Safety Assessment of Dimer Dilinoleates as Used in Cosmetics

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 M. Cohen, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. 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 Christina Burnett, M.S., Senior Scientific Analyst/Writer, CIR.

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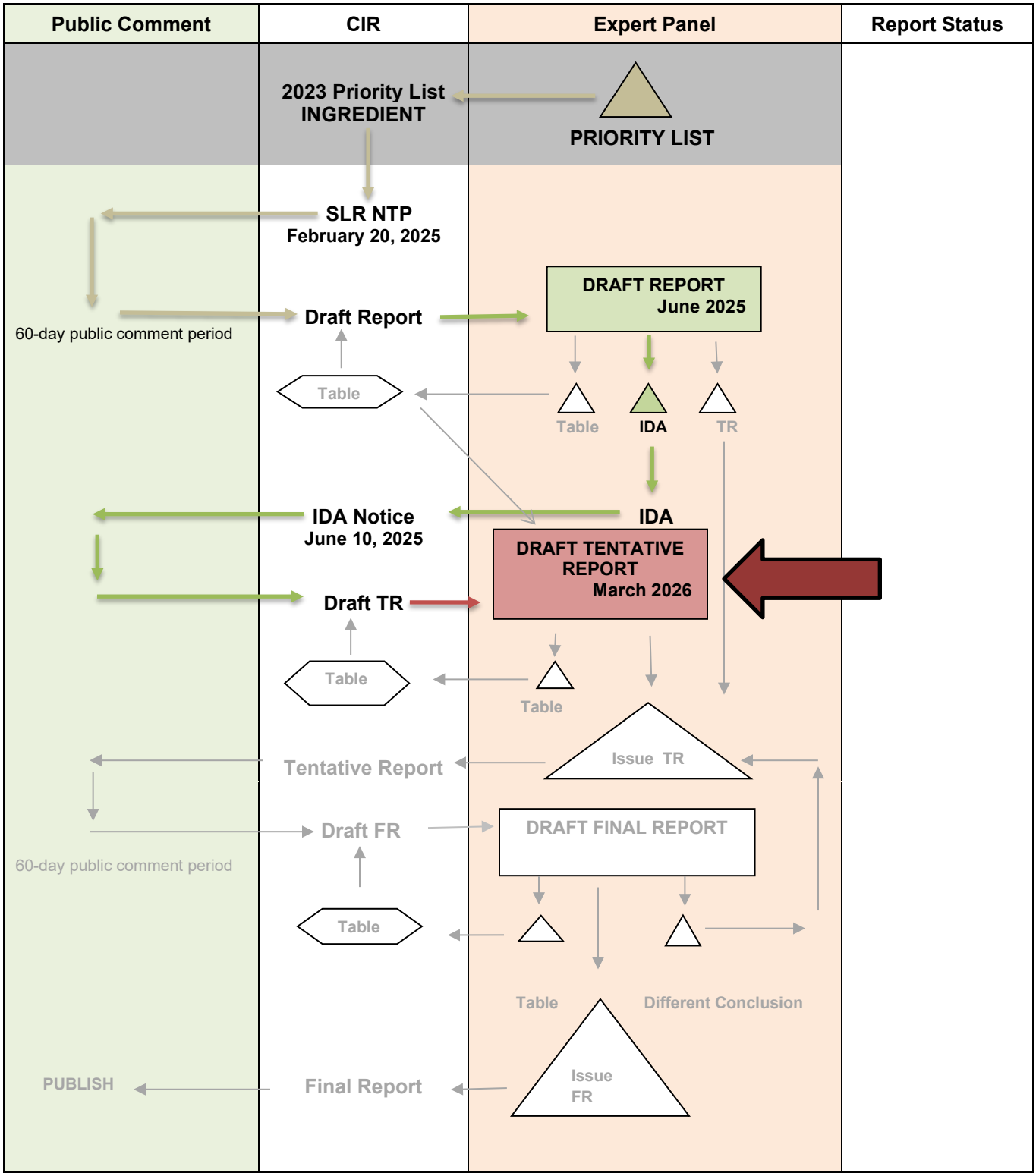
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Dimer Dilinoleates

MEETING March 2026



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Christina L. Burnett, M.S., Senior Scientific Analyst/Writer, CIR
Date: February 17, 2026
Subject: Safety Assessment of Dimer Dilinoleates as Used in Cosmetics

Enclosed is the Draft Tentative Report on the Safety of Dimer Dilinoleates as Used in Cosmetics. (It is identified as *report_DimerDilinoleates_032026* in the pdf document). At the June 2025 meeting, the Panel issued an Insufficient Data Announcement (IDA) for these 7 ingredients. The additional data needs are:

- structures for all ingredients
- method of manufacturing for all ingredients
- impurities/composition data for all ingredients
- repeated oral-dose toxicity data for Dimer Dilinoleyl Dimer Dilinoleate at maximum concentration of use
- developmental and reproductive toxicity data
- ocular irritation data
- dermal irritation and sensitization data at maximum concentration of use for Octyldodecyl/PPG-3 Myristyl Ether Dimer Dilinoleate and Stearyl/PPG-3 Myristyl Ether Dimer Dilinoleate

Since the IDA, CIR staff have received some of the requested data and more details on some of the data that was already in the report. (The table provided at the end of this memo identifies the needs that were fulfilled.) These data have been incorporated into the Draft Tentative Report and highlighted for ease of review:

- *data1_DimerDilinoleates_032026* – study submissions of the acute and ocular toxicity data that were received as brief summaries prior to the June 2025 meeting
- *data2_DimerDilinoleates_032026* – additional generic method of manufacturing and impurities data
- *data3_DimerDilinoeates_032026* – summary of the data from data1
- *data4_DimerDilinoleates_032026* – clarification of the structure for Dimer Dilinoleyl Dimer Dilinoleate found in data 2

The frequency of use has been updated with 2025 RLD in both the text and the use table (Table 3); of note, Bis-Behenyl/ Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate went from having no uses in the 2024 RLD to having uses in 2474 formulations. Increases were also observed in several of the other ingredients. The update provided in text in the Use section is highlighted in blue for your attention. (The only changes highlighted in the Use table are the updated total number of uses and any new categories reported to have use in 2025.)

Comments from the Council on the Draft Report that were received prior to the June 2025 meeting and on the Draft Tentative Report that was prepared for the postponed December meeting have been addressed (*PCPCcomments1_DimerDilinoleates_032026, PCPCcomments2_DimerDilinoleates_032026, response1-PCPCcomments_DimerDilinoleates_032026,* and *response2-PCPCcomments_DimerDilinoleates_032026*). Additional supporting documents for this report package include a flow chart (*flow_DimerDilinoleates_032026*), report history (*history_DimerDilinoleates_032026*), a search strategy (*search_DimerDilinoleates_032026*), a data profile (*dataprofile_DimerDilinoleates_032026*), and meeting transcripts (*transcripts_DimerDilinoleates_032026*).

A draft Abstract and Discussion have been added to the report. The Panel should carefully consider and discuss the data (or lack thereof), and 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 your recollection:

Ingredient	Data insufficiency	Data received
Dimer Dilinoleyl Dimer Dilinoleate	Repeated oral-dose toxicity data for Dimer Dilinoleyl Dimer Dilinoleate at maximum concentration of use	N
Octyldodecyl/PPG-3 Myristyl Ether Dimer Dilinoleate	Dermal irritation and sensitization data at maximum concentration of use	N
Stearyl/PPG-3 Myristyl Ether Dimer Dilinoleate	Dermal irritation and sensitization data at maximum concentration of use	N
All Ingredients	Structures	Y
	Method of manufacture	Y
	Impurities and composition	Y
	Developmental and reproductive toxicity data	N
	Ocular irritation data	Y

Dimer Dilinoleates History

February 2025 – A Scientific Literature Review (SLR) Notice to Proceed (NTP) was issued by CIR

March/April 2025 – CIR received unpublished data on some of the dimer dilinoleate ingredients.

June 2025 - The Panel issued an IDA for the following 7 dimer dilinoleate ingredients:

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate
Bis-Behenyl/Phytosteryl Dimer Dilinoleate
Dimer Dilinoleyl Dimer Dilinoleate
Octyldodecyl/PPG-3 Myristyl Ether Dimer Dilinoleate
Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate
Phytosteryl Isostearyl Dimer Dilinoleate
Stearyl/PPG-3 Myristyl Ether Dimer Dilinoleate

The additional data needed to determine safety for these ingredients are:

- Structures for all ingredients
- Method of manufacturing for all ingredients
- Impurities/composition data for all ingredients
- Repeated oral-dose toxicity data for Dimer Dilinoleyl Dimer Dilinoleate at maximum concentrations of use
- Developmental and reproductive toxicity (DART) data
- Ocular irritation data
- Dermal irritation and sensitization data at maximum concentration of use for Octyldodecyl/PPG-3 Myristyl Ether Dimer Dilinoleate and Stearyl/PPG-3 Myristyl Ether Dimer Dilinoleate

July 2025 – Additional unpublished data received from the Council.

Dimer Dilinoleates Data Profile* – March 2026 – Christina Burnett																														
				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-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	X	X	X					X							X					X	X		X	X		X	X		
Bis-Behenyl/Phytosteryl Dimer Dilinoleate	X	X	X												X														
Dimer Dilinoleyl Dimer Dilinoleate	X	X	X					X							X					X	X		X	X		X	X		
Octyldodecyl/PPG-3 Myristyl Ether Dimer Dilinoleate	X																												
Phytosteryl/Isostearyl/Cetyl/Stearyl/ Behenyl Dimer Dilinoleate	X	X	X					X							X					X	X		X	X			X		
Phytosteryl Isostearyl Dimer Dilinoleate	X	X	X					X							X					X	X		X				X		
Stearyl/PPG-3 Myristyl Ether Dimer Dilinoleate	X																												
dimer dilinoleates - generic		X	X																										

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

Dimer Dilinoleates

Ingredient	CAS #	PubMed	FDA	CompTox	ChemPort	NIOSH	NTIS	NTP	FEMA	EU	ECHA	SIDS	SCCS	AICIS	FAO	WHO	Web
Bis-Behenyl/Isostearyl/ Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	654651-30-6	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Bis-Behenyl/ Phytosteryl Dimer Dilinoleate	None in dictionary	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Dimer Dilinoleyl Dimer Dilinoleate	378789-58-3	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Octyldodecyl/PPG-3 Myristyl Ether Dimer Dilinoleate	None in dictionary	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Phytosteryl/Isostearyl/ Cetyl/Stearyl/Behenyl Dimer Dilinoleate	None in dictionary	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Phytosteryl Isostearyl Dimer Dilinoleate	None in dictionary	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Stearyl/PPG-3 Myristyl Ether Dimer Dilinoleate	None in dictionary	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Search Strategy

PubMed

(Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate) OR (654651-30-6[EC/RN Number]) – 1 hit, 1 useful
Bis-Behenyl/Phytosteryl Dimer Dilinoleate – 1 hit, 1 useful (same as above)
(Dimer Dilinoleyl Dimer Dilinoleate) OR (378789-58-3[EC/RN Number]) - 1 hit, 1 useful (same as above)
Octyldodecyl/PPG-3 Myristyl Ether Dimer Dilinoleate – 0 hits
Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate – 0 hits
Phytosteryl Isostearyl Dimer Dilinoleate – 1 hit, 1 useful (same as above)
Stearyl/PPG-3 Myristyl Ether Dimer Dilinoleate – 0 hits
Dimer Dilinoleate – 8 hits, 1 useful (same as above) and 2 related CIR reports

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
- CompTox: https://comptox.epa.gov/dashboard/chemical/pubmed-abstract-sifter/DTXSID3039242; https://www.epa.gov/comptox-tools/downloadable-computational-toxicology-data#LM
- eChemPortal: https://www.echemportal.org/echemportal/
- DeepDyve: https://www.deepdyve.com/
- 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
- 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: June 4, 2025

SUBJECT: Draft Report: Safety Assessment of Dimer Dilinoleates as Used in Cosmetics (draft prepared for the June 9-10, 2025 meeting)

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

Key Issues

As information on dilinoleic acid was included in the original dimer dilinoleate report, it would be helpful if an updated literature search was completed on this component common to all the ingredients.

This report should make it clear that "phytosteryl alcohol" is a mixture, and that phytosterols have been reviewed by CIR and found safe as used (final 2014). It should also be noted that isostearyl, cetyl, and behenyl alcohols (published 1988) and stearyl alcohol (published 1985) have all been reviewed by CIR.

Additional Considerations

Definition and Structure; Summary – Should all components to which dimer dilinoleate is bound be listed? Should PPG-3 Myristyl Ether and the dimer of linoleyl alcohol also be mentioned?

UV Absorption – A supplier provided UV spectra on 5 of the ingredients included in this report. Rather than saying "According to a supplier", it would be more appropriate to say that based on the UV spectra provided by a supplier no UV absorption was observed (measured from 280 or 290 to 700 nm).

Table 3 – The 2025 PCPC concentration of use information provided for these ingredients was provided by FDA MoCRA cosmetic product categories. It is not clear why the concentration of use information by FDA MoCRA cosmetic product categories can be summarized by likely duration and exposure while the FDA registration and listing data (RLD data) by FDA MoCRA product categories cannot be summarized by likely duration and exposure. The FDA and PCPC information by FDA MoCRA cosmetic product categories should be treated in the same manner.

Dimer Dilinoleates – March 2026 – Christina Burnett	
Comment Submitter: Alexandra Kowcz, Personal Care Products Council **Date of Submission: June 4, 2025**	
Comment	**Response/Action**
Key Issue: As information on dilinoleic acid was included in the original dimer dilinoleate report, it would be helpful if an updated literature search was completed on this component common to all the ingredients.	A literature search was performed: no additional relevant data were found.
Key Issue: This report should make it clear that "phytosteryl alcohol" is a mixture, and that phytosterols have been reviewed by CIR and found safe as used (final 2014). It should also be noted that isostearyl, cetyl, and behenyl alcohols (published 1988) and stearyl alcohol (published 1985) have all been reviewed by CIR.	Additional language regarding phytosteryl alcohol was added. Additional related reports have been noted in the Introduction
Definition and Structure; Summary – Should all components to which dimer dilinoleate is bound be listed? Should PPG-3 Myristyl Ether and the dimer of linoleyl alcohol also be mentioned?	Dr. Heldreth added structures and additional language to the Chemistry section.
UV Absorption – A supplier provided UV spectra on 5 of the ingredients included in this report. Rather than saying "According to a supplier", it would be more appropriate to say that based on the UV spectra provided by a supplier no UV absorption was observed (measured from 280 or 290 to 700 nm).	Sentence rewritten.
Table 3 – The 2025 PCPC concentration of use information provided for these ingredients was provided by FDA MoCRA cosmetic product categories. It is not clear why the concentration of use information by FDA MoCRA cosmetic product categories can be summarized by likely duration and exposure while the FDA registration and listing data (RLD data) by FDA MoCRA product categories cannot be summarized by likely duration and exposure. The FDA and PCPC information by FDA MoCRA cosmetic product categories should be treated in the same manner.	The Use Table and the paragraphs related to MoCRA in the Use section have been updated, thus resolving this issue.

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 Dimer Dilinoleates as Used in Cosmetics (December 2025 meeting draft)

The Personal Care Products Council respectfully submits the following comments on the draft tentative report, Amended Safety Assessment of Dimer Dilinoleates as Used in Cosmetics.

Definition and Structure – In addition to the structures of the components of these ingredients, the generalized structures (pdf p. 212; with a correction in supplemental data) should be added to the CIR report.

Summary – It is not clear why the summary does not also include octyldodecanol and PPG-3 myristyl ether in the list of components to which the carboxylic acid groups are esterified.

Dimer Dilinoleates – March 2026 – Christina Burnett	
Comment Submitter: Jaap Venema, Ph.D., Personal Care Products Council **Date of Submission: November 26, 2025**	
Comment	**Response/Action**
Definition and Structure – In addition to the structures of the components of these ingredients, the generalized structures (pdf p. 212; with a correction in supplemental data) should be added to the CIR report.	Comment ignored per instruction by Dr. Heldreth. Generalized structures are vague.
Summary – It is not clear why the summary does not also include octyldodecanol and PPG-3 myristyl ether in the list of components to which the carboxylic acid groups are esterified.	List of components corrected.

JUNE 2025 MEETING – FIRST REVIEW/DRAFT REPORT

Belsito Team – June 9, 2025

DR. SNYDER: Okay, now the Dimer Dilinoleates. Let me bring that up. This is a Draft Report. There are seven ingredients, they're listed on Page 3. Most uses are in lipsticks, up to 48.7 percent. In February of 2025, we issued an SLR. We received some data that's listed, again, on Page 3 of 52.

There are 801 formulations for the Dimer Dilinoleyl Dimer Dilinoleate. There are 78 formulations with Phytosteryl Isostearyl Dimer Dilinoleate. We have two choices, again, with this Draft Report. If no further data are needed, then we can issue a Discussion and a Tentative Report. Or if we need additional data needs, we need to issue an Insufficient Data Announcement and delineate what data needs we need. So, what was your choice there?

DR. BELSITO: Well, we have lipstick use at 58.7 percent. And we have no in vivo genotox, and we have no DART data. And we have no repeated dose data. I mean, granted, the high level in lipstick, how much are you going to absorb? But I don't know that.

DR. SNYDER: Well, it's a Draft Report, so I think we should go out insufficient for in vivo genotox, DART, and repeat dose tox studies.

DR. RETTIE: I thought those were fine, but a bigger issue -- or a big issue for me -- was the heterogeneity.

DR. BELSITO: Allan, turn on your mic.

DR. RETTIE: Oh, sorry. Yeah, a big issue for me was the heterogeneity composition. I wasn't sure what we were looking at. I thought we needed to have some clarification on what these Dilinoleates are.

Bart took on the, I thought, fairly heroic job of drawing them out for us. And for even a single ingredient, it was possible to come up with a lot of structures. And so, I think we need to have that clarified as to the extent of the heterogeneity.

And in the report, once we get that clarified, I'd like to see the structures, all of them in there. Because we have ethers and we have esters, and we can't read across, in my opinion, from the ethers to the esters for a lot of the missing data. So, there will be read across questions, so we feel like we really need to know what we're dealing with, and I just don't know at the moment.

DR. SNYDER: Okay. Well, we can ask for it. It's, again, a draft report. So, now we have an Insufficient Data Announcement, and we're going to go for in vitro genotox, DART, repeat dose tox data, and then more information on the heterogeneity of the composition, clarification of what they are. And would like to see all of the structures in the next draft of the report.

DR. BELSITO: And also the UV absorption I wasn't happy with it. They said they have almost no UV absorption. What does that mean? They didn't provide any molar extinction coefficients. In the data that the company sent, in the blurb, it says the data was attached but it wasn't attached. And I would like to see the data. You know, could they please attach the data?

DR. SNYDER: Any particular one you want to see?

DR. BELSITO: Well, they said they had UV absorption, almost no UV absorption, on the Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate.

DR. EISENMANN: They sent a spectrum, and I provided it.

DR. BELSITO: I can't hear you, Carol.

DR. EISENMANN: They did send some spectrum that I provided; I don't know where they are, though.

MS. BURNETT: It's PDF Page 44, it starts.

DR. RETTIE: I'm looking at them right now. They don't have any bumps.

DR. EISENMANN: Right.

DR. BELSITO: Yeah, there's nothing in there. There's a box, but there's no graph.

DR. EISENMANN: They didn't find anything, I don't think.

MS. BURNETT: I think they're showing a straight line.

DR. BELSITO: So they're showing zero? You think that the line is the zero line from 290 to 700?

DR. RETTIE: Yep. They're running all these at 100 parts per million. It doesn't seem like a lot. But there's no evidence of a UV peak in the region we'd care about, even a tiny one.

DR. SNYDER: So, okay, we'll take that one off.

DR. BELSITO: Okay.

DR. SNYDER: All right.

DR. BELSITO: I thought it was missing.

DR. EISENMANN: My question, in the original Dimer Dilinoleates report, you included some data on dilinoleic acid, and I wonder if that should be brought over. I don't know, Christina, if you did an updated literature search on dilinoleic acid, but that might be worthwhile doing.

DR. KOWCZ: Just to make it more complete.

DR. SNYDER: Yeah. So we could ask to bring some of that data in as part of the Insufficient Data Announcement?

DR. KOWCZ: Just to make it more complete.

DR. SNYDER: Yep. Yep.

DR. RETTIE: I mean, the chemical names just didn't mean an awful lot to me. This was terminology that I was not familiar with, so the structures will be helpful.

DR. SNYDER: Okay. Do you have that, Christina?

MS. BURNETT: Yep.

