of safety
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide
MW	molecular weight
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NR	not reported
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
OECD	Organisation for Economic Co-operation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
PBS	phosphate-buffered saline
PND	post-natal day
POD	point of departure
RLD	Registration and Listing Data
SED	systemic exposure dose
SCCS	Scientific Committee on Consumer Safety
SIDS	screening information dataset
TG	test guideline
TI	tail intensity
US	United States
UV	ultraviolet

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. 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 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 web-based *International Cosmetic Ingredient Dictionary and Handbook* (*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 January 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 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.

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.[3,5,8-10] These ingredients have low vapor pressures, limited water solubility, and moderate to high lipophilicity. All 3 photoinitators exhibit UV light absorption, with reported maxima between 230 and 400 nm.[6,11,12] 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.[13] 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.[13] 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.[14] 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.[9] 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 (MoCRA) of 2022, 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.[15]

According to RLD obtained from the FDA in 2025 and the results of the Council concentration of use survey, 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).[16-18] However 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.[19] The primary reported use of all 3 ingredients reviewed in this report is in nail products.

These ingredients may result in eye exposure and incidental ingestion as they are used in products near the eye (e.g., Ethyl Trimethylbenzoyl Phenylphosphinate is used in a mascara formulation (concentration not stated)) and mucous membranes (e.g., Trimethylbenzoyl Diphenylphosphine Oxide is used in lipstick and lip gloss formulations (concentration not stated)). In addition, these ingredients are used in children's makeup (e.g., Ethyl Trimethylbenzoyl Phenylphosphinate is used in children's lipstick and lip glosses (concentration not stated)).

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.

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 reprotoxic (CMR) substance of category IB (toxic for reproduction), that is prohibited in cosmetics (European Commission 1223/2009 Annex II).[20] Bis-Trimethylbenzoyl Phenylphosphine Oxide and Ethyl Trimethylbenzoyl Phenylphosphinate are not listed as restricted or prohibited under the EU Cosmetics Regulation and are permitted for use, 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 Diphenylphosphine 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)).

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.[21] 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.[9] According to an SCCS opinion on Trimethylbenzoyl Diphenylphosphine Oxide, this ingredient is a lipophilic substance and sparingly soluble in water and is therefore unlikely to penetrate the nail plate.[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.[22] 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)). 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.[3,6,23] 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 a 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 genotoxicity studies summarized below can be found in Table 7.

Bis-Trimethylbenzoyl Phenylphosphine Oxide (in DMSO; purity not stated) was evaluated in an Ames assay at up to 5000 µg/plate (using *Salmonella typhimurium* and *Escherichia coli*), in an in vitro mammalian chromosomal aberration assay at up to 100 µg/ml (using stimulated cultured human lymphocytes), and an in vitro mammalian cell gene mutation assay at up to 80 µg/ml (using mouse lymphoma L5178Y cells; all assays performed with and without metabolic activation).[5] Negative results were obtained for all assays. Ethyl Trimethylbenzoyl Phenylphosphinate (purity 95.7 – 100%) was evaluated in bacterial reverse mutation (Ames) assays using *S. typhimurium* and *E. coli* at concentrations up to 2500 – 5000 µg/plate, a mammalian cell gene mutation assay in Chinese hamster lung fibroblasts (V79) at up to 3300 µg/ml, and human lymphocyte and V79 cell micronucleus and chromosomal aberration assays using concentration ranges from 6.25 – 255 µg/ml, conducted both in the presence and absence of metabolic activation (DMSO used as vehicle in majority of assays).[4] Across these studies, the substance was non-genotoxic in bacteria, non-mutagenic in mammalian gene mutation assays, and non-clastogenic in V79 micronucleus assays. In human lymphocyte micronucleus and chromosomal aberration assays evaluating Ethyl Trimethylbenzoyl Phenylphosphinate (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 showed no genotoxicity in Ames assays performed with *S. typhimurium* (purity > 98%; up to 2500 µg/plate in ethanol) or in a 2-part Ames assay (purity 99%; up to 5000 µg/plate in

ethanol) performed with and without metabolic activation using *S. typhimurium* and *E. coli*.[3,6] In vitro mammalian studies indicated Trimethylbenzoyl Diphenylphosphine Oxide was non-clastogenic in a chromosomal aberration assay (purity 99%; in DMSO; up to 30 µg/ml; Chinese hamster lung cells) and non-mutagenic in a mammalian cell gene mutation assay (purity 99.5%; in ethanol; up to 40.5 µg/ml; Chinese hamster lung fibroblasts); assays performed with and without metabolic activation. However, in a comet assay using fetal lung fibroblasts, Trimethylbenzoyl Diphenylphosphine Oxide (purity > 99.8%; in ethanol) resulted in statistically significant increases in tail intensity at ≥ 0.04 µg/ml (tail intensity not increased at 0.008 µg/ml).[24]

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).[25] 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).[26] 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).[27] 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.