DR. HELDRETH: And then Dr. Rettie had mentioned something about the structures. When I discussed it with him, I provided just a handful of the estimated properties using EPISuite. Do you want them just for a representative from each one, or would you like to see estimated properties for all the structures?

DR. RETTIE: I don't think I need to see all that data. The two that I looked at, I think you drew an ether and an ester, a representative one. You know, the logPs were 30 for both of them. I wondered if they'd be different, but they weren't.

So, you know, I'd be good with a limited amount. Don't know what we can take from any of that data, really. Structures we can take something from.

DR. SNYDER: Okay, we're good?

DR. BELSITO: Yeah, I mean, do we -- when we're asking -- I mean, I think we need in vivo genotox. Did you ask for that, Paul?

DR. SNYDER: Yes.

DR. BELSITO: Okay. Do we want to say, like, dermal absorption, and if absorbed then we need DART data, rather than saying we need DART data?

DR. SNYDER: Well, I have skin absorption as in formulation. And then I should say if absorbed then we want additional data?

DR. BELSITO: Yeah, because if there's not significant absorption -- well, I guess the biggest issue with that is the largest use is mucosa, right? It's lipstick?

DR. SNYDER: Yeah.

DR. EISENMANN: I think the company would say you don't need absorption data based on the --

DR. BELSITO: I can't hear you, Carol.

DR. EISENMANN: I said, you may not need absorption data because the LogKOW is so large.

DR. RETTIE: It'll just sit in the skin, or -- yeah.

DR. SNYDER: Well, we don't have the data.

DR. BELSITO: I mean, we're going insufficient, so we could ask for it. If we don't get it, that could be an argument in the Discussion, where we don't think it's absorbed because of the LogKow, right?

DR. SNYDER: Yeah, right.

DR. KLAASSEN: So what are we saying about the Log-ow?

DR. SNYDER: K-O-W.

DR. RETTIE: LogP is 30, so it's probably going to get into a skin layer and just stay there, rather than be available for systemic absorption.

DR. KLAASSEN: Is there -- I'm asking this for my own edification. Is there good data for that concept? Or is there any data for that concept?

DR. RETTIE: That's a good scientific question that I can't answer, so it's still open. I don't know.

DR. KLAASSEN: yeah, I wonder. I mean, I've often wondered about that. You know, in general, we say if something is very lipid soluble it's well absorbed. But I know there's an exception to that. But I've never been able to find any data to support my hypothesis. I've never looked that diligently. Does anybody in the audience know?

DR. BJERKE: Can you repeat the question, please?

DR. KLAASSEN: Do you know of any data that shows that if a compound is extremely lipid soluble, super lipid soluble, like a ratio of 30 to 1, that it wouldn't be absorbed?

DR. BJERKE: Yeah. There is the guidelines in the old Crowe's manuscript that talks about kind of the optimal absorption, I think, between minus one and four.

DR. KLAASSEN: Okay.

DR. BJERKE: So, if you get to the extreme, I think it's less bioavailable across the spectrum.

DR. RETTIE: Okay. But has anybody done an experiment, I wonder?

DR. KLAASSEN: Well, you always wonder, just because you read something, if it's based on science. But I'll assume it is. Could you send me the name of that so I could find that? I would like to at least read through it.

DR. BJERKE: Yeah.

DR. KLAASSEN: I think the concept is correct. I've just never been able to find any data to support the concept. In fact, I haven't even found anybody previously that had written it down. But apparently you have found it written down.

DR. BJERKE: Yeah, I think there are three. There's the Crow's Report, there's Potts and Guy, and then there's, like, Bremer.

DR. KLAASSEN: Okay.

DR. BJERKE: I'll get you those.

DR. KLAASSEN: I appreciate that.

DR. RETTIE: That's a super hard concept for students to put across, that we have a parabolic kind of relationship. It's good only within a certain amount. I don't know, I've never been very good at putting that across.

While we're talking about insufficiencies, I was wondering whether we needed to go all in -- pretty much all in -- on at least one of the ethers, because we will be reading across -- or we'll want to read across -- from the non-ethers to the ethers for just about every endpoint that we have. Because there's just no data in the data tables, unlike the Dimer Dilinoleates. So, for there and there, we have no data.

DR. SNYDER: So, what do you want to ask for then?

DR. RETTIE: That data for the ethers.

DR. SNYDER: What data?

DR. RETTIE: Okay. repeat dose, acute tox?

DR. BELSITO: Which ethers are we talking about?

DR. RETTIE: The fourth and the seventh entry in the data table. Those are different beasts, although their logP's are the same.

DR. HELDRETH: So, the PPG?

DR. RETTIE: PPG ethers, yes.

DR. BELSITO: Oh, yeah. Okay, I see what you're talking about now. So should they be in the same group?

DR. RETTIE: The fact that the ethers don't change the logP that much, or at least the estimated logP, makes me think that they probably belong in the same group. Splitting them out, hmm, I could go that way, too.

DR. SNYDER: So, what are we specifically asking for?

DR. RETTIE: We're asking whether the ethers, the two ethers, belong in the same group as the Dilinoleates. And I'm kind of on the fence.

DR. SNYDER: What table is that table?

DR. BELSITO: I missed that, too. They're part of the group we're looking at, so it's PDF Page 11, in the Introduction. And then we never see any more data on either one of the ethers.

DR. RETTIE: Yeah.

DR. SNYDER: Okay.

DR. RETTIE: Maybe it'll be a productive conversation with the Cohen group tomorrow.

DR. SNYDER: Yep, perfect.

DR. RETTIE: Since I can't really say.

DR. SNYDER: All right. So, that's a complicated insufficient data; do you have it all?

MS. BURNETT: I think so.

DR. SNYDER: You want me to repeat it?

MS. BURNETT: Or I can repeat it to you to make sure I got it straight.

DR. SNYDER: You do that, please.

MS. BURNETT: Dermal absorption data and then, if absorbed, DART and any other supportive data. In vivo genotox, repeated dose genotox, clarification on the heterogeneity composition. And for the future draft, add the dilinoleic acid information.

DR. SNYDER: Yep.

MS. BURNETT: Estimated property values on some of these. The ones that I know about. And then structures drawn for each.

DR. SNYDER: Okay. And then the question of -- we'll have a discussion about whether the two ethers belong with this group.

MS. BURNETT: Right.

DR. SNYDER: Okay. I think you've got it.

MS. BURNETT: Okay.

DR. BELSITO: And then eventually, in the Discussion, the heavy-metal boilerplate.

DR. SNYDER: Okay. Thank you.

DR. RETTIE: It seems to me they've done a report in the past on PPG ethers in general, and for some reason these were not included. Do you have any recollection of those discussions?

DR. SNYDER: No. I don't.

DR. HELDRETH: Those ones only differed -- they didn't have the Dimer Dilinoleate other piece of the puzzle there. We did lots of PPGs all by themselves, just like, you know, PPG 40 or something like that.

DR. RETTIE: Yeah, those are different for sure.

DR. HELDRETH: We also did alkyl-substituted PPG ethers and so forth.

DR. RETTIE: I mean, the fact that the physical-chemical parameters that got spat out for the ones you looked at, the representative "ether" and "ester" looked like they were the same, it's an argument for clustering them together.

DR. HELDRETH: Right. I mean, they're all esters as well.

DR. RETTIE: They're all esters as well.

DR. HELDRETH: The ether is just their ether-ester chain.

DR. RETTIE: Yes.

DR. BELSITO: The ether is just a component of the ester.

DR. SNYDER: Right, exactly.

DR. BELSITO: Say that three times fast.

Cohen Team – June 9, 2025

DR. DAVID COHEN: We have a Draft Report for Dimer Dilinoleates. And there's seven ingredients reported to function as hair conditioning agents, skin conditioning agents, and viscosity-increasing agents in cosmetics.

For brevity, the seven ingredients are listed in the report. According to the RLD in 2024, the ingredients in this group with the most reported uses is Dimer Dilinoleyl Dimer Dilinoleate. And it has 801 formulations. Phytosteryl Isostearyl Dimer Dilinoleate has the second most reported uses at 78 formulations. The results of a concentration of use survey by the Council, in 2025, indicated that Dimer Dilinoleyl Dimer Dilinoleate is used up to 48.7 percent in lipsticks and lip glosses.

So we come to our data needs. It looks like there's several.

DR. BERGFELD: Can I ask you a question first? Is there any read-across?

DR. DAVID COHEN: That was my first question. It is can we read-across?

DR. ROSS: Susan, you want to go or do you want me to go?

DR. TILTON: Go ahead.

DR. ROSS: So, we did look at this the first problem here is there's a -- well, many of them are esters, but you've also got a couple of them that are ethers, okay? So that raised a little bit of the flag.

But then Bart helped us out and drew some structures from a program he has. And it turns out that a couple of the ethers have up to 12 possible different structures. So we need some information on compound heterogeneity on each of these before I think we can make resolutions. And, you know, at this point, it's difficult --

DR. DAVID COHEN: So it's not a read across?

DR. ROSS: It's not a read across at this point.

DR. BERGFELD: Are the esters read across and ethers aren't, or what?

DR. ROSS: I only have different structures, as you can see here, on the ethers. I haven't got those on the esters. But I would imagine there's a similar heterogeneity with at least some of the esters.

DR. DAVID COHEN: So we want structural heterogeneity on all of them?

DR. ROSS: Yeah.

DR. DAVID COHEN: So we're issuing an IDA.

DR. SAM COHEN: Do you think they'll be able to actually do that?

DR. ROSS: I think so. We have no repeat dose toxs, we've got no DART or carcinogenicity studies.

DR. DAVID COHEN: Wait, let's start the list, because I have a few things here, too.

DR. ROSS: Okay. Well, first of all, the molecular weights are over 1000, so I don't think you've got to worry too much about dermal absorption.

DR. DAVID COHEN: And we have good irritation and sensitization.

DR. ROSS: Yeah.

DR. SAM COHEN: And the genotox is totally negative.

DR. ROSS: We don't have a maximum concentration of use, again, of Compound 2. I'm numbering these as they were in the list. We don't have dermal irritation and sensitization on the ethers.

DR. DAVID COHEN: What's their molecular weight?

DR. ROSS: They're over 1000.

DR. DAVID COHEN: Unlikely could it be --

DR. ROSS: If you just go down the list, they're compounds 4 and 7.

DR. DAVID COHEN: 4, and 7 we have.

MS. BURNETT: The one with PPG in the title.

DR. DAVID COHEN: Yeah.

DR. ROSS: So they're the ones with PPG-3 in their title.

DR. DAVID COHEN: So since we can't read across, you think we need sensitization on those. What about the Bis-Behenyl?

DR. ROSS: I thought that was okay.

DR. DAVID COHEN: I don't know if we have sensitization on that, do we?

DR. ROSS: First compound can be cleared based on HRIPT at neat. The others we have dermal sensitization at neat in animals. The HRIPT with compounds 3, 5, and 6, for example, is not at the max, which is 48.7 percent. The max HRIPT is it 19 percent, but we have the animal data. You know? So I think that's probably okay. Ocular irritation for the ethers we don't have.

DR. DAVID COHEN: Okay. So we're going back to the list building.

DR. ROSS: Okay.

DR. DAVID COHEN: Can you start enumerating?

DR. ROSS: Sure. The heterogeneity.

DR. DAVID COHEN: Yup.

DR. ROSS: We need dermal irritation and sensitization on the compounds 4 and 7, which are the two ethers. All of the others, I feel, can be cleared on dermal irritation using data from animals and/or humans. With respect to dermal sensitization that's also needed on the two ethers. I didn't see that. That's compounds 4 and 7 in my nomenclature. And we need ocular irritation there also.

DR. DAVID COHEN: For both of those?

DR. ROSS: Yeah.

DR. BERGFELD: So you are concentrating on the ethers?

DR. ROSS: Pretty much. Yeah.

DR. DAVID COHEN: Yeah.

DR. TILTON: And you mentioned one of the others doesn't have a concentration of use, but other than that, I mean, due to the large molecular weight and the negative genotox, general irritation and sensitization data, I would be okay clearing the others.

DR. ROSS: Yeah. I think it would still be nice to have some information on heterogeneity, but that could be editorial to some degree.

DR. DAVID COHEN: What do you think of the impurities and method of manufacturing?

DR. TILTON: We also don't have that for the ethers.

DR. ROSS: That's probably true.

DR. DAVID COHEN: I don't know how you make these, but I couldn't figure out how you made them from the method of manufacturing. And consequently, if we don't have method of manufacturing and we don't have impurities, then aren't we missing something, if we had one or the other?

DR. ROSS: You do have some in the method of manufacturing and impurities, though.

DR. DAVID COHEN: Hmm?

DR. BERGFELD: We have some there.

DR. ROSS: Yeah, there is some there. Generic method of manufacturing.

DR. DAVID COHEN: Is what? What does it say?

DR. ROSS: Very little.

DR. DAVID COHEN: It doesn't say anything.

DR. ROSS: No. Impurities you've got --

DR. DAVID COHEN: Just heavy metals.

DR. ROSS: Heavy metals and arsenic.

DR. DAVID COHEN: But how are those in there?

DR. ROSS: Yeah, you can ask for that.

DR. DAVID COHEN: Both?

DR. ROSS: Um-hmm. Certainly method of manufacture, which I think it's a little lacking.

DR. TILTON: That one or the composition.

DR. ROSS: I think it's the heterogeneity more than anything. You don't know what you're dealing with exactly.

DR. DAVID COHEN: What was that comment, Susan? I wanted to add that.

DR. TILTON: Method of manufacturing in addition to the heterogeneity.

DR. DAVID COHEN: Okay. There's a comment: "According to a supplier, the following ingredients have almost no UV absorption." I'm not sure I know what that meant.

DR. EISENMANN: They provided UV spectra that were straight lines.

DR. DAVID COHEN: Straight lines, okay.

MS. BURNETT: On PDF, I think, 44. Yeah, starting there.

MS. FIUME: Dr. Ross, so you're asking for ocular irritation for 4 and 7, but do they have ocular uses?

DR. ROSS: That's a good point, actually. I didn't know that, I think.

DR. DAVID COHEN: It's 4 and 7; I got to keep the compounds straight.

DR. ROSS: Yeah.

MS. FIUME: Ones with the PPG. That's how I do it. It makes it easier.

DR. DAVID COHEN: It does.

DR. TILTON: It appears not.

DR. ROSS: Well, if it don't then we don't need it. Good point, Monice. Yeah, if they don't have ocular we don't need it.

DR. DAVID COHEN: I think it's in lipsticks, but okay. Any other needs? So are we -- we're not clearing anything in the group right now. Is that right, Susan?

DR. ROSS: I think a summary was mainly on the ethos being used, David. With respect to -- before we started discussing heterogeneity we probably would have cleared, I think, the majority of the esters. But we just need some clarity with respect to heterogeneity on all of these compounds.

DR. DAVID COHEN: What data comes back that doesn't clear it?

DR. ROSS: Well, maybe one is primarily an Isostearyl ester, and another is a phytosterol ester. So maybe they're just different esters. So, for example, reading across would be different.

DR. DAVID COHEN: So you're saying -- okay. So the read across leaves compound 4 and 7, needing irritation and sensitization because you can't read across?

DR. ROSS: At this point, I think that's correct. Any other comments, Susan, from our discussion?

DR. TILTON: That could potentially be used.

DR. DAVID COHEN: What's that?

DR. TILTON: To support read across.

DR. DAVID COHEN: Say that again.

DR. TILTON: I said it could potentially be used to support read across. We just don't have any information.

DR. BERGFELD: Are we talking the non-ether, the esters?

DR. TILTON: Yes.

DR. ROSS: I think the esters are fine. You could probably go ahead and clear the esters with respect to a lot of this. But again, we just don't know a lot of information about what's in there.

MS. FIUME: Method of manufacture is needed for all ingredients, correct? The method of manufacture is needed for all ingredients?

DR. DAVID COHEN: And impurities.

DR. ROSS: I suspect it's going to be similar in the esters, i.e., just depending on the reagents used. I think it's going to be kind of generic, but you need some detail, I think, as David pointed out. There's no detail on that part of it. At least the way I read it.

DR. DAVID COHEN: Okay.

DR. ROSS: Do you have this one? Yeah, you have this one.

DR. DAVID COHEN: I do have this one.

DR. ROSS: So conclusion is heterogeneity and all of them. We felt we could just about clear the esters, but we need some information on heterogeneity. And the ethers we need more data.

DR. DAVID COHEN: Yeah, so what's the last comment again?

DR. ROSS: And the ethers, we need more data. And they may go tomorrow clearing.

DR. DAVID COHEN: I know.

DR. ROSS: That's quite a possibility I would think.

DR. BERGFELD: All of them? Clearing all of them?

DR. ROSS: It's possible.

DR. BERGFELD: Or just the esters?

DR. ROSS: Either or.

DR. DAVID COHEN: Yes. My gut is there. My gut is there. Yeah, we may not get a second.

DR. ROSS: Yeah. We're expecting that.

DR. DAVID COHEN: It's okay. We've been there before.

Full Panel – June 10, 2025

DR. DAVID COHEN: Okay so this is a Draft Report on Dimer Dilinoleates. There are seven ingredients reported to function as hair conditioning agents, skin conditioning agents and viscosity increasing agents. The seven ingredients are listed in the report. According to the RLD submitted to CIR in 2024, the ingredients in this group with the most reported use is Dimer Dilinoleyl Dimer Dilinoleate, and it is reported in 801 formulations. Phytosteryl Isostearyl Dimer Dilinoleate has the second most reported uses at 78 formulations. According to the 2023 VCRP dataset, lipsticks are common uses.

Concentration of use survey by the Council in 2025 indicate that Dimer Dilinoleyl Dimer Dilinoleate is used in up to 48.7 percent in lipsticks and lip glosses. Our group had a discussion about reading across with these seven ingredients and had difficulty coming to a full conclusion. Many are esters, some are ethers. The ethers can have up to 12 different structures and we had some difficulty with the read across there.

Our motion, therefore, is an Insufficient Data Announcement. Our needs are as follows: Structural heterogeneity on all of them to facilitate read across, dermal irritation and sensitization for compounds number 4 and 7, those are both with the PPG-3 in them, and we need a method of manufacturing and impurities for all of them. That's our motion. We can capture the discussion.

DR. SNYDER: I'll second the Insufficient Data Announcement where we had some additional needs.

DR. BERGFELD: Okay. Can we hear these?

DR. ROSS: And I had some additional needs also. I thought we had additional needs to that.

DR. SNYDER: We have in vivo genotox, we have no DART. We have no repeat dose tox data. We also agreed about the heterogeneity and Allan in particular said he would like -- Allan and Curt -- would like to see the structures. That heterogeneity and regards to the read across, we agree with that. We wanted the dilinoleic acid data added to the report. And then a minor thing with the Discussion to have the heavy metals boilerplate.

DR. DAVID COHEN: So you're adding an ingredient?

DR. SNYDER: Well, just the data from the dilinoleic acid.

DR. HELDRETH: Do you just want to have a reference back to that report? I mean, it's going to be significantly different from all of these esters. I mean you maybe -- if the enzyme could handle it, you could consider it a metabolite, but.

DR. SNYDER: What do you think about that, Don?

DR. BELSITO: Yeah, I mean it is going to be different from the esters, but wouldn't you expect some esterification in the skin? I think we can just summarize the data. Doesn't hurt.

DR. ROSS: Desterification.

DR. RETTIE: Desterification, yeah.

DR. BERGFELD: Allan, are you saying something?

DR. RETTIE: Oh, I may have misheard Don. I thought he said --

DR. BELSITO: Allan, your mic please.

DR. RETTIE: I may have misheard, Don. I thought you said esterification in the skin and I'm sure you must have said desterification, yeah?

DR. BELSITO: That's what I meant, yes.

DR. RETTIE: Okay. Then that's good.

DR. BERGFELD: David?

DR. ROSS: Yeah, I thought with these -- I agree with Paul. I thought, David, we had talked about for the ethers -- which I think we referred to as compounds 4 and 7 just the nomenclature taking by numbers there -- we needed acute toxicity data as well as dermal irritation and sensitization. I think we also talked about ocular.

Because if you look at the toxicity data on the table, you know if you look at those ethers, there's nothing all the way across there. Which I think was getting at Paul's point that he needed more data.

DR. BERGFELD: Did you include ocular?

DR. ROSS: I did, there was nothing listed and I think they have ocular uses.

DR. SNYDER: I'll amended the data request to also include ocular.

DR. SAM COHEN: For the esters, do we really need more tox data because the LD50 is greater than 2 grams per kilogram, and so I doubt if there's going to be any toxicity issues.

DR. SNYDER: We have no data, so, I mean.

DR. BELSITO: But we also discussed that it's not likely to be absorbed.

DR. ROSS: Yeah, we discussed that. Yeah.

DR. BERGFELD: All right, have we commented enough about what we need for the IDA?

DR. BELSITO: Allan, do you want to comment?

DR. RETTIE: Well, just following up on the last comment about absorption. We have molecular weights in excess of 1000, so I don't think there's an issue there.

The structures can be drawn in so many different ways, as Bart has shown us. But if we could get clarification on the structure of one of the Dimer Dilinoleates, we could extrapolate to the others. And if we could get clarification of the structure of one of the PPG-3 ethers, then we could extrapolate to the others, I think.

I didn't think we needed all that information in the report, but we do need clarification on a representative ether and a representative Dimer Dilinoleate.

DR. ROSS: I think that's a fair point. And getting back to that toxicity data and the molecular weight, we did actually discuss that. I'll retract that comment about needing that.

DR. SNYDER: Well, our concern on that was that these are lipsticks so we were assuming their potential for ingestion is high, so we wanted some data on systemic exposure.

DR. ROSS: You wanted oral toxicity data?

DR. SNYDER: Yeah.

DR. ROSS: And I would agree with that, but you don't necessarily need dermal, yeah.

DR. SNYDER: Correct.

DR. ROSS: Yeah, I agree, Paul.

DR. SNYDER: Okay.

DR. DAVID COHEN: I think before Wilma asks us to clarify this again, because I think it will be a fair comment, we've gone back and forth a lot.

DR. BELSITO: David, are you saying something?

DR. DAVID COHEN: Sounds like home. I'm sorry. I said, I think before Wilma asks me to clarify our IDA, I'm going to try to clarify the IDA more. Paul, could you run your list? I'll compare it to ours and then we could restate it.

DR. SNYDER: Well because it's an Insufficient Data Announcement and we have no in vivo genotox, we wanted some genotox data. We have no DART, again that supports that. We wanted repeat dose tox data on oral because of the potential for ingestion. We added ocular based upon the discussion. We wanted information on the heterogeneity of the composition of the different ingredients. And I think that was it.

DR. DAVID COHEN: And we wanted irritation and sensitization on the two PPG products, and we needed method of manufacturing and impurities for all of them.

DR. SNYDER: That's correct.

DR. SAM COHEN: Why do you need in vivo genotox data because all the in vitro is negative?

DR. SNYDER: But we're just going out insufficient so we -- I mean, because we're -- Don, Allan, Curt?

DR. SAM COHEN: Especially since you can't get --

DR. BELSITO: All right. My question was we have multiple negative in vitros, do we need in vivo is what I had in my report.

DR. SNYDER: It was kind of a question. I guess if Sam's comfortable with the data then we can remove that.

DR. SAM COHEN: Yeah, I don't think you need in vivo.

DR. SNYDER: Okay. We can take that off then.

DR. DAVID COHEN: Don, were you saying something that -- to keep it on?

DR. BELSITO: No, I was deferring to Sam as the expert. Because typically we do ask for in vivo, but you know we haven't really had a genotox expert on the Panel for a while. So, you know, we do have multiple negative in vitros and if Sam is happy with that then I'm more than happy with it.

DR. SAM COHEN: I'm happy.

DR. SNYDER: Okay. So, I'll amend that proposed Insufficient Data Announcement and take that one out.

DR. BERGFELD: All right, David, give your list please.

DR. DAVID COHEN: Okay. We need a structural -- we need data on structure, dermal sensitization and irritation on compounds 4 and 7, method of manufacturing and impurity of all of them, ocular tox, oral tox.

DR. BELSITO: And structures.

DR. DAVID COHEN: And structures. Yeah, the structural heterogeneity.

DR. SNYDER: We're in alignment.

DR. DAVID COHEN: Yeah. Okay.

DR. BERGFELD: You're in alignment. I can call in the question.

DR. SNYDER: Okay. Wait, Christina has a question.

DR. BERGFELD: You have a question, Christina?

MS. BURNETT: Yeah. I just wanted clarification, did you want --

DR. BELSITO: Is you mic on, Christina?

MS. BURNETT: Yes. Did you want the data from the dilinoleic acid report pulled in, or did you just want it to be referred back to?

DR. SNYDER: Just summarize. Right? Is that what you said, Don, just a summary of that data?

MS. BURNETT: Like italics for each --

DR. BELSITO: Well, then, that's the question is do we pull in the report or how do you summarize it? I mean I guess maybe just a referral back to that report without summarizing. We could say in the Introduction that we previously looked at dilinoleic acid and found it to be safe as used, da, da, da, da, da.

DR. DAVID COHEN: Can't we just reference that report?

DR. SNYDER: That's fine. That's fine.

DR. HELDRETH: It's historically what we have done.

DR. DAVID COHEN: We'll just reference the report.

DR. SNYDER: That's fine.

DR. BELSITO: Right.

DR. RETTIE: Just one last thing on the structural stuff. Can we be clear that -- it would be helpful if it was also clarified the extent of diesters versus monoesters. This came up in another report. The heterogeneity is profound, but if we list that within the insufficient data for composition, maybe we'll get it.

DR. BERGFELD: I think that can be just added. Can we just add that? Okay. I'm going to call the question then.

We've listed our Insufficient Data Announcement and the items within it. We've had an adequate discussion and especially with the structure. I'll call the question. All those in favor of this movement, please indicate by raising your hands. Okay. Unanimous. All right. Thank you so much.

MS. FIUME: Can I clarify for the IDA?

DR. BERGFELD: Sure.

MS. FIUME: So for the ocular irritation, I think they were on 4 and 7. The oral data, did it need to be on esters versus ethers, both? What is needed for that for the IDA?

DR. BELSITO: Well, it's the Dimer Dilinoleyl Dimer Dilinoleate that is used in a lipstick, right, 48.7 percent?

DR. DAVID COHEN: At very high concentration, yeah.

DR. BELSITO: So wouldn't we want it on that product?

DR. DAVID COHEN: I think that's right, Don.

DR. BERGFELD: Any other questions, Monice?

MS. FIUME: No. Thank you.

DR. DAVID COHEN: No, that's the clarification.

DR. BERGFELD: Okay, great. We're going to move on then to our next ingredient in this group of reports advancing. Dr. Snyder.

DR. SNYDER: Did you call the question?

DR. BERGFELD: I thought we all voted. We voted yes and then Monice had some questions.

DR. SNYDER: My apology. Okay. I’m sorry.

Safety Assessment of Dimer Dilinoleates as Used in Cosmetics

Status:	Draft Tentative Report for Panel Review
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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 M. Cohen, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. 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 Christina Burnett, M.S., Senior Scientific Analyst/Writer, CIR.

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ABBREVIATIONS

CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
Dictionary	*International Cosmetic Ingredient Dictionary and Handbook*
ET_{50}	time of exposure to reduce viability to 50%
FDA	Food and Drug Administration
FOU	frequency of use
HRIPT	human repeated-insult patch test
l.o.	leave-on
MoCRA	Modernization of Cosmetics Regulation Act
NA	not applicable
NR	not reported
OECD	Organisation for Economic Co-operation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
QRA	quantitative risk assessment
RLD	Registration and Listing Data
r.o.	rinse-off
TG	test guideline

DRAFT ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 7 dimer dilinoleate ingredients, which are reported to function as hair conditioning agents, skin conditioning agents, and viscosity increasing agents in cosmetic products. The Panel reviewed all relevant data related to these ingredients. The Panel concluded…[to be determined].

INTRODUCTION

This assessment reviews the safety of the following 7 dimer dilinoleate ingredients as used in cosmetic formulations:

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate
Bis-Behenyl/Phytosteryl Dimer Dilinoleate
Dimer Dilinoleyl Dimer Dilinoleate
Octyldodecyl/PPG-3 Myristyl Ether Dimer Dilinoleate
Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate
Phytosteryl Isostearyl Dimer Dilinoleate
Stearyl/PPG-3 Myristyl Ether Dimer Dilinoleate

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*), most of the ingredients named above are reported to function in cosmetics as hair conditioning agents, skin conditioning agents, and viscosity increasing agents; additional functions are listed in Table 1.[1] Each ingredient is a mixture of esters formed from the reaction of alcohols with dilinoleic acid. The precursor core, dilinoleic acid, is produced by catalytic dimerization of linoleic acid.

The Panel concluded in a safety assessment that was finalized in 2019 that Dilinoleic Acid is safe in the present practice of use and concentration described in the safety assessment when formulated to be non-irritating and non-sensitizing, which may be based on a quantitative risk assessment (QRA).[2] The Panel also previously reviewed dialkyl dimer dilinoleate ingredients in a report that was published in 2023 with the conclusion that the 8 ingredients reviewed therein were safe in cosmetics in the present practices of use and concentration described in the safety assessment.[3] Additional reports related to the ingredients in this safety assessment and the respective conclusions are:

- Diisostearoyl Polyglyceryl-3 Dimer Dilinoleate (published in 2023) - safe in cosmetics in the present practices of use and concentration when formulated to be non-irritating[4]
- Phytosterols (final report issued in 2014) - safe in the present practices of use and concentration[5]
- Isostearyl Alcohol, Cetyl Alcohol, and Behenyl Alcohol (published in 1988, re-review published in 2008) - safe in the present practices of use[6,7]
- Stearyl Alcohol (published in 1985, re-review published in 2006) - safe as used[8,9]

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 April 2025. 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 Expert Panel for Cosmetic Ingredient Safety (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.

CHEMISTRY

Definition and Structure

The definitions of the ingredients included in this review are provided in Table 1.[1] Each of these ingredients is an ester (or diester) of dilinoleic acid (itself a dimer of linoleic acid) and a mixture of alcohols. For example, Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate is a mixture of esters wherein one or more of the carboxylic acid groups in Figure 1 are esterified with phytosteryl (a mixture of sterols obtained from higher plants, including β-sitosterol, campesterol, stigmasterol, and brassicasterol), isostearyl, cetyl, stearyl, and/or behenyl alcohols.

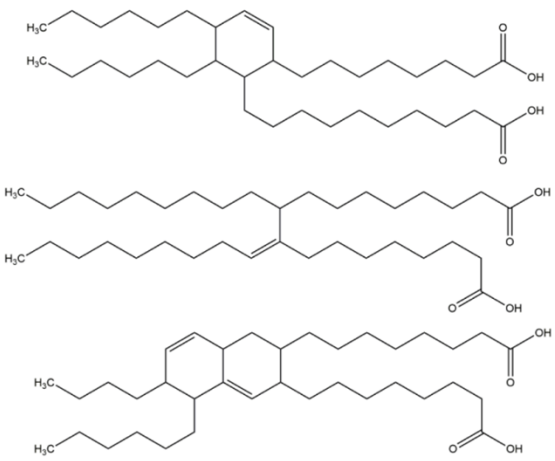

Figure 1. Dilinoleic acid ("dimer acid") (hydrogenated form (i.e., no double bond) is also possible)

Stearyl/PPG-3 Myristyl Ether Dimer Dilinoleate is a mixture of esters wherein one or more of the carboxylic acid functional groups in Figure 1 are esterified with stearyl alcohol and PPG-3 myristyl ether (which comprises a secondary alcohol functional group). The various alcohols used to prepare these esters are shown in Figure 2.

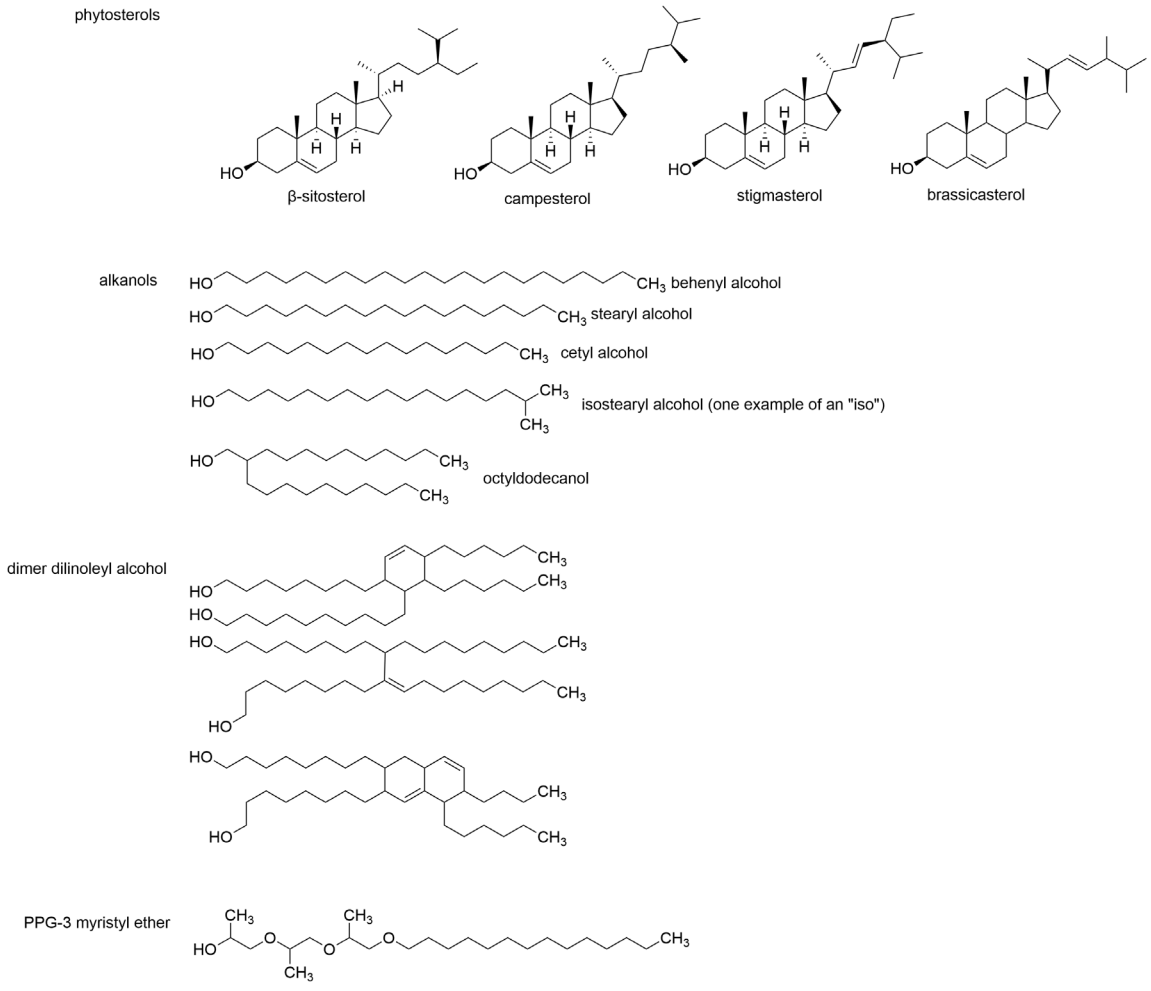

Figure 2. Alcohols

Chemical Properties

Chemical properties of Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate, Octyldodecyl/PPG-3 Myristyl Ether Dimer Dilinoleate, Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate, and Stearyl/PPG-3 Myristyl Ether Dimer Dilinoleate are described in Table 2. Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer

Dilinoleate is a white to pale yellow hydrophobic paste with a molecular weight > 1000 g/mol.[10] Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate is also a white to pale yellow paste, with a melting point of 38ºC.[11] Log K_{ow} estimated for Octyldodecyl/PPG-3 Myristyl Ether Dimer Dilinoleate and Stearyl/PPG-3 Myristyl Ether Dimer Dilinoleate were 32.55 and 30.66, respectively.[12]

Method of Manufacture

A generic method of manufacturing scheme for Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate; Bis-Behenyl/Phytosteryl Dimer Dilinoleate; Dimer Dilinoleyl Dimer Dilinoleate; Phytosteryl/Isostearyl/Cetyl/Stearyl/ Behenyl Dimer Dilinoleate; and Phytosteryl Isostearyl Dimer Dilinoleate was reported by a supplier.[13] For these ingredients, the raw materials are reacted and undergo purification and filtration prior to packaging. No further details were provided.

General method of manufacturing information of dimer dilinoleate reported by the same supplier states that the ester of dimer acid and alcohol can be synthesized by directly esterifying dimer acid and alcohol at high temperatures (180 - 240ºC) while removing the water produced in the reaction.[14] The reaction temperature can be lowered by using acid or alkaline catalysts. The catalysts are removed after the reaction by neutralizing with an acid or alkali wash. Antioxidants may be added to the resulting ester to improve its stability.

Impurities

According to a supplier, heavy metal content and arsenic content are at maximum 20 ppm and 2 ppm, respectively, for the following ingredients: Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate; Bis-Behenyl/ Phytosteryl Dimer Dilinoleate; Dimer Dilinoleyl Dimer Dilinoleate; Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate; and Phytosteryl Isostearyl Dimer Dilinoleate.[13] General composition information of dimer dilinoleate reported by the same supplier states that trace amounts of free alcohol, free fatty acids, and salts of free fatty acids derived from raw materials may be present.[14]

UV Absorption

Based on the UV spectra provided by a supplier, no UV absorption was observed for the following ingredients (measured from 280 or 290 to 700 nm): Bis-Behenyl/Isostearyl/ Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate; Bis-Behenyl/Phytosteryl Dimer Dilinoleate; Dimer Dilinoleyl Dimer Dilinoleate; Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate; and Phytosteryl Isostearyl Dimer Dilinoleate.[15] No UV absorption data were provided for the remaining dimer dilinoleate ingredients.

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 dimer dilinoleates 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.[16]

According to RLD obtained from the FDA in 2025, the ingredient in this group with the most reported uses is Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate; it is reported to be used in 2474 formulations (Table 3).[17,18] Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate has the second most reported uses in the RLD; it is reported to be used in 1998 formulations. The results of the concentration of use survey conducted by the Council in 2025 (using MoCRA product categories) indicate Dimer Dilinoleyl Dimer Dilinoleate has the highest reported maximum concentration of use, at up to 48.7% in lipsticks and lip glosses.[19] Phytosteryl/Isostearyl/Cetyl/Stearyl/ Behenyl Dimer Dilinoleate has the highest maximum concentration of use reported for leave-on dermal exposure, at 13% in foundations.

Some of the ingredients named in this report may be used in products that can be incidentally ingested or be used near the eye or mucous membranes. For example, Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate has been reported to be used in lipsticks and lip glosses at up to 30.1% and in eyeliners at up to 11.7%, and Dimer Dilinoleyl Dimer Dilinoleate has been reported to be used in lipsticks and lip glosses at up to 48.7% and in eyebrow pencils at up to 10%.[19] Additionally, some of the dimer dilinoleates may be used in cosmetic powders, and could possibly be inhaled; for example, Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate is reported to be used at up to 2.9% in face powders. 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 cosmetics 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.

Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.

Products containing dimer dilinoleates 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. Some of the reported product categories for these ingredients as listed in the RLD do require designation if airbrush application is used (e.g., foundations), but no airbrush use was indicated. Additionally, no concentration of use data were provided indicating airbrush application. 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.

None of the dimer dilinoleate ingredients named in the report are restricted from use in any way under the rules governing cosmetic products in the European Union.[20]

TOXICOKINETIC STUDIES

Toxicokinetics studies were not found in the published literature, and unpublished data were not submitted.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Acute toxicity studies are summarized in Table 4. In studies performed in accordance with Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 423 with the following ingredients, the LD_{50} was greater than 2000 mg/kg in rats: Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate; Bis-Behenyl/Isostearyl/ Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate; Dimer Dilinoleyl Dimer Dilinoleate; Phytosteryl/Isostearyl/Cetyl/Stearyl/ Behenyl Dimer Dilinoleate; and Phytosteryl Isostearyl Dimer Dilinoleate.[10,13,21-24]

Repeated-Dose Toxicity Studies

Repeated-dose toxicity studies were not found in the published literature, and unpublished data were not submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Developmental and reproductive toxicity studies were not found in the published literature, and unpublished data were not submitted.