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 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.[28]

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 Phenyl-phosphinate (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

Margin of exposure (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 European Commission (EC) 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.

An MOE calculation for the use of Trimethylbenzoyl Diphenylphosphine Oxide in artificial nail gel systems was calculated by the SCCS and determined to be 1515, which is based off a maximum concentration of use at 5%.[6] CIR staff have conducted an MOE calculation for Ethyl Trimethylbenzoyl Phenylphosphinate following the same approach with the current maximum concentration of use at 6.2%, according to the 2025 concentration of use survey conducted by the Council.[29] The calculations were based on a corrected NOAEL of 150 mg/kg bw/d for DART, assuming 100% absorption through the nail plate, and a 1% residual level remaining after polymerization reaction under the conditions of use. The resulting MOE is 3632. Details regarding the parameters used to perform this calculation can be found in Table 10.

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. 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 a 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.

Bis-Trimethylbenzoyl Phenylphosphine Oxide (purity not stated) was non-genotoxic in Ames (up to 5000 µg/plate), chromosomal aberration (up to 100 µg/ml), and mammalian cell gene mutation (up to 80 µg/ml) assays, performed with and without metabolic activation. Ethyl Trimethylbenzoyl Phenylphosphinate (purity 95.7 – 100%) was non-genotoxic in bacterial and mammalian cell assays (up to 5000 µg/plate or 3300 µg/ml). In human lymphocyte assays, Ethyl Trimethylbenzoyl Phenylphosphinate showed limited, non-dose-dependent effects at high concentrations. Trimethylbenzoyl Diphenylphosphine Oxide (purity 99 - 99.8%) was non-genotoxic in Ames (up to 5000 µg/plate), chromosomal aberration (up to 30 µg/ml), and mammalian cell gene mutation (up to 40.5 µg/ml) assays (performed with and without metabolic activation), but significant increases in tail intensity in a comet assay in fetal lung fibroblasts at ≥ 0.04 µg/ml were noted.

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.

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 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.

An MOE calculation for the use of 5% Trimethylbenzoyl Diphenylphosphine Oxide in artificial nail gel systems was calculated by the SCCS and determined to be 1515. An MOE calculation based on the same approach was performed for Ethyl Trimethylbenzoyl Phenylphosphinate by CIR staff. The resulting MOE was 3632.

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 that these ingredients are…[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.

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]

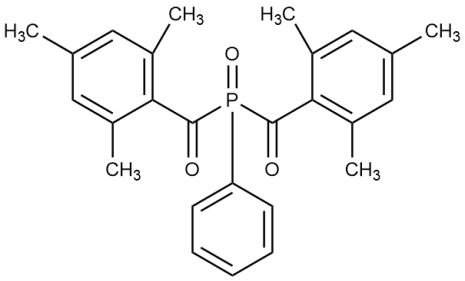
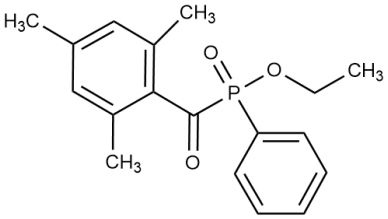
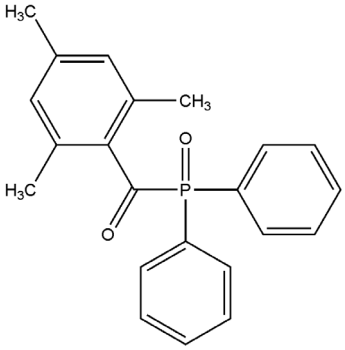
Ingredient/CAS No.	Definition	Function(s)
Bis-Trimethylbenzoyl Phenylphosphine Oxide (162881-26-7)	Bis-Trimethylbenzoyl Phenylphosphine Oxide is the organic compound that conforms to the structure: 	light stabilizer
Ethyl Trimethylbenzoyl Phenylphosphinate (84434-11-7)	Ethyl Trimethylbenzoyl Phenylphosphinate 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	10
Color	yellow	5
Molecular Weight (g/mol)	418.5	10
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	12
Particle Size Distribution (mean mass median diameter; µm)	25.5	5
Ethyl Trimethylbenzoyl Phenylphosphinate		
Physical Form	liquid	9
Color	yellow	9
Molecular Weight (g/mol)	316.3	9
Vapor Pressure (Pa @ 20 ºC)	0.00021	9
Boiling Point (ºC)	257.4	9
Water Solubility (mg/l @ 20 ºC)	35	9
log K_{ow} (@ 25 ºC)	2.9	9
UV Absorption (λ_{max}) (nm)	230, 275, 370	11
Trimethylbenzoyl Diphenylphosphine Oxide		
Physical Form	liquid, pellets, large crystals, or dry powder	3,8
Color	yellow	3
Molecular Weight (g/mol)	348.4	8
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[16-19]