GENOTOXICITY STUDIES

In vitro genotoxicity studies are summarized in Table 5. The following ingredients were not mutagenic in an Ames test when tested at 100% (no further details provided): Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate; Bis-Behenyl/Phytosteryl Dimer Dilinoleate; Dimer Dilinoleyl Dimer Dilinoleate; Phytosteryl/Isostearyl/Cetyl/Stearyl/ Behenyl Dimer Dilinoleate; and Phytosteryl Isostearyl Dimer Dilinoleate.[10,13] Additionally, Bis-Behenyl/Phytosteryl Dimer Dilinoleate; Dimer Dilinoleyl Dimer Dilinoleate; Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate; and Phytosteryl Isostearyl Dimer Dilinoleate were not genotoxic in chromosome aberration tests when tested at 100% (no further details provided).[13] Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate was not genotoxic in a chromosome aberration test when tested at 100% or in a micronucleus assay (no further details provided for either study).[10,13]

CARCINOGENICITY STUDIES

Carcinogenicity studies were not found in the published literature, and unpublished data were not submitted.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Dermal irritation and sensitization studies are summarized in Table 6. Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate and Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate at 100% concentration were non-irritating in primary skin irritation studies in animals, while Dimer Dilinoleyl Dimer Dilinoleate and Phytosteryl Isostearyl Dimer Dilinoleate were mild irritants.[10,13] Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate and Phytosteryl Isostearyl Dimer Dilinoleate, each at 100% concentration, were non-irritating and practically non-irritating, respectively, in cumulative skin irritation studies in guinea pigs (no further details provided).[13] In 24-h closed patch tests in

42 - 45 subjects, Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate, Dimer Dilinoleyl Dimer Dilinoleate, Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate, and Phytosteryl Isostearyl Dimer Dilinoleate at 100% concentration were not irritating.[11,13]

No sensitization was observed in animal studies performed in accordance with OECD TG 406 with the following ingredients: Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate (up to 25%); Dimer Dilinoleyl Dimer Dilinoleate (at 100%); Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate (at 100%); and Phytosteryl Isostearyl Dimer Dilinoleate (at 100%) (no further details provided on these studies).[10,13] No sensitization was observed in human repeated-insult patch tests (HRIPTs) with the following ingredients: Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate (at 100% in 42 subjects and at 3% in a lip balm formulation in 106 subjects); Dimer Dilinoleyl Dimer Dilinoleate (at 19% in a lip treatment formulation in 53 subjects); and Phytosteryl/Isostearyl/Cetyl/ Stearyl/Behenyl Dimer Dilinoleate (at 15% in a lip gloss formulation in 100 subjects).[25-27]

OCULAR IRRITATION STUDIES

Ocular irritation studies are summarized in Table 7. Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate at 100% concentration was determined to be non-irritating in an EpiOcular corneal assay.[13,28] Dimer Dilinoleyl Dimer Dilinoleate at 100% concentration was also determined to be non-irritating in an EpiOcular corneal assay, and it was not categorized as an eye irritant in an in vitro short-time exposure test performed in accordance with OECD TG 491 at concentrations of 0.05 or 5%.[13,29,30] In rabbit studies performed in accordance with OECD TG 405, Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate at 100% was practically non-irritating in one study and slightly irritating in another study).[10,13,31] Minimal irritation was observed in rabbit studies with Dimer Dilinoleyl Dimer Dilinoleate; Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate; and Phytosteryl Isostearyl Dimer Dilinoleate when tested undiluted.[11,13,32-34]

SUMMARY

This assessment reviews the safety of the following 7 dimer dilinoleate ingredients as used in cosmetic formulations: Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate; Bis-Behenyl/Phytosteryl Dimer Dilinoleate; Dimer Dilinoleyl Dimer Dilinoleate; Octyldodecyl/PPG-3 Myristyl Ether Dimer Dilinoleate; Phytosteryl/Isostearyl/Cetyl/Stearyl/ Behenyl Dimer Dilinoleate; Phytosteryl Isostearyl Dimer Dilinoleate; and Stearyl/PPG-3 Myristyl Ether Dimer Dilinoleate. According to the *Dictionary*, most of the ingredients named above are reported to function as hair conditioning agents, skin conditioning agents, and viscosity increasing agents. These dimer dilinoleates have carboxylic acid functional groups that are esterified with octyldodecanol, PPG-3 myristyl ether, dimer dilinoleyl, phytosteryl, isostearyl, cetyl, stearyl, and/or behenyl chains.

According to RLD obtained from the FDA in 2025, the ingredient in this group with the most reported uses is Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate; it is reported to be used in 2474 formulations. Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate has the second most reported uses in the RLD; it is reported to be used in 1998 formulations. The results of the concentration of use survey conducted by the Council in 2025 (using MoCRA product categories) indicate Dimer Dilinoleyl Dimer Dilinoleate has the highest reported maximum concentration of use, at up to 48.7% in lipsticks and lip glosses. Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate has the highest maximum concentration of use reported for leave-on dermal exposure, at 13% in foundations.

None of the dimer dilinoleate ingredients named in the report are restricted from use in any way under the rules governing cosmetic products in the European Union.

In studies performed in accordance with OECD TG 423 with the following ingredients, the LD_{50} was greater than 2000 in rats: Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate; Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate; Dimer Dilinoleyl Dimer Dilinoleate; Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate; and Phytosteryl Isostearyl Dimer Dilinoleate. .

The following ingredients were not mutagenic in an Ames test when tested at 100% (no further details provided): Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate; Bis-Behenyl/Phytosteryl Dimer Dilinoleate; Dimer Dilinoleyl Dimer Dilinoleate; Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate; and Phytosteryl Isostearyl Dimer Dilinoleate. Additionally, Bis-Behenyl/Phytosteryl Dimer Dilinoleate, Dimer Dilinoleyl Dimer Dilinoleate, Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate, and Phytosteryl Isostearyl Dimer Dilinoleate were not genotoxic in chromosome aberration tests when tested at 100% (no further details provided). Bis-Behenyl/Isostearyl/ Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate was not genotoxic in a chromosome aberration test when tested at 100% or in a micronucleus assay (no further details provided for either study).

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate and Phytosteryl/Isostearyl/Cetyl/Stearyl/ Behenyl Dimer Dilinoleate at 100% concentration were non-irritating in primary skin irritation studies in animals, while Dimer Dilinoleyl Dimer Dilinoleate and Phytosteryl Isostearyl Dimer Dilinoleate were mild irritants. Phytosteryl/Isostearyl/ Cetyl/Stearyl/Behenyl Dimer Dilinoleate and Phytosteryl Isostearyl Dimer Dilinoleate, each at 100% concentration, were

non-irritating and practically non-irritating, respectively, in cumulative skin irritation studies in guinea pigs (no further details provided). In 24-h closed patch tests in 42-45 subjects, Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate, Dimer Dilinoleyl Dimer Dilinoleate, Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate, and Phytosteryl Isostearyl Dimer Dilinoleate, all tested at 100% concentration, were not irritating. No sensitization was observed in animal studies performed in accordance with OECD TG 406 with the following ingredients: Bis-Behenyl/Isostearyl/ Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate (up to 25%); Dimer Dilinoleyl Dimer Dilinoleate (at 100%); Phytosteryl/ Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate (at 100%); and Phytosteryl Isostearyl Dimer Dilinoleate (at 100%) (no further details provided on these studies). No sensitization was observed in HRIPTs with the following ingredients: Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate (at 100% in 42 subjects and at 3% in a lip balm formulation in 106 subjects); Dimer Dilinoleyl Dimer Dilinoleate (at 19% in a lip treatment formulation in 53 subjects); and Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate (at 15% in a lip gloss formulation in 100 subjects).

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate at 100% concentration was determined to be non-irritating in an EpiOcular corneal assay. Dimer Dilinoleyl Dimer Dilinoleate at 100% concentration was also determined to be non-irritating in an EpiOcular corneal assay, and it was not categorized as an eye irritant in an in vitro short-time exposure test performed in accordance with OECD TG 491 at concentrations of 0.05 or 5%. In rabbit studies performed in accordance with OECD TG 405, Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate at 100% was practically non-irritating in one study and slightly irritating in another study. Minimal irritation was observed in rabbit studies with Dimer Dilinoleyl Dimer Dilinoleate, Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate, and Phytosteryl Isostearyl Dimer Dilinoleate at 100% concentration.

Toxicokinetics studies, repeated-dose toxicity studies, developmental and reproductive toxicity studies, and carcinogenicity studies on the dimer dilinoleate ingredients were not found in a literature search, and unpublished data were not submitted.

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 dimer dilinoleates as used in cosmetic formulations, in accordance with the product categories and concentrations of use identified in the Use section and Use table. The Panel concluded…**[**to be determined**]**.

The Panel noted that it had previously concluded that Dilinoleic Acid is safe in the present practice of use and concentration described in the safety assessment when formulated to be non-irritating and non-sensitizing, and other components of the ingredients found in this report had also been found to be safe as cosmetic ingredients. While toxicokinetics data are lacking, significant dermal absorption for these dimer dilinoleate ingredients is not expected due to the high molecular weights. [To be further developed…]

The Panel discussed the issue of incidental inhalation exposure resulting from these ingredients. 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 expressed concern regarding heavy metals that may be present in these ingredients. They stressed that the cosmetics industry should continue to use the necessary procedures to minimize impurities in cosmetic formulations according to limits set by the US FDA and EPA.

The Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings) 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 and reported functions[1]

Ingredient/CAS No.	Definition	Function(s)
Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate CAS No. 654651-30-6	Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate is Dimer Dilinoleyl Dimer Dilinoleate end-capped with a mixture of phytosterols, behenyl alcohol, and isostearyl alcohol.	hair condition agent; skin-conditioning agent – emollient; skin-conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Bis-Behenyl/Phytosteryl Dimer Dilinoleate	Bis-Behenyl/Phytosteryl Dimer Dilinoleate is the ester of a mixture of behenyl alcohol and phytosterols with dimer dilinoleic acid.	hair condition agent; skin-conditioning agent – emollient; skin-conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Dimer Dilinoleyl Dimer Dilinoleate CAS No. 378789-58-3	Dimer Dilinoleyl Dimer Dilinoleate is the diester of dilinoleic acid with dimer dilinoleyl alcohol.	binders; skin-conditioning agent – emollient; skin-conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Octyldodecyl/PPG-3 Myristyl Ether Dimer Dilinoleate	Octyldodecyl/PPG-3 Myristyl Ether Dimer Dilinoleate is the diester formed by the reaction of octyldodecanol and PPG-3 myristyl ether with dilinoleic acid.	dispersing agent – nonsurfactant; skin-conditioning agent – emollient; skin-conditioning agent - occlusive
Phytosteryl/Isostearyl/Cetyl/Stearyl/ Behenyl Dimer Dilinoleate	Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate is the ester of dilinoleic acid with a mixture of phytosterols, isostearyl alcohol, cetyl alcohol, stearyl alcohol, and behenyl alcohol.	hair conditioning agent; skin-conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Phytosteryl Isostearyl Dimer Dilinoleate	Phytosteryl Isostearyl Dimer Dilinoleate is the diester of dilinoleic acid with phytosterol and isostearyl alcohol.	binders; hair conditioning agent; skin-conditioning agent – emollient; skin-conditioning agent – occlusive; viscosity increasing agent - nonaqueous
Stearyl/PPG-3 Myristyl Ether Dimer Dilinoleate CAS No. 522632-67-3	Stearyl/PPG-3 Myristyl Ether Dimer Dilinoleate is the diester formed by the reaction of stearyl alcohol and PPG-3 myristyl ether with dilinoleic acid.	dispersing agent – nonsurfactant; skin-conditioning agent – emollient; skin-conditioning agent - occlusive

Table 2. Chemical properties

Property	Value	Reference
Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate		
Physical Form	White to pale yellow hydrophobic paste	10
Molecular Weight (g/mol)	> 1000	10
Density (g/ml @ 50 ºC)	0.89	10
Melting Point (ºC)	~40	10
Water Solubility	Insoluble	10
Octyldodecyl/PPG-3 Myristyl Ether Dimer Dilinoleate		
Vapor Pressure (mmHg @ 25ºC)	7.52×10^{-28}	12
Melting Point (ºC)	349.8	12
Boiling Point (ºC)	1082.6	12
Water Solubility @ 25ºC (mg/l)	1.12×10^{-30} (WSKOW v1.42 estimate)	12
log K_{ow}	32.6 (KOWWIN v1.68 estimate)	12
Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate		
Physical Form	White to pale yellow paste	11
Viscosity (kg/(s x m)@ 60 ºC)	0.18	11
Melting Point (ºC)	38	11
Stearyl/PPG-3 Myristyl Ether Dimer Dilinoleate		
Vapor Pressure (mmHg @ 25ºC)	1.01×10^{-26}	12
Melting Point (ºC)	349.8	12
Boiling Point (ºC)	1043.2	12
Water Solubility @ 25ºC (mg/l)	1.13×10^{-28} (WSKOW v1.42 estimate)	12
log K_{ow}	30.7 (KOWWIN v1.68 estimate)	12

Table 3. Frequency and concentration of use according to likely duration and exposure and by product category

	# of Uses RLD (2025)[17,18]	Max Conc of Use % (2025)[19]	# of Uses RLD (2025)[17,18]	Max Conc of Use % (2025)[19]	# of Uses RLD (2025)[17,18]	Max Conc of Use % (2025)[19]
	Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate		Bis-Behenyl/Phytosteryl Dimer Dilinoleate		Dimer Dilinoleyl Dimer Dilinoleate	
Totals*	**2474**	**0.15-30.1**	**45**	**NR**	**1189**	**0.1-48.7**
summarized by likely duration and exposure**						
Duration of Use						
Leave-On	*2506*	*0.15-30.1*	*45*	*NR*	*1163*	*0.1-48.7*
Rinse-Off	*12*	*0.2-3.6*	*NR*	*NR*	*88*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Permanent Tattoo Ink	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Unknown	*7*	*NR*	*NR*	*NR*	*12*	*NR*
Exposure Type						
Baby Products	NR	NR	NR	NR	NR	NR
Children's Makeup	1	NR	NR	NR	2	NR
Eye Area	348	0.15-11.7	4	NR	191	0.8-10
Incidental Ingestion	1802	3-30.1	39	NR	634	11.3-48.7
Mucous Membrane	1802	3-30.1	39	NR	634	11.3-48.7
Incidental Inhalation-Spray	36[a];73[b]	0.6[a]; 1.6[b]	1[a]; 1[b]	NR	3; 47[a]; 57[b]	NR
Incidental Inhalation-Airbrush	NR	NR	NR	NR	NR	6[a]; 57[b]
Incidental Inhalation-Powder	43; 73[b]	0.4-2.9; 0.4-3[c]	1[b]	NR	38; 57[b]	38; 57[b]
Dermal Contact	700	0.15-11.7	6	NR	463	463
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	14	1.6	NR	NR	102	102
Hair-Coloring	NR	NR	NR	NR	2	2
Nail	2	NR	NR	NR	7	7
Tattoo Preparations	NR	NR	NR	NR	NR	NR
Other Preparations (Unknown Exposure Type)	7	NR	NR	NR	12	12
as reported by product category						
Baby Products						
Baby Shampoos						
Baby Lotions/Oils/Powders/Creams						
Other Baby Products						
Eye Makeup Preparations (not children's)						
Eyebrow Pencil	36	0.15-2.5	4	NR	25	10
Eyeliner	23	0.98-11.7			2	NR
Eye Shadow	270	1.4-7			85	1.5-2
Eye Lotion	2	NR			1	
False Eyelashes						
Mascara					44	0.8-3
Eyelash and Eyebrow Adhesives/Glues/Sealants					1	NR
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)	1	4			8	2
Other Eye Makeup Preparations	16	2.1			25	NR
Fragrance Preparations						
Powders (dusting/talcum, excl aftershave talc)						
Other Fragrance Preparation					3	NR
Hair Preparations (non-coloring)						
Hair Conditioners	1 (l.o.); 9 (r.o.)	1.6 (r.o.)			10 (l.o.); 43 (r.o.)	NR
Hair Straighteners					3	NR

Table 3. Frequency and concentration of use according to likely duration and exposure and by product category

	# of Uses RLD (2025)[17,18]	Max Conc of Use % (2025)[19]	# of Uses RLD (2025)[17,18]	Max Conc of Use % (2025)[19]	# of Uses RLD (2025)[17,18]	Max Conc of Use % (2025)[19]
Permanent Waves					1	NR
Rinses (non-coloring)					9	NR
Shampoos (non-coloring)					20 (r.o.)	NR
Tonics, Dressings, Other Hair Grooming Aids	1	1.6			7	NR
Other Hair Preparations	3 (l.o.)	NR			4 (l.o.); 5 (r.o.)	NR
Hair Coloring Preparations						
Other Hair Coloring Preparation					2	NR
Makeup Preparations (not eye or children's)						
Blushers and Rouges (all types)	77	2.9			39	7-8
Face Powders	43	0.4-2.9			38	NR
Foundations	69	0.5			98	0.1-4.3
Leg and Body Paints	1	NR				
Lipsticks and Lip Glosses	1801	3-30.1	39	NR	632	11.3-48.7
Makeup Bases	3	NR			1	NR
Makeup Fixatives	2	NR			4	NR
Other Makeup Preparations	50	NR			42	NR
Makeup Preparations for Children (not eye)						
Children's Lipsticks and Lip Glosses	1	NR			2	NR
Manicuring Preparations						
Cuticle Softeners					1	NR
Nail Creams and Lotions					3	NR
Nail Polish and Enamel	2	NR				
Other Manicuring Preparations					3	NR
Personal Cleanliness						
Bath Soaps and Body Washes						
Shaving Preparations						
Beard Softeners					1	NR
Pre-shave Lotions (all types)					1	NR
Shaving Cream (aerosol, brushless, lather)	NR	0.6				
Skin Care Preparations						
Cleansing	2	NR			2	NR
Face and Neck (excluding shaving preps)	49 (l.o.)	0.4-3 (l.o.); 0.2 (r.o.)	1 (l.o.)	NR	28 (l.o.)	3.2 (l.o.)
Body and Hand (excluding shaving preps)	1 (l.o.)	NR			3 (l.o.)	NR
Foot Powders and Sprays	1	NR				
Moisturizing	33	1-3			27	NR
Night	2	NR	1	NR	5	3.2
Paste Masks (mud packs)	NR	3.6				
Skin Fresheners					7	NR
Other Skin Care Preparations	18 (l.o.); 1 (r.o.)	NR			15 (l.o.); 1 (r.o.)	6 (l.o.)
Suntan Preparations						
Suntan Gels, Creams, and Liquids						
Indoor Tanning Preparations						
Other Preparations (i.e., those that do not fit another category)	7	NR			12	

Table 3. Frequency and concentration of use according to likely duration and exposure and by product category

	# of Uses	Max Conc of Use	# of Uses	Max Conc of Use	# of Uses	Max Conc of Use
	RLD (2025)[17,18]	% (2025)[19]	RLD (2025)[17,18]	% (2025)[19]	RLD (2025)[17,18]	% (2025)[19]
	Octyldodecyl/PPG-3 Myristyl Ether Dimer Dilinoleate		Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate		Phytosteryl Isostearyl Dimer Dilinoleate	
Totals*	**32**	**10**	**1998**	**0.6-30**	**202**	**0.099**
summarized by likely duration and exposure**						
Duration of Use						
Leave-On	*32*	*10*	*2197*	*0.6-30*	*230*	*0.099*
Rinse-Off	*NR*	*NR*	*30*	*NR*	*8*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Permanent Tattoo Ink	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Unknown	*NR*	*NR*	*2*	*NR*	*1*	*NR*
Exposure Type						
Baby Products	NR	NR	3	NR	2	NR
Children's Makeup	NR	NR	NR	NR	3	NR
Eye Area	NR	NR	110	0.88-12.6	5	NR
Incidental Ingestion	31	10	1393	15.1-30	145	NR
Mucous Membrane	31	10	1393	15.1-30	146	NR
Incidental Inhalation-Spray	NR	NR	1; 165[a]; 264[b]	NR	12[a]; 19[b]	NR
Incidental Inhalation-Airbrush	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	37; 264[b]; 1[c]	1.4-1.6; 0.6-3[c]	2; 19[b]; 1[c]	0.099
Dermal Contact	1	NR	820	0.6-13	83	0.099
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	10	NR	4	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	4	NR	6	NR
Tattoo Preparations	NR	NR	NR	NR	NR	NR
Other Preparations (Unknown Exposure Type)	NR	NR	2	NR	1	NR
as reported by product category						
Baby Products						
Baby Shampoos					1	NR
Baby Lotions/Oils/Powders/Creams			1	NR	1	NR
Other Baby Products			2 (l.o.)	NR		
Eye Makeup Preparations (not children's)						
Eyebrow Pencil			28	0.88-4.8	2	NR
Eyeliner			2	NR	1	NR
Eye Shadow			65	3.6-12.6		
Eye Lotion			2	NR	1	NR
False Eyelashes			1	NR		
Mascara						
Eyelash and Eyebrow Adhesives/Glues/Sealants						
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)						
Other Eye Makeup Preparations			12	NR	1	NR
Fragrance Preparations						
Powders (dusting/talcum, excl aftershave talc)					1	NR
Other Fragrance Preparation			1	NR		
Hair Preparations (non-coloring)						
Hair Conditioners			2 (r.o.)	NR	1 (r.o.)	NR
Hair Straighteners						
Permanent Waves						

Table 3. Frequency and concentration of use according to likely duration and exposure and by product category

	# of Uses RLD (2025)[17,18]	Max Conc of Use % (2025)[19]	# of Uses RLD (2025)[17,18]	Max Conc of Use % (2025)[19]	# of Uses RLD (2025)[17,18]	Max Conc of Use % (2025)[19]
Rinses (non-coloring)			1	NR	1	NR
Shampoos (non-coloring)					1 (r.o.)	NR
Tonics, Dressings, Other Hair Grooming Aids			5	NR		
Other Hair Preparations			2 (r.o.)	NR		
Hair Coloring Preparations						
Other Hair Coloring Preparation						
Makeup Preparations (not eye or children's)						
Blushers and Rouges (all types)			106	12	29	NR
Face Powders			37	1.4-1.6	1	0.099
Foundations			57	13	5	NR
Leg and Body Paints					1	NR
Lipsticks and Lip Glosses	31	10	1393	15.1-30	142	NR
Makeup Bases			10	NR	1	NR
Makeup Fixatives			23	NR		
Other Makeup Preparations	1	NR	33	NR	3	NR
Makeup Preparations for Children (not eye)						
Children's Lipsticks and Lip Glosses					3	NR
Manicuring Preparations						
Cuticle Softeners			1	NR		
Nail Creams and Lotions			1	NR	3	NR
Nail Polish and Enamel			2	NR		
Other Manicuring Preparations					3	NR
Personal Cleanliness						
Bath Soaps and Body Washes					1	NR
Shaving Preparations						
Beard Softeners						
Pre-shave Lotions (all types)						
Shaving Cream (aerosol, brushless, lather)						
Skin Care Preparations						
Cleansing			14	NR	2	NR
Face and Neck (excluding shaving preps)			200 (l.o.); 3 (r.o.)	0.6-3 (l.o.)	14 (l.o.)	NR
Body and Hand (excluding shaving preps)			10 (l.o.)	3	1 (l.o.)	NR
Foot Powders and Sprays						
Moisturizing			141	3.4	10	NR
Night			14	NR	1	NR
Paste Masks (mud packs)			4	NR	1	NR
Skin Fresheners			2	NR		
Other Skin Care Preparations			49 (l.o.); 3 (r.o.)	NR	4 (l.o.)	NR
Suntan Preparations						
Suntan Gels, Creams, and Liquids					1	NR
Indoor Tanning Preparations					1	NR
Other Preparations (i.e., those that do not fit another category)					1	NR

Table 3. Frequency and concentration of use according to likely duration and exposure and by product category

	# of Uses RLD (2025)[17,18]	Max Conc of Use % (2025)[19]	# of Uses RLD (2025)[17,18]	Max Conc of Use % (2025)[19]	# of Uses RLD (2025)[17,18]	Max Conc of Use % (2025)[19]
	Stearyl/PPG-3 Myristyl Ether Dimer Dilinoleate					
Totals*	**44**	**4.7-8.9**				
summarized by likely duration and exposure**						
Duration of Use						
Leave-On	*44*	*4.7-8.9*				
Rinse-Off	*NR*	*NR*				
Diluted for (Bath) Use	*NR*	*NR*				
Permanent Tattoo Ink	*NR*	*NR*				
Unknown	*NR*	*NR*				
Exposure Type						
Baby Products	NR	NR				
Children's Makeup	NR	NR				
Eye Area	NR	NR				
Incidental Ingestion	43	4.7-8.9				
Mucous Membrane	43	4.7-8.9				
Incidental Inhalation-Spray	NR	NR				
Incidental Inhalation-Airbrush	NR	NR				
Incidental Inhalation-Powder	NR	NR				
Dermal Contact	1	6.7				
Deodorant (underarm)	NR	NR				
Hair - Non-Coloring	NR	NR				
Hair-Coloring	NR	NR				
Nail	NR	NR				
Tattoo Preparations	NR	NR				
Other Preparations (Unknown Exposure Type)	NR	NR				
as reported by product category						
Baby Products						
Baby Shampoos						
Baby Lotions/Oils/Powders/Creams						
Other Baby Products						
Eye Makeup Preparations (not children's)						
Eyebrow Pencil						
Eyeliner						
Eye Shadow						
Eye Lotion						
False Eyelashes						
Mascara						
Eyelash and Eyebrow Adhesives/Glues/Sealants						
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)						
Other Eye Makeup Preparations						
Fragrance Preparations						
Powders (dusting/talcum, excl aftershave talc)						
Other Fragrance Preparation						
Hair Preparations (non-coloring)						
Hair Conditioners						
Hair Straighteners						
Permanent Waves						
Rinses (non-coloring)						

Table 3. Frequency and concentration of use according to likely duration and exposure and by product category

	# of Uses RLD (2025)[17,18]	Max Conc of Use % (2025)[19]	# of Uses RLD (2025)[17,18]	Max Conc of Use % (2025)[19]	# of Uses RLD (2025)[17,18]	Max Conc of Use % (2025)[19]
Shampoos (non-coloring)						
Tonics, Dressings, Other Hair Grooming Aids						
Other Hair Preparations						
Hair Coloring Preparations						
Other Hair Coloring Preparation						
Makeup Preparations (not eye or children's)						
Blushers and Rouges (all types)	1	6.7				
Face Powders						
Foundations						
Leg and Body Paints						
Lipsticks and Lip Glosses	43	4.7-8.9				
Makeup Bases						
Makeup Fixatives						
Other Makeup Preparations						
Makeup Preparations for Children (not eye)						
Children's Lipsticks and Lip Glosses						
Manicuring Preparations						
Cuticle Softeners						
Nail Creams and Lotions						
Nail Polish and Enamel						
Other Manicuring Preparations						
Personal Cleanliness						
Bath Soaps and Body Washes						
Shaving Preparations						
Beard Softeners						
Pre-shave Lotions (all types)						
Shaving Cream (aerosol, brushless, lather)						
Skin Care Preparations						
Cleansing						
Face and Neck (excluding shaving preps)						
Body and Hand (excluding shaving preps)						
Foot Powders and Sprays						
Moisturizing						
Night						
Paste Masks (mud packs)						
Skin Fresheners						
Other Skin Care Preparations						
Suntan Preparations						
Suntan Gels, Creams, and Liquids						
Indoor Tanning Preparations						
Other Preparations (i.e., those that do not fit another category)						

NR – not reported
l.o. – leave-on; r.o. – rinse-off
*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)
[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.

Table 3. Acute toxicity studies

Test Article	Vehicle	Animals/Group	Concentration/Dose	Protocol	LD_{50}/LC_{50}/Results	Reference
ORAL						
Bis-Behenyl/Isostearyl/ Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	DMSO	6 female Sprague-Dawley CD (Crl: CD (SD) IGS BR rats	2000 mg/kg bw	Acute toxicity test performed in accordance with OECD TG 423; rats received 10 ml/kg test material in a single gavage treatment. Clinical signs and body weight development were monitored during the study for up to 14 d after dosing. All animals subjected to gross necropsy	LD_{50} > 2000 mg/kg; no deaths or clinical signs of toxicity were observed. All animals had expected body weight gains and no abnormalities were noted at necropsy.	13,24
Bis-Behenyl/Isostearyl/ Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	not reported	rats; no further details provided	at most 2000 mg/kg	Acute toxicity test performed in accordance with OECD TG 423; no further details provided	LD_{50} > 2000 mg/kg	10
Dimer Dilinoleyl Dimer Dilinoleate	arachis oil	3 male and 3 female Sprague-Dawley CD (Crl: CD (SD) IGS BR rats	2000 mg/kg bw	Acute toxicity test performed in accordance with OECD TG 423; rats received 10 ml/kg test material in a single gavage treatment. Clinical signs and body weight development were monitored during the study for up to 14 d after dosing. All animals subjected to gross necropsy	LD_{50} > 2000 mg/kg; no deaths occurred during study. Hunched posture was noted in all female rats 1 d after dosing. No signs of systemic toxicity noted in males. All animals had expected body weight gains and no abnormalities were noted at necropsy.	13,23
Phytosteryl/Isostearyl/ Cetyl/Stearyl/Behenyl Dimer Dilinoleate	arachis oil	6 female Sprague-Dawley CD (Crl: CD (SD) IGS BR rats	2000 mg/kg bw	Acute toxicity test performed in accordance with OECD TG 423; rats received 10 ml/kg test material in a single gavage treatment. Clinical signs and body weight development were monitored during the study for up to 14 d after dosing. All animals subjected to gross necropsy	LD_{50} > 2000 mg/kg; no deaths or clinical signs of toxicity were observed. All animals had expected body weight gains and no abnormalities were noted at necropsy.	13,22
Phytosteryl/Isostearyl/ Cetyl/Stearyl/Behenyl Dimer Dilinoleate	undiluted	not reported	at most 2500 mg/kg	Acute toxicity test performed in accordance with OECD TG 423; no further details provided	LD_{50} > 2500 mg/kg	11,13
Phytosteryl Isostearyl Dimer Dilinoleate	arachis oil	3 male and 3 female Sprague-Dawley CD (Crl: CD (SD) IGS BR rats	2000 mg/kg bw	Acute toxicity test performed in accordance with OECD TG 423; rats received 10 ml/kg test material in a single gavage treatment. Clinical signs and body weight development were monitored during the study for up to 14 d after dosing. All animals subjected to gross necropsy	LD_{50} > 2000 mg/kg; no deaths or clinical signs of toxicity were observed. All animals had expected body weight gains and no abnormalities were noted at necropsy.	13,21

Table 4. Genotoxicity studies

Test Article	Vehicle	Concentration/Dose	Test System	Protocol	Results	Reference
IN VITRO						
Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	not reported	not reported	not reported	Ames test in accordance with OECD TG 471; no further details provided	Not mutagenic	[10]
Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	undiluted	100%	not reported	Ames test in accordance with OECD TG 471; no further details provided	Not mutagenic	[13]
Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	undiluted	100%	not reported	Chromosome aberration test using mammalian cell cultures; no further details provided	Not genotoxic	[13]
Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	not reported	not reported	not reported	In vitro micronucleus assay in accordance with OECD TG 487; no further details provided	Not genotoxic	[10]
Bis-Behenyl/Phytosteryl Dimer Dilinoleate	undiluted	100%	not reported	Ames test; no further details provided	Not mutagenic	[13]
Dimer Dilinoleyl Dimer Dilinoleate	undiluted	100%	not reported	Ames test in accordance with OECD TG 471; no further details provided	Not mutagenic	[13]
Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate	undiluted	100%	not reported	Ames test in accordance with OECD TG 471; no further details provided	Not mutagenic	[13]
Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate	undiluted	100%	not reported	Ames test in accordance with OECD TG 471; no further details provided	Not mutagenic	[13]
Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate	undiluted	100%	not reported	Chromosome aberration test using mammalian cell cultures; no further details provided	Not genotoxic	[13]
Phytosteryl Isostearyl Dimer Dilinoleate	undiluted	100%	not reported	Ames test in accordance with OECD TG 471; no further details provided	Not mutagenic	[13]
Phytosteryl Isostearyl Dimer Dilinoleate	undiluted	100%	not reported	Chromosome aberration test using mammalian cell cultures; no further details provided	Not genotoxic	[13]

Table 5. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration	Test Population	Protocol	Results	Reference
IRRITATION						
ANIMAL						
Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	undiluted	100%	not reported	Primary skin irritation study in accordance with OECD TG 404; no further details provided	Non-irritating	[13]
Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	undiluted	100%	rabbit; no further details provided	Primary skin irritation study in accordance with OECD TG 404; no further details provided	Non-irritating	[10]
Dimer Dilinoleyl Dimer Dilinoleate	undiluted	100%	not reported	Primary skin irritation study in accordance with OECD TG 404; no further details provided	Mild irritant	[13]
Phytosteryl/Isostearyl/Cetyl/Stearyl/ Behenyl Dimer Dilinoleate	undiluted	100%	not reported	Primary skin irritation study in accordance with OECD TG 404; no further details provided	Non-irritating	[13]
Phytosteryl/Isostearyl/Cetyl/Stearyl/ Behenyl Dimer Dilinoleate	undiluted	100%	not reported	Primary skin irritation study in accordance with OECD TG 404; no further details provided	Non-irritating	[13]
Phytosteryl/Isostearyl/Cetyl/Stearyl/ Behenyl Dimer Dilinoleate	undiluted	100%	guinea pigs; no further details provided	Cumulative skin irritation study; no further details provided	Non-irritating	[13]
Phytosteryl Isostearyl Dimer Dilinoleate	undiluted	100%	not reported	Primary skin irritation study in accordance with OECD TG 404; no further details provided	Mild irritant	[13]
Phytosteryl Isostearyl Dimer Dilinoleate	undiluted	100%	guinea pigs; no further details provided	Cumulative skin irritation study; no further details provided	Practically non-irritating	[13]

Table 5. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration	Test Population	Protocol	Results	Reference
HUMAN						
Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	undiluted	100%	42 subjects	24-h closed patch test; no further details provided	Not irritating	[13]
Dimer Dilinoleyl Dimer Dilinoleate	undiluted	100%	42 subjects	24-h closed patch test; no further details provided	Not irritating	[13]
Phytosteryl/Isostearyl/Cetyl/Stearyl/ Behenyl Dimer Dilinoleate	undiluted	100%	45 subjects	24-h closed patch test; no further details provided	Not irritating	[13]
Phytosteryl/Isostearyl/Cetyl/Stearyl/ Behenyl Dimer Dilinoleate	undiluted	100%	45 subjects	24-h closed patch test; no further details provided	Not irritating	[11,13]
Phytosteryl Isostearyl Dimer Dilinoleate	undiluted	100%	45 subjects	24-h closed patch test; no further details provided	Not irritating	[13]
SENSITIZATION						
ANIMAL						
Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	not reported	not reported	not reported	Skin sensitization adjuvant test (maximization test) in accordance with OECD TG 406; no further details provided	Not sensitizing	[10]
Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	not reported	25%	not reported	Skin sensitization study in accordance with OECD TG 406; no further details provided	Not sensitizing	[13]
Dimer Dilinoleyl Dimer Dilinoleate	undiluted	100%	not reported	Skin sensitization study in accordance with OECD TG 406; no further details provided	Not sensitizing	[13]
Phytosteryl/Isostearyl/Cetyl/Stearyl/ Behenyl Dimer Dilinoleate	undiluted	100%	not reported	Skin sensitization study in accordance with OECD TG 406; no further details provided	Not sensitizing	[13]
Phytosteryl/Isostearyl/Cetyl/Stearyl/ Behenyl Dimer Dilinoleate	undiluted	100%	not reported	Skin sensitization study in accordance with OECD TG 406; no further details provided	Not sensitizing	[13]
Phytosteryl Isostearyl Dimer Dilinoleate	undiluted	100%	not reported	Skin sensitization study in accordance with OECD TG 406; no further details provided	Not sensitizing	[13]
HUMAN						
Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	undiluted	100%	42 subjects	HRIPT; no further details provided	Not sensitizing	[13]
Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate in a lip balm formulation	tested neat	3%	106 subjects	HRIPT; lip balm formulation containing test article was tested undiluted; no further details provided	Not sensitizing	[27]
Dimer Dilinoleyl Dimer Dilinoleate in a lip treatment formulation	tested neat	19%	53 subjects	HRIPT; lip treatment formulation containing test article was tested undiluted; no further details provided	Not irritating or sensitizing	[26]
Phytosteryl/Isostearyl/Cetyl/Stearyl/ Behenyl Dimer Dilinoleate in a lip gloss formulation	tested neat	15%	100 subjects	HRIPT; lip gloss formulation containing test article was tested undiluted; no further details provided	Not sensitizing	[25]

Table 6. Ocular irritation studies

Test Article	Vehicle	Concentration	Test System	Protocol	Results	Reference
IN VITRO						
Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	undiluted	100%	human-derived epidermal keratinocytes	MatTek EpiOcular™ corneal model; 100 µl of test material added to Millicells. Exposure was up to 4 h	Non-irritating; test material elicited in vitro results that indicate the time of exposure to reduce viability to 50% (ET_{50}) is > 256 min. The estimated Draize ocular irritation score is 0.	13,28
Dimer Dilinoleyl Dimer Dilinoleate	undiluted	100%	human-derived epidermal keratinocytes	MatTek EpiOcular™ corneal model; 100 µl of test material added to Millicells. Exposure was up to 4 h	Non-irritating; the ET_{50} is > 256 min. The estimated Draize ocular irritation score is 0.	13,29
Dimer Dilinoleyl Dimer Dilinoleate	mineral oil	0.05 or 5%	epithelial cell line from rabbit cornea	Eye irritation study using the short time exposure method in accordance with OECD TG 491; 200 µl of test material added to cells for 5 min. Tested in triplicate	Not categorized as eye irritant; mean cell viability was 89.5% at 0.05% concentration and 93.1% at 5% concentration	13,30
ANIMAL						
Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	undiluted	100%	3 female New Zealand albino rabbits	Ocular irritation study in accordance with OECD TG 405; 0.1 ml of the test material was instilled in the conjunctival sac of the left eye of each rabbit. Untreated right eye served as a control. Eyes were not rinsed and evaluated at 1, 24, 48, and 72 h post-instillation	Practically non-irritating; slight redness (score 1) was observed in all animals at 1 h	13,31
Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	undiluted	100%	rabbits; no further details provided	Ocular irritation study in accordance with OECD TG 405; no further details provided	Slightly irritating	10
Dimer Dilinoleyl Dimer Dilinoleate	undiluted	100%	3 New Zealand White rabbits; sex not reported	Ocular irritation study in accordance with OECD TG 405; 0.1 ml of the test material was instilled in the conjunctival sac of the right eye of each rabbit. Untreated left eye served as a control. Eyes were not rinsed and evaluated at 1, 24, 48, and 72 h post-instillation	Minimal irritation; no corneal or iridial effects were observed, but moderate conjunctival irritation was noted in all treated eyes 1 h after treatment with minimal conjunctival irritation at 24 h	13,33
Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate	undiluted	100%	3 New Zealand White rabbits; sex not reported	Ocular irritation study in accordance with OECD TG 405; 0.1 ml of the test material was instilled in the conjunctival sac of the right eye of each rabbit. Untreated left eye served as a control. Eyes were not rinsed and evaluated at 1, 24, 48, and 72 h post-instillation	Minimal irritation; no corneal or iridial effects were observed, but moderate conjunctival irritation was noted in all treated eyes 1 h after treatment with minimal conjunctival irritation at 24 h	13,32
Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate	undiluted	100%	not reported	Ocular irritation study in accordance with OECD TG 405; no further details provided	Minimal irritation	11,13
Phytosteryl Isostearyl Dimer Dilinoleate	undiluted	100%	3 New Zealand White rabbits; sex not reported	Ocular irritation study in accordance with OECD TG 405; 0.1 ml of the test material was instilled in the conjunctival sac of the right eye of each rabbit. Untreated left eye served as a control. Eyes were not rinsed and evaluated at 1, 24, 48, and 72 h post-instillation	Minimal irritation; no corneal or iridial effects were observed, but moderate conjunctival irritation was noted in 1 rabbit with minimal conjunctival irritation in the other 2 rabbits 1 h after treatment. Minimal conjunctival irritation was observed in the 1 rabbit at 24 h	13,34

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: July 30, 2025

SUBJECT: Dimer Dilinoleate Ingredients

Attached, please find the full acute oral and eye irritation studies previously summarized in a table provided with memo 4, and also summarized in the revised table that is attached.

Note, that general structures of these ingredients were provided in a table provided with memo 4 (and in the revised table that is attached). Please add these structures to the CIR report.

Nippon Fine Chemical Co., Ltd. 2025. Revised: The information of dimer dilinoleate ingredients (method of manufacture and impurities). (Excel file)

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[redacted]

SafePharm Laboratories

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

[redacted]

ACUTE ORAL TOXICITY IN THE RAT - ACUTE TOXIC CLASS METHOD

[redacted]

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QUALITY ASSURANCE REPORT

This study type is classed as short-term. The standard test method for this study type ("General Study Plan" in OECD terminology) was reviewed for compliance once only on initial production. Inspection of the routine and repetitive procedures that constitute the study is carried out as a continuous process designed to encompass the major phases at or about the time this study was in progress.

This report has been audited by Safepharm Quality Assurance Unit, and is considered to be an accurate account of the data generated and of the procedures followed.