	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.)					
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
Other Manicuring Preparations	39	NR	1054	0.25	993	1.5

Table 3. Frequency and concentration of use according to likely duration and exposure and by product category[16-19]

	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 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.	4,9

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.	22

Table 5. Repeated-dose oral toxicity studies

Test Article	Vehicle	Animals/ Group	Study Duration	Dose/ Concentration	Protocol	Results	Reference
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.	22
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.	[3,6,23]
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	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	[3]

Table 6. Oral developmental and reproductive toxicity studies

Test Article	Vehicle	Animals/Group	Dose/Concentration	Procedure	Results	References
				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	presented with 0 implantation sites (and 0 corpora lutea). At 60 and 200 mg/kg, the mean number of implantation sites remained in the same range of controls. Fertility indices were 100%, 90%, 100% and 0% for the control, 60, 200, and 600 mg/kg groups, respectively. Gestation indices were 100%, 100%, and 90% for the control, 60 and 200 mg/kg groups, respectively. Average live litter sizes were 10.6, 10.8, and 10.4 living fetuses/litter for the control, 60 and 200 mg/kg groups, respectively. One female at 200 mg/kg had only 1 living pup. Tubular atrophy was present in all males treated with the highest dose (correlating with decreased testes weight/reduced testes size). Atypical residual bodies and multinucleated giant cells were present in all males treated at 200 mg/kg at a slight to moderate degree. Atypical residual bodies were present in all males treated at 200 mg/kg at a slight to moderate degree. Multinucleated giant cells were present in a single male treated at 200 mg/kg and in a single male treated at 600 mg/kg at a moderate degree. Degeneration and depletion of germ cells were present in a single male treated at 200 mg/kg at moderate degree. Cell debris was present in the epididymis of a single male treated at 200 mg/kg to a moderate degree and in most males treated at 600 mg/kg up to moderate degree. Reduced sperm was present in a single male treated at 200 mg/kg to a slight degree and in all males treated at 600 mg/kg at a high degree. A minimal increase in hypertrophy of the follicular epithelium of the thyroid glands was noted in males at 200 and 600 mg/kg and in females at 600 mg/kg (considered non-adverse at current severity and in absence of any other pathological finding). No treatment-related clinical signs or adverse gross pathological findings were observed in pups. Live birth indices (number of live offspring on PND 1 as percentage of total number of offspring born) were 97% for the control and 99% for the 60 and 200 mg/kg groups. Parental toxicity NOAEL: 200 mg/kg bw/d**.** Developmental toxicity NOAEL: 200 mg/kg bw/d. Overall reproductive toxicity NOAEL: 60 mg/kg bw/d.	

Table 6. Oral developmental and reproductive toxicity studies

Test Article	Vehicle	Animals/Group	Dose/Concentration	Procedure	Results	References
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
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 (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-mutagenic	[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]

Table 7. In vitro genotoxicity studies

Test Article	Vehicle	Concentration/Dose	Test System	Procedure	Results	References
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]
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]

Table 7. In vitro genotoxicity studies

Test Article	Vehicle	Concentration/Dose	Test System	Procedure	Results	References
Trimethylbenzoyl Diphenylphosphine Oxide (purity > 98%)	methanol	0, 500, and 2500 µg/plate	*S. typhimurium* strains TA1535, TA1537, TA98, and TA 100	Ames assay; OECD TG 471; performed with and without metabolic activation; negative controls: untreated and vehicle; positive controls: cyclophosphamide, methyl-N-nitro-N-nitrosoguanidine, 2-aminoanthracene	Non-genotoxic; cytotoxicity was observed at 2500 µg/plate in the presence of metabolic activation in all strains, and without S9 in TA1535, but no increase in the number of his-positive revertants could be detected under all conditions tested; controls gave expected results.	[3,6]
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]
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]
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]
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	[24]