In each case, the outcome of QA evaluation is reported to the Study Director and Management on the day of evaluation. Audits of study documentation, and process inspections appropriate to the type and schedule of this study were as follows:

	07 June 2002	Standard Test Method Compliance Audit
	14 October 2003	Test Material Preparation
	14 October 2003	Animal Preparation
	14 October 2003	Dosing
	21 October 2003	Assessment of Response
	13 October 2003	Necropsy
§	21 November 2003	Draft Report Audit
§	Date of QA Signature	Final Report Audit

§ Evaluation specific to this study

..... DATE: 05 MAY 2004

For Safepharm Quality Assurance Unit*

***Authorised QA Signatures:**

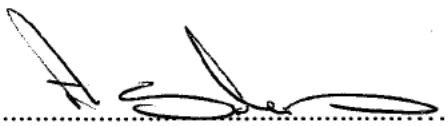
Head of Department:	JR Pateman CBiol MIBiol DipRQA FRQA
Deputy Head of Department:	JM Crowther MIScT MRQA
Senior Audit Staff:	JV Johnson BSc MRQA; G Wren ONC MRQA

GLP COMPLIANCE STATEMENT

The work described was performed in compliance with UK GLP standards (Schedule 1, Good Laboratory Practice Regulations 1999 (SI 1999/3106)). These Regulations are in accordance with GLP standards published as OECD Principles on Good Laboratory Practice (revised 1997, ENV/MC/CHEM(98)17); and are in accordance with, and implement, the requirements of Directives 87/18/EEC (as amended by Directive 1999/11/EC) and 88/320/EEC (as amended by Directive 1999/12/EC).

These international standards are acceptable to the Regulatory agencies of the following countries: Australia, Austria, Belgium, Canada, the Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Republic of Korea, Luxembourg, Mexico, The Netherlands, New Zealand, Norway, Poland, Portugal, Slovenia, Spain, Sweden, Switzerland, Turkey, the United Kingdom, and the United States of America.

This report fully and accurately reflects the procedures used and data generated.



..... DATE: 03 MAY 2004

A Sanders
Study Director

CONTENTS

ACUTE ORAL TOXICITY IN THE RAT – ACUTE TOXIC CLASS METHOD

SUMMARY

Introduction. The study was performed to assess the acute oral toxicity of the test material following a single oral administration in the Sprague-Dawley CD strain rat. The method was designed to meet the requirements of the following:

- OECD Guidelines for the Testing of Chemicals No. 423 "Acute Oral Toxicity – Acute Toxic Class Method" (adopted 17 December 2001)

Method. A group of three fasted females was treated with the test material at a dose level of 2000 mg/kg bodyweight. This was followed by a further group of three fasted females at the same dose level.

The test material was administered orally as a solution in dimethyl sulphoxide. Clinical signs and bodyweight development were monitored during the study. All animals were subjected to gross necropsy.

Mortality. There were no deaths.

Clinical Observations. There were no signs of systemic toxicity.

Bodyweight. All animals showed expected gains in bodyweight over the study period.

Necropsy. No abnormalities were noted at necropsy.

Conclusion. The acute oral median lethal dose (LD_{50}) of the test material in the female Sprague-Dawley CD strain rat was estimated from the flow chart in Appendix 1 as being greater than 2500 mg/kg bodyweight.

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

[redacted]

ACUTE ORAL TOXICITY IN THE RAT - ACUTE TOXIC CLASS METHOD

1. INTRODUCTION

The study was performed to assess the acute oral toxicity of the test material following a single oral administration in the Sprague-Dawley CD strain rat. The method was designed to meet the requirements of the following:

- OECD Guidelines for the Testing of Chemicals No. 423 "Acute Oral Toxicity – Acute Toxic Class Method" (adopted 17 December 2001)

The rat was selected for this study as it is a readily available rodent species, historically used in safety evaluation studies, and is acceptable to appropriate regulatory authorities. The oral route was selected as the most appropriate route of exposure and the results are believed to be of value in predicting the likely toxicity of the test material to man.

The study was performed between 21 October 2003 and 12 November 2003.

2. TEST MATERIAL AND EXPERIMENTAL PREPARATION

2.1 Description, Identification and Storage Conditions

Sponsor's identification	:	[redacted] Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate
Description	:	pale yellow paste
Batch number	:	[redacted]
Date received	:	11 August 2003
Storage conditions	:	room temperature in the dark

Data relating to the identity, purity and stability of the test material are the responsibility of the Sponsor.

2.2 Preparation of Test Material

For the purpose of the study the test material was freshly prepared, as required, as a solution at the appropriate concentration in dimethyl sulphoxide. Dimethyl sulphoxide was used because the test material did not dissolve/suspend in distilled water.

Determination by analysis of the concentration, homogeneity and stability of the test material preparations was not appropriate because it was not specified in the Study Plan and is not a requirement of the Test Guideline.

3. METHODS

3.1 Animals and Animal Husbandry

Female Sprague-Dawley CD (Crl: CD® (SD) IGS BR) strain rats were supplied by Charles River (UK) Ltd, Margate, Kent, UK. On receipt the animals were randomly allocated to cages. The animals were nulliparous and non-pregnant. After an acclimatisation period of at least five days the animals were selected at random and given a number unique within the study by indelible ink-marking on the tail and a number written on a cage card. At the start of the study the animals were eight to twelve weeks of age. The bodyweights fell within an interval of ± 20% of the mean initial bodyweight of the first treated group.

The animals were housed in groups of three in suspended solid-floor polypropylene cages furnished with woodflakes. With the exception of an overnight fast immediately before dosing and for approximately three to four hours after dosing, free access to mains drinking water and food (Certified Rat and Mouse Diet (Code 5LF2) supplied by International Product Supplies Limited, Wellingborough, Northants, UK) was allowed throughout the study. The diet, drinking water and bedding were routinely analysed and were considered not to contain any contaminants that would reasonably be expected to affect the purpose or integrity of the study.

The temperature and relative humidity were set to achieve limits of 19 to 25°C and 30 to 70% respectively. Any occasional deviations from these targets were considered not to have affected the purpose or integrity of the study. The rate of air exchange was at least fifteen changes per hour and the lighting was controlled by a time switch to give twelve hours continuous light (06:00 to 18:00) and twelve hours darkness.

The animals were provided with environmental enrichment items which were considered not to contain any contaminant of a level that might have affected the purpose or integrity of the study.

3.2 Procedure

Using all available information on the toxicity of the test material, 2000 mg/kg was chosen as the starting dose.

Groups of fasted animals were treated as follows:

Dose Level (mg/kg)	Concentration (mg/ml)	Dose Volume (ml/kg)	Number of Rats
			Female
2000	200	10	3
2000	200	10	3

All animals were dosed once only by gavage, using a metal cannula attached to a graduated syringe. The volume administered to each animal was calculated according to the fasted bodyweight at the time of dosing. Treatment of animals was sequential. Sufficient time was allowed between each group to confirm the survival of the previously dosed animals.

The animals were observed for deaths or overt signs of toxicity ½, 1, 2 and 4 hours after dosing and subsequently once daily for fourteen days.

Individual bodyweights were recorded prior to dosing and seven and fourteen days after treatment.

At the end of the observation period the animals were killed by cervical dislocation. All animals were subjected to gross pathological examination. This consisted of an external examination and opening of the abdominal and thoracic cavities for examination of major organs. The appearance of any macroscopic abnormalities was recorded. No tissues were retained.

3.3 Evaluation of Data

Data evaluations included the relationship, if any, between the exposure of the animal to the test material and the incidence and severity of all abnormalities including behavioural and clinical observations, gross lesions, bodyweight changes, mortality and any other toxicological effects.

Using the mortality data obtained, an estimate of the acute oral median lethal dose (LD_{50}) of the test material was made as shown in the schematic diagram in Appendix 1.

4. ARCHIVES

Unless instructed otherwise by the Sponsor, all original data and the final report will be retained in the Safepharm archives for five years, after which instructions will be sought as to further retention or disposal.

5. RESULTS

5.1 Mortality Data

Individual mortality data are given in Table 1.

There were no deaths.

5.2 Clinical Observations

Individual clinical observations are given in Table 2.

There were no signs of systemic toxicity.

5.3 Bodyweight

Individual bodyweights and weekly bodyweight changes are given in Table 3.

All animals showed expected gains in bodyweight over the study period.

5.4 Necropsy

Individual necropsy findings are given in Table 4.

No abnormalities were noted at necropsy.

6. CONCLUSION

The acute oral median lethal dose (LD_{50}) of the test material in the female Sprague-Dawley CD strain rat was estimated from the flow chart in Appendix 1 as being greater than 2500 mg/kg bodyweight.

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

[redacted] ACUTE ORAL TOXICITY IN THE RAT – ACUTE TOXIC CLASS METHOD

Table 1 Mortality Data

Dose Level mg/kg	Sex	Number of Animals Treated	Deaths During Day of Dosing (Hours)				Deaths During Period After Dosing (Days)								Deaths
			½	1	2	4	1	2	3	4	5	6	7	8-14	
2000	Female	3	0	0	0	0	0	0	0	0	0	0	0	0	0/3
	Female	3	0	0	0	0	0	0	0	0	0	0	0	0	0/3

Bis-Behenyl/Isostearyl/Phytosteryl
Dimer Dilinoleyl Dimer Dilinoleate

[redacted]: ACUTE ORAL TOXICITY IN THE RAT – ACUTE TOXIC CLASS METHOD

Table 2 Individual Clinical Observations

Dose Level mg/kg	Animal Number and Sex	Effects Noted After Dosing (Hours)				Effects Noted During Period After Dosing (Days)													
		½	1	2	4	1	2	3	4	5	6	7	8	9	10	11	12	13	14
2000	1-0 Female	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1-1 Female	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1-2 Female	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2-0 Female	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2-1 Female	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2-2 Female	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

0 = No signs of systemic toxicity

Bis-Behenyl/Isostearyl/Phytosteryl
Dimer Dilinoleyl Dimer Dilinoleate

[redacted]: ACUTE ORAL TOXICITY IN THE RAT – ACUTE TOXIC CLASS METHOD

Table 3 Individual Bodyweights and Weekly Bodyweight Changes

Dose Level mg/kg	Animal Number and Sex	Bodyweight (g) at Day			Bodyweight Gain (g) During Week	
		0	7	14	1	2
2000	1-0 Female	186	221	229	35	8
	1-1 Female	207	246	274	39	28
	1-2 Female	189	216	236	27	20
	2-0 Female	198	233	253	35	20
	2-1 Female	197	216	227	19	11
	2-2 Female	201	231	240	30	9

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

[redacted]: ACUTE ORAL TOXICITY IN THE RAT – ACUTE TOXIC CLASS METHOD

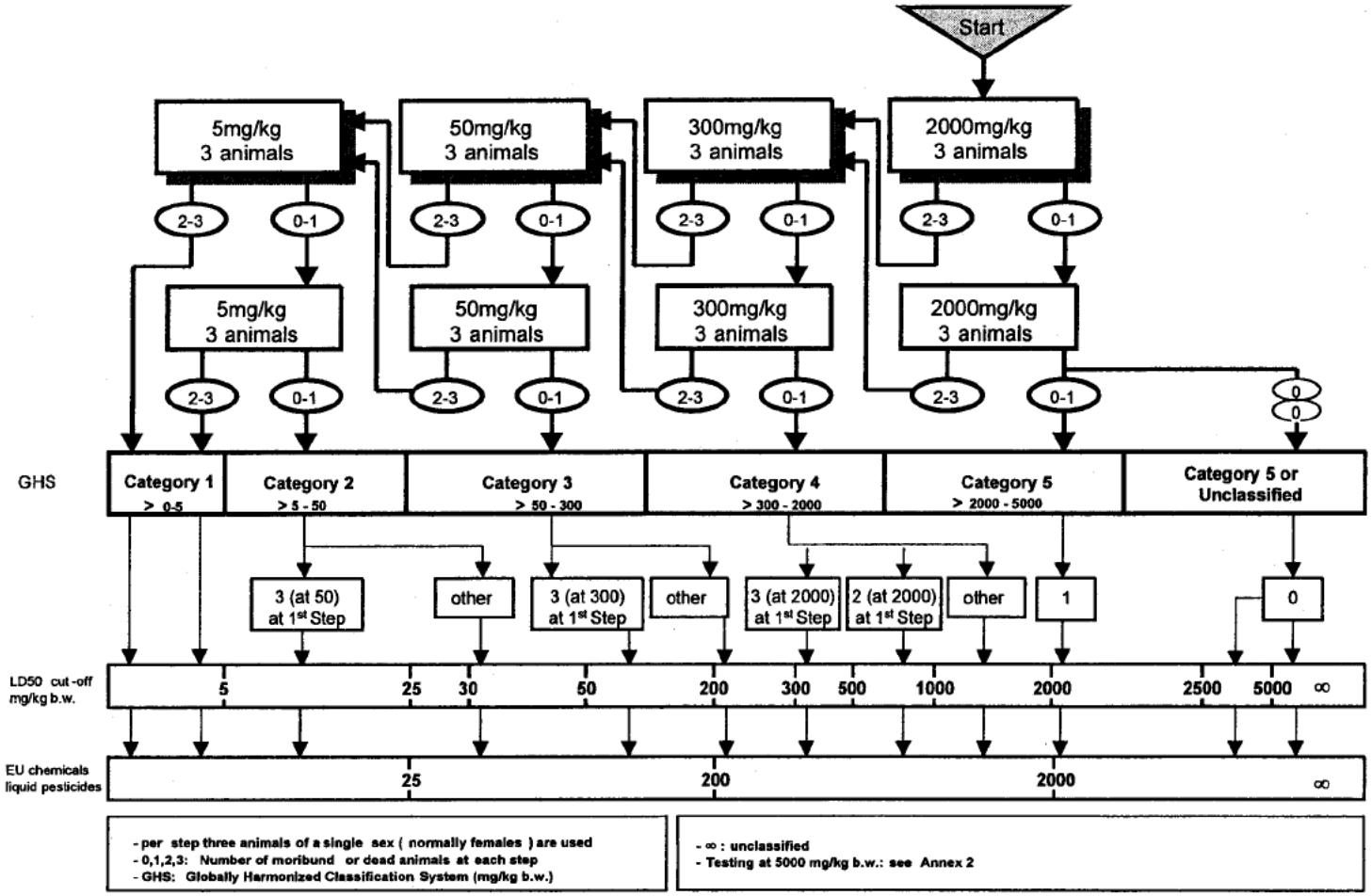
Table 4 Individual Necropsy Findings

Dose Level mg/kg	Animal Number and Sex	Time of Death	Macroscopic Observations
2000	1-0 Female	Killed Day 14	No abnormalities detected
	1-1 Female	Killed Day 14	No abnormalities detected
	1-2 Female	Killed Day 14	No abnormalities detected
	2-0 Female	Killed Day 14	No abnormalities detected
	2-1 Female	Killed Day 14	No abnormalities detected
	2-2 Female	Killed Day 14	No abnormalities detected

Bis-Behenyl/Isostearyl/Phytosteryl
Dimer Dilinoleyl Dimer Dilinoleate

[redacted] ACUTE ORAL TOXICITY IN THE RAT – ACUTE TOXIC CLASS METHOD

Appendix 1 Test Procedure with a Starting Dose of 2000 mg/kg Bodyweight



Appendix 2 Statement of GLP Compliance in Accordance with Directive 88/320/EEC

THE DEPARTMENT OF HEALTH OF THE GOVERNMENT OF THE UNITED KINGDOM

GOOD LABORATORY PRACTICE

STATEMENT OF COMPLIANCE IN ACCORDANCE WITH DIRECTIVE 88/320 EEC

LABORATORY
SafePharm Limited
Shardlow Business Park,
London Road,
Shardlow,
Derbyshire,
DE72 2GD

TEST TYPE
Analytical/Clinical Chemistry
Environmental tox.
Environmental fate
Mutagenicity
Phys./Chem. tests
Toxicology

DATE OF INSPECTION

2nd December 2002

A general inspection for compliance with the Principles of Good Laboratory Practice was carried out at the above laboratory as part of UK GLP Compliance Programme.

At the time of the inspection no deviations were found of sufficient magnitude to affect the validity of non-clinical studies performed at these facilities.

Roger G. Alexander 13/2/03

Dr. Roger G. Alexander
Head, UK GLP Monitoring Authority

[redacted]

SAFEPHARM LABORATORIES LTD

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

[redacted]

ACUTE ORAL TOXICITY IN THE RAT
– ACUTE TOXIC CLASS METHOD

[redacted]

I verify that this is an exact copy of the original report which is located in the Archives of Safepharm Laboratories Ltd., Derby, UK.

..... DATE: 07 MAY 2004

A Sanders
Study Director

[redacted]

SafePharm Laboratories

Dimer Dilinoleyl Dimer Dilinoleate

[redacted]

ACUTE ORAL TOXICITY IN THE RAT - ACUTE TOXIC CLASS METHOD

[redacted]

AUTHOR: A Sanders

[redacted]

[redacted]

ISSUED BY:

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P.O. Box No. 45
DERBY
DE1 2BT
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Facsimile: (01332) 799018

QUALITY ASSURANCE REPORT

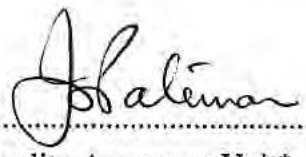
This study type is classed as short-term. The standard test method for this study type ("General Study Plan" in OECD terminology) was reviewed for compliance once only on initial production. Inspection of the routine and repetitive procedures that constitute the study is carried out as a continuous process designed to encompass the major phases at or about the time this study was in progress.

This report has been audited by Safepharm Quality Assurance Unit, and is considered to be an accurate account of the data generated and of the procedures followed.

In each case, the outcome of QA evaluation is reported to the Study Director and Management on the day of evaluation. Audits of study documentation, and process inspections appropriate to the type and schedule of this study were as follows:

	23 December 1999	Standard Test Method Compliance Audit
	26 September 2000	Test Material Preparation
	27 September 2000	Animal Preparation
	26 September 2000	Dosing
	12 September 2000	Assessment of Response
	04 September 2000	Necropsy
§	31 October 2000	Draft Report Audit
§	Date of QA Signature	Final Report Audit

§ Evaluation specific to this study



..... DATE: - 2 MAR 2001 .....

For Safepharm Quality Assurance Unit*

***Authorised QA Signatures:**

Head of Department:	JR Pateman CBiol MIBiol DipRQA
Deputy Head of Department:	JM Crowther MIScT
Senior Audit Staff:	JV Johnson BSc; G Wren ONC; RJ Gilbert BSc

GLP COMPLIANCE STATEMENT

The work described was performed in compliance with UK GLP standards (Schedule 1, Good Laboratory Practice Regulations 1999 (SI 1999/3106)). These Regulations are in accordance with GLP standards published as OECD Principles on Good Laboratory Practice (revised 1997, ENV/MC/CHEM(98)17); and are in accordance with, and implement, the requirements of Directives 87/18/EEC (as amended by Directive 1999/11/EC) and 88/320/EEC (as amended by Directive 1999/12/EC).

These international standards are acceptable to the United States Environmental Protection Agency and Food and Drug Administration, and fulfil the requirements of 40 CFR Part 160, 40 CFR Part 792 and 21 CFR Part 58 (as amended).

This report fully and accurately reflects the procedures used and data generated.

..... DATE: 01 MAR 2001

A Sanders
Study Director

CONTENTS

Dimer Dilinoleyl Dimer Dilinoleate

[redacted]

ACUTE ORAL TOXICITY IN THE RAT – ACUTE TOXIC CLASS METHOD

SUMMARY

Introduction. The study was performed to assess the acute oral toxicity of the test material following a single oral administration in the Sprague-Dawley CD (Crl: CD® (SD) IGS BR) strain rat. The method was designed to meet the requirements of the following:

- OECD Guidelines for the Testing of Chemicals No. 423 "Acute Oral Toxicity – Acute Toxic Class Method" (adopted 22 March 1996)

- Commission Directive 96/54/EC Method B1 tris Acute Toxicity (Oral – Acute Toxic Class Method)

Method. A group of three fasted females was treated with 2000 mg/kg bodyweight. This was followed by a group of three fasted animals of the other sex at the same dose level.

The test material was administered orally as a solution in arachis oil BP. Clinical signs and bodyweight development were monitored during the study. All animals were subjected to gross necropsy examination.

Mortality. There were no deaths.

Clinical Observations. Hunched posture was noted in all females one day after dosing. No signs of systemic toxicity were noted in males.

Bodyweight. All animals showed expected gains in bodyweight over the study period.

Necropsy. No abnormalities were noted at necropsy.

Conclusion. The acute oral median lethal dose (LD_{50}) of the test material in the Sprague-Dawley CD (Crl: CD® (SD) IGS BR) strain rat was estimated from the flow chart in Appendix 1 as being greater than 2500 mg/kg bodyweight. No mortalities were noted in animals treated with 2000 mg/kg bodyweight.

The test material does not meet the criteria for classification according to EU labelling regulations Commission Directive 93/21/EEC.

Dimer Dilinoleyl Dimer Dilinoleate

[redacted]

ACUTE ORAL TOXICITY IN THE RAT
- ACUTE TOXIC CLASS METHOD

1. INTRODUCTION

The study was performed to assess the acute oral toxicity of the test material following a single oral administration in the Sprague-Dawley CD (Crl: CD® (SD) IGS BR) strain rat. The method was designed to meet the requirements of the following:

- OECD Guidelines for the Testing of Chemicals No. 423 "Acute Oral Toxicity – Acute Toxic Class Method" (adopted 22 March 1996)

- Commission Directive 96/54/EC Method B1 tris Acute Toxicity (Oral – Acute Toxic Class Method)

The rat was selected for this study as it is a readily available rodent species, historically used in safety evaluation studies, and is acceptable to appropriate regulatory authorities. The oral route was selected as the most appropriate route of exposure and the results are believed to be of value in predicting the likely toxicity of the test material to man.

The study was performed between 05 October 2000 and 24 October 2000.

2. TEST MATERIAL AND EXPERIMENTAL PREPARATION

2.1 Description, Identification and Storage Conditions

Sponsor's identification	:	[redacted] Dimer Dilinoleyl Dimer Dilinoleate
Description	:	pale yellow viscous liquid
Batch number	:	[redacted]
Date received	:	25 August 2000
Storage conditions	:	room temperature in the dark

Data relating to the identity, purity and stability of the test material are the responsibility of the Sponsor.

2.2 Preparation of Test Material

For the purpose of the study the test material was freshly prepared, as required, as a solution at the appropriate concentration in arachis oil BP. Arachis oil BP was used because the test material did not dissolve in distilled water.

Determination by analysis of the concentration, homogeneity and stability of the test material preparations was not appropriate because it was not specified in the Study Plan and is not a requirement of the Test Guideline.

3. METHODS

3.1 Animals and Animal Husbandry

Male and female Sprague-Dawley CD (Crl: CD® (SD) IGS BR) strain rats were supplied by Charles River (UK) Ltd, Margate, Kent, UK. On receipt the animals were randomly allocated to cages. The females were nulliparous and non-pregnant. After an acclimatisation period of at least five days the animals were selected at random and given a number unique within the study by indelible ink-marking on the tail and a number written on a cage card. At the start of the study the males weighed 215 to 217 g, and the females 234 to 239 g, and were approximately eight weeks of age.

The animals were housed in groups of three by sex in solid-floor polypropylene cages furnished with woodflakes. With the exception of an overnight fast immediately before dosing and for approximately three to four hours after dosing, free access to mains drinking water and food (Rat and Mouse Expanded Diet No.1, Special Diets Services Limited, Witham, Essex, UK) was allowed throughout the study. The diet, drinking water and bedding were routinely analysed and were considered not to contain any contaminants that would reasonably be expected to affect the purpose or integrity of the study.

The temperature and relative humidity were set to achieve limits of 19 to 25°C and 30 to 70% respectively. Any occasional deviations from these targets were considered not to have affected the purpose or integrity of the study. The rate of air exchange was at least fifteen changes per hour and the lighting was controlled by a time switch to give twelve hours continuous light (06:00 to 18:00) and twelve hours darkness.

3.2 Procedure

Groups of fasted animals were treated as follows:

Dose Level (mg/kg)	Concentration (mg/ml)	Dose Volume (ml/kg)	Number of Rats	
			Male	Female
2000	200	10	-	3
2000	200	10	3	-

All animals were dosed once only by gavage, using a metal cannula attached to a graduated syringe. The volume administered to each animal was calculated according to the fasted bodyweight at the time of dosing. Treatment of animals was sequential. Sufficient time was allowed between each sex to confirm the survival of the previously dosed animals.

The animals were observed for deaths or overt signs of toxicity ½, 1, 2 and 4 hours after dosing and subsequently once daily for fourteen days.

Individual bodyweights were recorded prior to dosing and seven and fourteen days after treatment.

At the end of the observation period the animals were killed by cervical dislocation. All animals were subjected to gross pathological examination. This consisted of an external examination and opening of the abdominal and thoracic cavities for examination of major organs. The appearance of any macroscopic abnormalities was recorded. No tissues were retained.

3.3 Evaluation of Data

Data evaluations included the relationship, if any, between the exposure of the animal to the test material and the incidence and severity of all abnormalities including behavioural and clinical observations, gross lesions, bodyweight changes, mortality and any other toxicological effects.

Using the mortality data obtained, an estimate of the acute oral median lethal dose (LD_{50}) of the test material was made as shown in the schematic diagram in Appendix 1.

The results were evaluated according to Commission Directive 93/21/EEC for classification and labelling of dangerous substances and preparations.

4. ARCHIVES

Unless instructed otherwise by the Sponsor, all original data and the final report will be retained in the Safepharm archives for five years, after which instructions will be sought as to further retention or disposal.

5. RESULTS

5.1 Mortality Data

Individual mortality data are given in Table 1.

There were no deaths.

5.2 Clinical Observations

Individual clinical observations are given in Table 2.

Hunched posture was noted in all females one day after dosing. No signs of systemic toxicity were noted in males.

5.3 Bodyweight

Individual bodyweights and weekly bodyweight changes are given in Table 3.

All animals showed an expected gain in bodyweight during the study.

5.4 Necropsy

Individual necropsy findings are given in Table 4.

No abnormalities were noted at necropsy.

6. CONCLUSION

The acute oral median lethal dose (LD_{50}) of the test material in the Sprague-Dawley CD (Crl: CD® (SD) IGS BR) strain rat was estimated from the flow chart in Appendix 1 as being greater than 2500 mg/kg bodyweight.

No mortalities were noted in animals treated with 2000 mg/kg bodyweight.

The test material does not meet the criteria for classification according to EU labelling regulations Commission Directive 93/21/EEC.

Table 1 Mortality Data

Dose Level mg/kg	Sex	Number of Animals Treated	Deaths During Day of Dosing (Hour)				Deaths During Period After Dosing (Days)								Deaths
			½	1	2	4	1	2	3	4	5	6	7	8-14	
2000	Female	3	0	0	0	0	0	0	0	0	0	0	0	0	0/3
	Male	3	0	0	0	0	0	0	0	0	0	0	0	0	0/3

Table 2 Individual Clinical Observations

Dose Level mg/kg	Animal Number and Sex	Effects Noted After Dosing (Hours)				Effects Noted During Period After Dosing (Days)													
		½	1	2	4	1	2	3	4	5	6	7	8	9	10	11	12	13	14
2000	1-0 Female	0	0	0	0	H	0	0	0	0	0	0	0	0	0	0	0	0	0
	1-1 Female	0	0	0	0	H	0	0	0	0	0	0	0	0	0	0	0	0	0
	1-2 Female	0	0	0	0	H	0	0	0	0	0	0	0	0	0	0	0	0	0
	2-0 Male	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2-1 Male	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2-2 Male	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

0 – no signs of systemic toxicity
H = hunched posture

Table 3 Individual Bodyweights and Weekly Bodyweight Changes

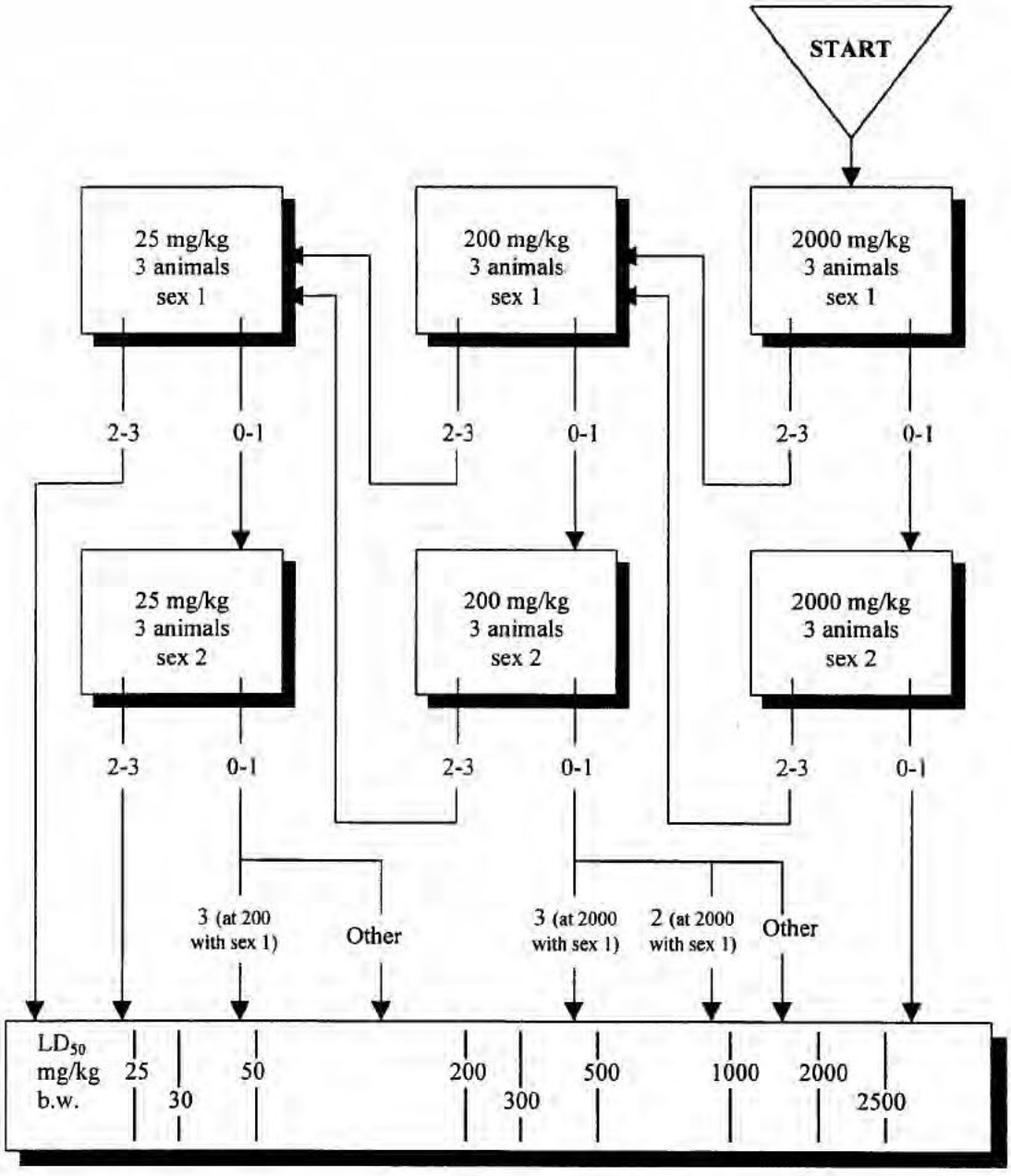
Dose Level mg/kg	Animal Number and Sex	Bodyweight (g) at Day			Bodyweight Gain (g) During Week	
		0	7	14	1	2
2000	1-0 Female	234	267	278	33	11
	1-1 Female	239	266	282	27	16
	1-2 Female	237	278	289	41	11
	2-0 Male	216	281	324	65	43
	2-1 Male	217	292	327	75	35
	2-2 Male	215	280	316	65	36

Table 4 Individual Necropsy Findings

Dose Level mg/kg	Animal Number and Sex	Macroscopic Observations
2000	1-0 Female	No abnormalities detected
	1-1 Female	No abnormalities detected
	1-2 Female	No abnormalities detected
	2-0 Male	No abnormalities detected
	2-1 Male	No abnormalities detected
	2-2 Male	No abnormalities detected

Dimer Dilinoleyl Dimer Dilinoleate [redacted] ACUTE ORAL TOXICITY IN THE RAT – ACUTE TOXIC CLASS METHOD

Appendix 1 Test Procedure with a Starting Dose of 2000 mg/kg Bodyweight



Legend:

0, 1, 2, 3 Number of moribund or dead animals of each sex

Appendix 2 Statement of GLP Compliance in Accordance with Directive 88/320/EEC

THE DEPARTMENT OF HEALTH OF THE GOVERNMENT OF THE UNITED KINGDOM

GOOD LABORATORY PRACTICE

STATEMENT OF COMPLIANCE IN ACCORDANCE WITH DIRECTIVE 88/320 EEC

LABORATORY

SafePharm Laboratories Ltd
Shardlow Business Park
London Road
Shardlow
Derbyshire
DE72 2GD

TEST TYPE

Analytical Chemistry
Environmental Fate
Environmental Toxicity
Mutagenicity
Phys/Chem Tests
Toxicology

DATE OF INSPECTION
28 February 2000

A general inspection for compliance with the Principles of Good Laboratory Practice was carried out at the above laboratory as part of UK GLP Compliance Programme.

At the time of the inspection no deviations were found of sufficient magnitude to affect the validity of non-clinical studies performed at these facilities.

Roger G. Alexander 26/4/00

Dr. Roger G. Alexander
Head. UK GLP Monitoring Authority

[redacted]

SafePharm Laboratories

Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate

[redacted]

ACUTE ORAL TOXICITY IN THE RAT - ACUTE TOXIC CLASS METHOD

[redacted]

AUTHOR: A Sanders

[redacted]

[redacted]

TEST FACILITY:

Safepharm Laboratories Limited
Shardlow Business Park
Shardlow
Derbyshire
DE72 2GD

Telephone: +44 (0) 1332 792896

Facsimile: +44 (0) 1332 799018

QUALITY ASSURANCE REPORT

This study type is classed as short-term. The standard test method for this study type ("General Study Plan" in OECD terminology) was reviewed for compliance once only on initial production. Inspection of the routine and repetitive procedures that constitute the study is carried out as a continuous process designed to encompass the major phases at or about the time this study was in progress.

This report has been audited by Safepharm Quality Assurance Unit, and is considered to be an accurate account of the data generated and of the procedures followed.

In each case, the outcome of QA evaluation is reported to the Study Director and Management on the day of evaluation. Audits of study documentation, and process inspections appropriate to the type and schedule of this study were as follows:

	07 June 2002	Standard Test Method Compliance Audit
	21 January 2003	Test Material Preparation
	29 January 2003	Animal Preparation
	21 January 2003	Dosing
	08 January 2003	Assessment of Response
	08 January 2003	Necropsy
§	21 February 2003	Draft Report Audit
§	Date of QA Signature	Final Report Audit

§ Evaluation specific to this study

..... DATE: 27 MAY 2003

For Safepharm Quality Assurance Unit*

***Authorised QA Signatures:**

Head of Department:	JR Pateman CBiol MIBiol DipRQA FRQA
Deputy Head of Department:	JM Crowther MIScT MRQA
Senior Audit Staff:	JV Johnson BSc MRQA; G Wren ONC MRQA

GLP COMPLIANCE STATEMENT

The work described was performed in compliance with UK GLP standards (Schedule 1, Good Laboratory Practice Regulations 1999 (SI 1999/3106)). These Regulations are in accordance with GLP standards published as OECD Principles on Good Laboratory Practice (revised 1997, ENV/MC/CHEM(98)17); and are in accordance with, and implement, the requirements of Directives 87/18/EEC (as amended by Directive 1999/11/EC) and 88/320/EEC (as amended by Directive 1999/12/EC).

These international standards are acceptable to the Regulatory agencies of the following countries: Australia, Austria, Belgium, Canada, the Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Republic of Korea, Luxembourg, Mexico, The Netherlands, New Zealand, Norway, Poland, Portugal, Slovenia, Spain, Sweden, Switzerland, Turkey, the United Kingdom, and the United States of America.

This report fully and accurately reflects the procedures used and data generated.

..... DATE: 23 MAY 2003

A Sanders
Study Director

CONTENTS

Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate

[redacted]

ACUTE ORAL TOXICITY IN THE RAT – ACUTE TOXIC CLASS METHOD

SUMMARY

Introduction. The study was performed to assess the acute oral toxicity of the test material following a single oral administration in the Sprague-Dawley CD strain rat. The method was designed to meet the requirements of the following:

- OECD Guidelines for the Testing of Chemicals No. 423 "Acute Oral Toxicity – Acute Toxic Class Method" (adopted 17 December 2001)

Method. A group of three fasted females was treated with the test material at a dose level of 2000 mg/kg bodyweight. This was followed by a further group of three fasted females at the same dose level.

The test material was administered orally as a solution in arachis oil BP. Clinical signs and bodyweight development were monitored during the study. All animals were subjected to gross necropsy.

Mortality. There were no deaths.

Clinical Observations. There were no signs of systemic toxicity.

Bodyweight. All animals showed expected gains in bodyweight over the study period.

Necropsy. No abnormalities were noted at necropsy.

Conclusion. The acute oral median lethal dose (LD_{50}) of the test material in the female Sprague-Dawley CD strain rat was estimated from the flow chart in Appendix 1 as being greater than 2500 mg/kg bodyweight.

The test material does not meet the criteria for classification according to EU labelling regulations Commission Directive 2001/59/EC.

Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate

[redacted]

ACUTE ORAL TOXICITY IN THE RAT
- ACUTE TOXIC CLASS METHOD

1. INTRODUCTION

The study was performed to assess the acute oral toxicity of the test material following a single oral administration in the Sprague-Dawley CD strain rat. The method was designed to meet the requirements of the following:

- OECD Guidelines for the Testing of Chemicals No. 423 "Acute Oral Toxicity – Acute Toxic Class Method" (adopted 17 December 2001)

The rat was selected for this study as it is a readily available rodent species, historically used in safety evaluation studies, and is acceptable to appropriate regulatory authorities. The oral route was selected as the most appropriate route of exposure and the results are believed to be of value in predicting the likely toxicity of the test material to man.

The study was performed between 15 January 2003 and 03 February 2003.

2. TEST MATERIAL AND EXPERIMENTAL PREPARATION

2.1 Description, Identification and Storage Conditions

Sponsor's identification	:	[redacted]
Description	:	pale yellow waxy solid
Batch number	:	[redacted]
Date received	:	27 November 2002
Storage conditions	:	room temperature in the dark

Phytosteryl/Isostearyl/Cetyl/Stearyl/
Behenyl Dimer Dilinoleate

Data relating to the identity, purity and stability of the test material are the responsibility of the Sponsor.

2.2 Preparation of Test Material

For the purpose of the study the test material was freshly prepared, as required, as a solution at the appropriate concentration in arachis oil BP.

Determination by analysis of the concentration, homogeneity and stability of the test material preparations was not appropriate because it was not specified in the Study Plan and is not a requirement of the Test Guideline.

3. METHODS

3.1 Animals and Animal Husbandry

Female Sprague-Dawley CD (Crl: CD® (SD) IGS BR) strain rats were supplied by Charles River (UK) Ltd, Margate, Kent, UK. On receipt the animals were randomly allocated to cages. The animals were nulliparous and non-pregnant. After an acclimatisation period of at least five days the animals were selected at random and given a number unique within the study by indelible ink-marking on the tail and a number written on a cage card. At the start of the study the animals were eight to twelve weeks of age. The bodyweights fell within an interval of ± 20% of the mean initial bodyweight of the first treated group.

The animals were housed in groups of three in suspended solid-floor polypropylene cages furnished with woodflakes. With the exception of an overnight fast immediately before dosing and for approximately three to four hours after dosing, free access to mains drinking water and food (Certified Rat and Mouse Diet (Code 5LF2) supplied by International Product Supplies Limited, Wellingborough, Northants, UK) was allowed throughout the study. The diet, drinking water and bedding were routinely analysed and were considered not to contain any contaminants that would reasonably be expected to affect the purpose or integrity of the study.

The temperature and relative humidity were set to achieve limits of 19 to 25°C and 30 to 70% respectively. Any occasional deviations from these targets were considered not to have affected the purpose or integrity of the study. The rate of air exchange was at least fifteen changes per hour and the lighting was controlled by a time switch to give twelve hours continuous light (06:00 to 18:00) and twelve hours darkness.

The animals were provided with environmental enrichment items which were considered not to contain any contaminant of a level that might have affected the purpose or integrity of the study.

3.2 Procedure

In the absence of data suggesting the test material was toxic, 2000 mg/kg was chosen as the starting dose.

Groups of fasted animals were treated as follows:

Dose Level (mg/kg)	Concentration (mg/ml)	Dose Volume (ml/kg)	Number of Rats
			Female
2000	200	10	3
2000	200	10	3

All animals were dosed once only by gavage, using a metal cannula attached to a graduated syringe. The volume administered to each animal was calculated according to the fasted bodyweight at the time of dosing. Treatment of animals was sequential. Sufficient time was allowed between each group to confirm the survival of the previously dosed animals.

The animals were observed for deaths or overt signs of toxicity ½, 1, 2 and 4 hours after dosing and subsequently once daily for fourteen days.