*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 within 8 d; unknown if this average includes both abraded and intact skin; mean of results observed at 24, 48, and 72 h; potential maximum value not provided). Mean erythema and edema scores for intact skin were 0.6/4 and 0.3/4, respectively. Mean erythema and edema scores for abraded skin were 0.9/4 and 0.4/4. The test substance was considered to be slightly irritating.	3,6
HUMAN						
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	28

Table 8. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
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

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 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 of Ethyl Trimethylbenzoyl Phenylphosphinate in gel product	6.2%	Maximum concentration of use according to PCPC 2025 survey
Total amount of Ethyl Trimethylbenzoyl Phenylphosphinate 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 10 mg/nail; considering total fingernail and toenail area of 22 cm^2)
Human body weight	60 kg	Default human body weight
Amount of Ethyl Trimethylbenzoyl Phenylphosphinate 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 (Ethyl Trimethylbenzoyl Phenylphosphinate)	0.0413 mg/kg bw/d	4.13 mg/kg bw * 0.01 = 0.0413 mg/kg bw/d
NOAEL (Ethyl Trimethylbenzoyl Phenylphosphinate)	300 mg/kg bw/d	Based on a prenatal developmental toxicity in rats (GD 6 – 19; can be found in the Developmental and Reproductive Toxicity section of this report)[4]
Corrected NOAEL (Ethyl Trimethylbenzoyl Phenylphosphinate) for 50% bioavailability	150 mg/kg bw/d	
MOE (Ethyl Trimethylbenzoyl Phenylphosphinate)	**3632**	150 mg/kg bw/d / 0.0413 mg/kg bw/d = 3632
MOE Calculation Parameters for Trimethylbenzoyl Diphenylphosphine Oxide		
Amount of gel applied	4 g	Full artificial nail systems are typically applied every 2 – 3 wk, with a refill application after 1 - 2 wk; full application of artificial nail systems range between 2 – 4 g of gel; refills consist of approximately 1 g of gel
Concentration of Trimethylbenzoyl Diphenylphosphine Oxide in gel product	5%	Maximum concentration of use according to PCPC 2025 survey
Total amount of Trimethylbenzoyl Diphenylphosphine Oxide 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 of Trimethylbenzoyl Diphenylphosphine Oxide 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 (Trimethylbenzoyl Diphenylphosphine Oxide)	0.033 mg/kg bw/d	3.33 mg/kg bw * 0.01 = 0.033 mg/kg bw/d
NOAEL (Trimethylbenzoyl Diphenylphosphine Oxide)	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)[3,6,23]
Corrected NOAEL (Trimethylbenzoyl Diphenylphosphine Oxide) for 50% bioavailability	50 mg/kg bw/d	Standard procedure according to SCCS's Notes of Guidance for the testing of cosmetic ingredients and their safety evaluation
MOE (Trimethylbenzoyl Diphenylphosphine Oxide)	**1515**	50 mg/kg bw/d / 0.033 mg/kg bw/d = 1515

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

* These ingredients are used as chemical photo-initiators in curable gel systems for artificial nails, where it rapidly splits into free radicals that integrate into the polymer chain ends and is mostly consumed during polymerization. Any residual 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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Concentration of Use by FDA Product Category[1]

Trimethylbenzoyl Diphenylphosphine Oxide

Product Category	Maximum Concentration of Use
Basecoats and undercoats (manicuring preparations)	0.25-0.7%
Nail polish and enamel	3-5%
Other manicuring preparations	1.5%

Information collected in 2025

Table prepared: October 21, 2025

[1] The new FDA cosmetic product categories under MoCRA were used for this survey.

Concentration of Use by FDA Product Category[1]

Ethyl Trimethylbenzoyl Phenylphosphinate
Bis-Trimethylbenzoyl Phenylphosphine Oxide

Ingredient	Product Category	Maximum Concentration of Use
Ethyl Trimethylbenzoyl Phenyl Phosphinate	Nail polish and enamel	4-6.2%
Ethyl Trimethylbenzoyl Phenyl Phosphinate	Other manicuring preparation	0.25%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2025
Table prepared: June 25, 2025

[1] The new FDA cosmetic product categories under MoCRA were used for this survey.