Individual bodyweights were recorded prior to dosing and seven and fourteen days after treatment.

At the end of the observation period the animals were killed by cervical dislocation. All animals were subjected to gross pathological examination. This consisted of an external examination and opening of the abdominal and thoracic cavities for examination of major organs. The appearance of any macroscopic abnormalities was recorded. No tissues were retained.

3.3 Evaluation of Data

Data evaluations included the relationship, if any, between the exposure of the animal to the test material and the incidence and severity of all abnormalities including behavioural and clinical observations, gross lesions, bodyweight changes, mortality and any other toxicological effects.

Using the mortality data obtained, an estimate of the acute oral median lethal dose (LD_{50}) of the test material was made as shown in the schematic diagram in Appendix 1.

The results were evaluated according to Commission Directive 2001/59/EC for classification and labelling of dangerous substances and preparations.

4. ARCHIVES

Unless instructed otherwise by the Sponsor, all original data and the final report will be retained in the Safepharm archives for five years, after which instructions will be sought as to further retention or disposal.

5. RESULTS

5.1 Mortality Data

Individual mortality data are given in Table 1.

There were no deaths.

5.2 Clinical Observations

Individual clinical observations are given in Table 2.

There were no signs of systemic toxicity.

5.3 Bodyweight

Individual bodyweights and weekly bodyweight changes are given in Table 3.

All animals showed expected gains in bodyweight over the study period.

5.4 Necropsy

Individual necropsy findings are given in Table 4.

No abnormalities were noted at necropsy.

6. CONCLUSION

The acute oral median lethal dose (LD_{50}) of the test material in the female Sprague-Dawley CD strain rat was estimated from the flow chart in Appendix 1 as being greater than 2500 mg/kg bodyweight.

The test material does not meet the criteria for classification according to EU labelling regulations Commission Directive 2001/59/EC.

Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate

[redacted] ACUTE ORAL TOXICITY IN THE RAT – ACUTE TOXIC CLASS METHOD

Table 1 Mortality Data

Dose Level mg/kg	Sex	Number of Animals Treated	Deaths During Day of Dosing (Hours)				Deaths During Period After Dosing (Days)								Deaths
			½	1	2	4	1	2	3	4	5	6	7	8-14	
2000	Female	3	0	0	0	0	0	0	0	0	0	0	0	0	0/3
	Female	3	0	0	0	0	0	0	0	0	0	0	0	0	0/3

Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate

[redacted] ACUTE ORAL TOXICITY IN THE RAT – ACUTE TOXIC CLASS METHOD

Table 2 Individual Clinical Observations

Dose Level mg/kg	Animal Number and Sex	Effects Noted After Dosing (Hours)				Effects Noted During Period After Dosing (Days)													
		½	1	2	4	1	2	3	4	5	6	7	8	9	10	11	12	13	14
2000	1-0 Female	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1-1 Female	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1-2 Female	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2-0 Female	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2-1 Female	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2-2 Female	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

0 = No signs of systemic toxicity

Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate

[redacted]: ACUTE ORAL TOXICITY IN THE RAT – ACUTE TOXIC CLASS METHOD

Table 3 Individual Bodyweights and Weekly Bodyweight Changes

Dose Level mg/kg	Animal Number and Sex	Bodyweight (g) at Day			Bodyweight Gain (g) During Week	
		0	7	14	1	2
2000	1-0 Female	194	214	230	20	16
	1-1 Female	183	209	224	26	15
	1-2 Female	186	204	224	18	20
	2-0 Female	201	222	245	21	23
	2-1 Female	223	262	289	39	27
	2-2 Female	187	214	228	27	14

Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate

[redacted]: ACUTE ORAL TOXICITY IN THE RAT – ACUTE TOXIC CLASS METHOD

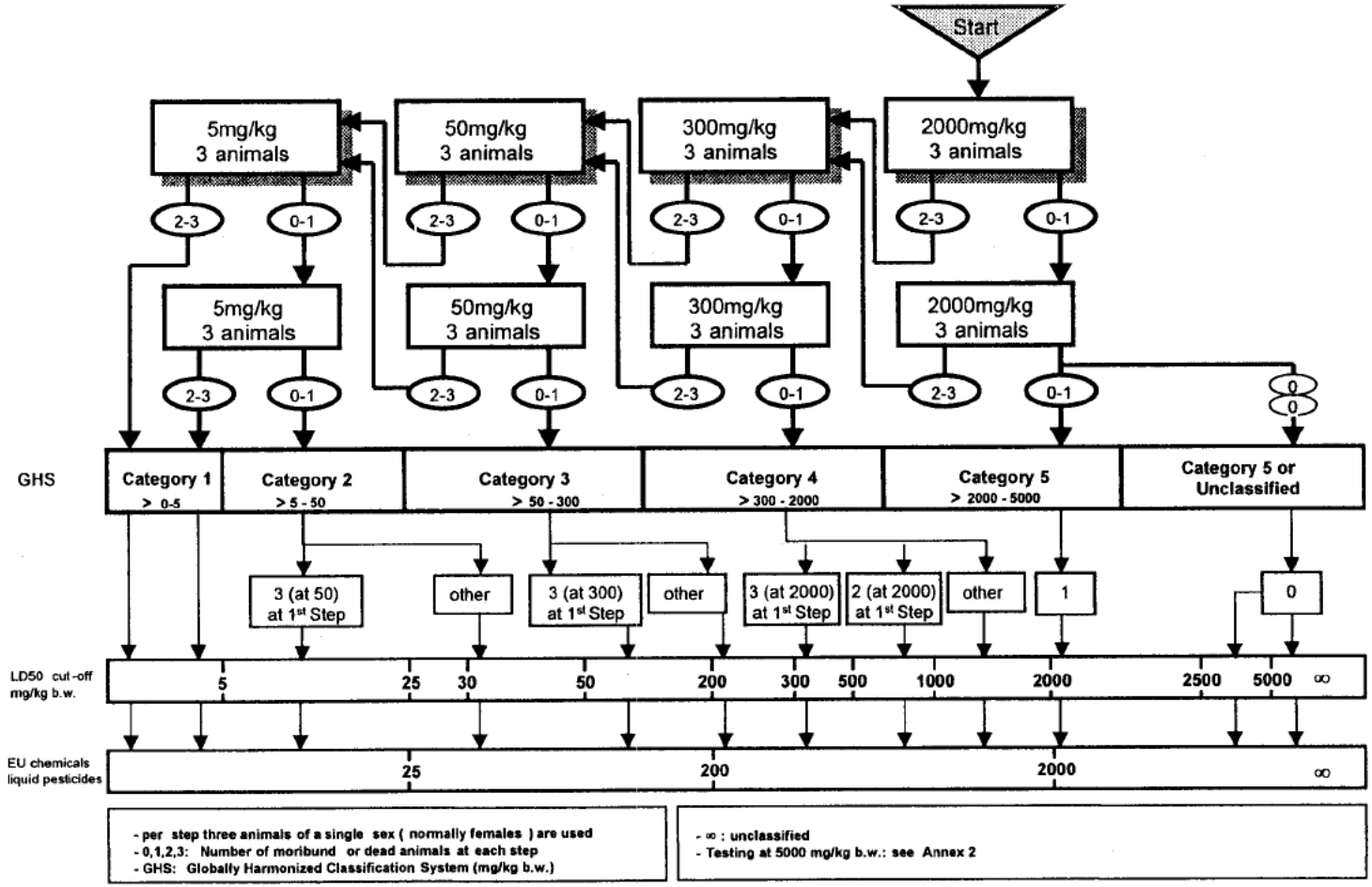
Table 4 Individual Necropsy Findings

Dose Level mg/kg	Animal Number and Sex	Time of Death	Macroscopic Observations
2000	1-0 Female	Killed Day 14	No abnormalities detected
	1-1 Female	Killed Day 14	No abnormalities detected
	1-2 Female	Killed Day 14	No abnormalities detected
	2-0 Female	Killed Day 14	No abnormalities detected
	2-1 Female	Killed Day 14	No abnormalities detected
	2-2 Female	Killed Day 14	No abnormalities detected

Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate

[redacted] ACUTE ORAL TOXICITY IN THE RAT – ACUTE TOXIC CLASS METHOD

Appendix 1 Test Procedure with a Starting Dose of 2000 mg/kg Bodyweight



Appendix 2 Statement of GLP Compliance in Accordance with Directive 88/320/EEC

THE DEPARTMENT OF HEALTH OF THE GOVERNMENT OF THE UNITED KINGDOM

GOOD LABORATORY PRACTICE

STATEMENT OF COMPLIANCE
IN ACCORDANCE WITH DIRECTIVE 88/320 EEC

LABORATORY

SafePharm Laboratories Ltd
Shardlow Business Park
London Road
Shardlow
Derbyshire
DE72 2GD

TEST TYPE

Analytical Chemistry
Environmental Fate
Environmental Toxicity
Mutagenicity
Phys/Chem Tests
Toxicology

DATE OF INSPECTION
28 February 2000

A general inspection for compliance with the Principles of Good Laboratory Practice was carried out at the above laboratory as part of UK GLP Compliance Programme.

At the time of the inspection no deviations were found of sufficient magnitude to affect the validity of non-clinical studies performed at these facilities.

Roger G. Alexander
26/4/00

Dr. Roger G. Alexander
Head, UK GLP Monitoring Authority

SAFEPHARM LABORATORIES LTD

Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate

[redacted]

ACUTE ORAL TOXICITY IN THE RAT – ACUTE TOXIC CLASS METHOD

[redacted]

I verify that this is an exact copy of the original report which is located in the Archives of Safepharm Laboratories Ltd., Derby, UK.

..... DATE: 29 MAY 2003

A Sanders
Study Director

[redacted]

Phytosteryl Isostearyl Dimer Dilinoleate

[redacted]

ACUTE ORAL TOXICITY STUDY

IN THE RAT - ACUTE TOXIC CLASS METHOD

[redacted]

AUTHOR: A Sanders

[redacted]

[redacted]

ISSUED BY:

Safepharm Laboratories Limited
PO Box No. 45
DERBY
DE1 2BT
UK

Telephone: DERBY (01332) 792896

Facsimile: (01332) 799018

QUALITY ASSURANCE REPORT

The routine inspection of short term studies at Safepharm is carried out as a continuous process designed to encompass all major phases of each study type once per month. Inspection findings are reported to Management/Study Directors on the day of inspection in each case. The standard test method for each study type ("Standardised Study Plan" in OECD terminology) is inspected for compliance once only on initial issue of the document.

This report has been audited by Safepharm Quality Assurance Unit. It is considered to be an accurate account of the data generated and of the procedures followed.

Inspection and audit occasions relevant to this study are as follows:

10 November 1998	Standard Test Method Compliance Audit
01 December 1999	Test Material Preparation
01 December 1999	Animal Preparation
01, 07 December 1999	Dosing
13, 16 December 1999	Assessment of Response
09 December 1999	Necropsy
27 January 2000	Draft Report Audit
Date of QA Signature	Final Report Audit

..... DATE: 22 FEB 2000

For Safepharm Quality Assurance Unit*

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*Authorised QA Signatures:

Head of Department: JR Pateman CBiol MIBiol DipRQA
Deputy Head of Department: JM Crowther MIScT
Senior Audit Staff: JV Johnson BSc; G Wren ONC; RJ Gilbert BSc

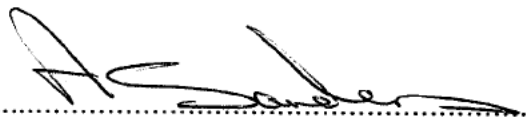
[redacted]

GLP COMPLIANCE STATEMENT

I, the undersigned, hereby declare that the objectives laid down in the protocol were achieved and as nothing occurred to adversely affect the quality or integrity of the study, I consider the data generated to be valid. This report fully and accurately reflects the procedures used and data generated.

The work described was performed in compliance with UK GLP standards (Schedule 1, Good Laboratory Practice Regulations 1999 (SI 1999/3106)). These Regulations are in accordance with GLP standards published as OECD Principles on Good Laboratory Practice (revised 1997, ENV/MC/CHEM(98)17); and are in accordance with, and implement, the requirements of Directives 87/18/EEC (as amended by Directive 199/11/EC) and 88/320/EEC (as amended by Directive 1999/12/EC).

These international standards are acceptable to the United States Environmental Protection Agency and Food and Drug Administration, and fulfil the requirements of 40 CFR Part 160, 40 CFR Part 792 and 21 CFR Part 58 (as amended).



..... DATE: 21 FEB 2000

A Sanders
Study Director
for Safepharm Laboratories

[redacted]

CONTENTS

[redacted]

SUMMARY

STUDY SPONSOR : [redacted]

STUDY TITLE : ACUTE ORAL TOXICITY STUDY IN THE RAT - ACUTE TOXIC CLASS METHOD

TEST MATERIAL : [redacted]
Phytosteryl Isostearyl Dimer Dilinoleate

1. A study was performed to assess the acute oral toxicity of the test material following a single oral administration to the Sprague-Dawley CD strain rat. The method followed that in the OECD Guidelines for Testing of Chemicals No. 423 "Acute Oral Toxicity - Acute Toxic Class Method" (adopted 22 March 1996) and Method B1 tris of Commission Directive 96/54/EC (which constitutes Annex V of Council Directive 67/548/EEC).

   The results may be used as a basis for classification and labelling under Annex VI of Council Directive 67/548/EEC (as adapted to technical progress by Commission Directive 93/21/EEC) relating to the classification, packaging and labelling of dangerous substances.

2. Using all available information, 2000 mg/kg bodyweight was selected as the starting dose.

   A group of three fasted females was treated with the starting dose. This was followed by a group of three fasted animals of the other sex at the same dose level.

   The test material was administered orally as a solution in arachis oil BP. The animals were observed ½, 1, 2 and 4 hours after dosing and then once daily for up to fourteen days. Bodyweights were recorded on Day 0 (day of dosing) and on Days 7 and 14, or at death. At the end of the observation period all animals were killed by cervical dislocation and subjected to gross necropsy.

3. There were no deaths.

4. There were no clinical signs of toxicity.

5. All animals showed expected gains in bodyweight over the study period.

6. No abnormalities were noted at necropsy.

7. The acute oral median lethal dose, (LD_{50}) of the test material, in the Sprague-Dawley CD strain rat, was estimated as being greater than 2000 mg/kg bodyweight. No mortalities were noted in animals treated with 2000 mg/kg bodyweight.

   No symbol and risk phrase are required according to EU labelling regulations.

[redacted]

Phytosteryl Isostearyl Dimer Dilinoleate

[redacted]

ACUTE ORAL TOXICITY STUDY
IN THE RAT - ACUTE TOXIC CLASS METHOD

1. INTRODUCTION

The purpose of the study was to assess the acute oral toxicity of the test material following a single oral administration to the Sprague-Dawley CD strain rat. The method followed the OECD Guidelines for Testing of Chemicals No. 423 "Acute Oral Toxicity - Acute Toxic Class Method" (adopted 22 March 1996) and Method B1 tris of Commission Directive 96/54/EC (which constitutes Annex V of Council Directive 67/548/EEC).

The results may be used as a basis for classification and labelling under Annex VI of Council Directive 67/548/EEC (as adapted to technical progress by Commission Directive 93/21/EEC) relating to the classification, packaging and labelling of dangerous substances.

The rat was the species of choice for this study as it is widely used for safety evaluation studies and was recommended in the test method.

The study was performed between 06 December 1999 and 22 December 1999.

2. TEST MATERIAL AND EXPERIMENTAL PREPARATION

2.1 Description, Identification and Storage Conditions

Sponsor's identification	:	[redacted]
Lot number	:	[redacted] Phytosteryl Isostearyl Dimer Dilinoleate
Date received	:	22 November 1999
Description	:	yellow turbid viscous liquid
Storage conditions	:	room temperature in the dark

Data relating to the identity, purity and stability of the test material are the responsibility of the Sponsor.

[redacted]

2.2 Experimental Preparation

For the purpose of the study the test material was freshly prepared, as required, as a solution at the appropriate concentration in arachis oil BP. Arachis oil BP was used because the test material did not dissolve in distilled water or other aqueous vehicles. Preparation was aided by the use of a vortex mixer.

Determination by analysis of the concentration, homogeneity and stability of the test material preparations was not appropriate because it was not specified in the Study Plan and is not a requirement of the Test Guideline.

3. METHODS

3.1 Animals and Animal Husbandry

Male and female Sprague-Dawley CD (Crl : CD ® (SD) IGS BR) strain rats supplied by Charles River (UK) Ltd, Margate, Kent, UK were used. At the start of the study the males weighed 231 to 235g, and the females 206 to 225g, and were eight to twelve weeks old. After an acclimatisation period of at least five days the animals were selected at random and given a number unique within the cage by tail marking.

The animals were housed in groups of three by sex in solid-floor polypropylene cages furnished with woodflakes. With the exception of an overnight fast immediately before dosing and for approximately three to four hours after dosing, free access to mains drinking water and food (Rat and Mouse Expanded Diet No.1, Special Diets Services Limited, Witham, Essex, UK) was allowed throughout the study.

The temperature and relative humidity were set to achieve limits of 19 to 25°C and 30 to 70% respectively. The rate of air exchange was approximately fifteen changes per hour and the lighting was controlled by a time switch to give twelve hours continuous light and twelve hours darkness.

3.2 Study Design

The information available suggested a starting dose of 2000 mg/kg. The testing sequence followed the flow chart described in Appendix Ic.

Groups of fasted animals were therefore treated as follows:

DOSE LEVEL mg/kg	CONCENTRATION mg/ml	DOSE VOLUME ml/kg	NUMBER OF RATS	
			MALE	FEMALE
2000	200	10	-	3
2000	200	10	3	-

All animals were dosed once only by gavage, using a metal cannula attached to a graduated syringe. The volume administered to each animal was calculated according to the fasted bodyweight at the time of dosing. Treatment of animals was sequential. Sufficient time was allowed between each sex and each dose level to confirm the survival of the previously dosed animals.

The animals were observed for deaths or overt signs of toxicity ½, 1, 2 and 4 hours after dosing and subsequently once daily for fourteen days.

Individual bodyweights were recorded prior to dosing and seven and fourteen days after treatment.

At the end of the observation period the animals were killed by cervical dislocation. All animals were subjected to gross pathological examination. This consisted of an external examination and opening of the abdominal and thoracic cavities for examination of major organs. The appearance of any macroscopic abnormalities was recorded. No tissues were retained.

3.3 Evaluation of Data

The number of animals dying during the study, or killed for humane reasons, was determined. The nature, severity, time of onset and duration of toxic effects were also determined. Effects on bodyweights and abnormalities noted at necropsy were identified.

Using the mortality data obtained, an estimate of the acute oral median lethal dose (LD_{50}) of the test material was made as shown in the schematic diagram in Appendix Ic.

3.3.1 Interpretation According to Annex VI Section 3.2

The results were interpreted according to the Commission Directive 93/21/EEC which adapts Council Directive 67/548/EEC on the regulations relating to the classification, packaging and labelling of dangerous substances.

The test material will be classified and assigned the appropriate symbol and risk phrase as follows:

CATEGORY	ACUTE ORAL LD_{50} mg/kg	SYMBOL	RISK PHRASE
VERY TOXIC	≤25	T+	R 28 "VERY TOXIC IF SWALLOWED"
TOXIC	>25 to 200	T	R 25 "TOXIC IF SWALLOWED"
HARMFUL	>200 to 2000	Xn	R 22 "HARMFUL IF SWALLOWED"

Test materials with acute oral LD_{50} values greater than 2000 mg/kg require no symbol and risk phrase.

4. ARCHIVES

Unless instructed otherwise by the Sponsor, all original data and the final report will be retained in the Safepharm archives for a period of five years. After this period, the Sponsor's instructions will be sought.

5. RESULTS

5.1 Mortality Data

Individual mortality data are given in Table 1.

There were no deaths.

5.2 Clinical Observations

Individual clinical observations are given in Tables 2 and 3.

There were no clinical signs of toxicity.

5.3 Bodyweight

Individual bodyweights and weekly bodyweight changes are given in Tables 4 and 5.

All animals showed expected gains in bodyweight over the study period.

5.4 Necropsy

Individual necropsy findings are given in Tables 6 and 7.

No abnormalities were noted at necropsy.

6. CONCLUSION

Phytosteryl Isostearyl Dimer Dilinoleate

The acute oral median lethal dose, (LD_{50}) of the test material, [redacted], in the Sprague-Dawley CD strain rat was estimated to be greater than 2000 mg/kg bodyweight.

No mortalities were noted at 2000 mg/kg bodyweight.

No symbol and risk phrase are required according to EU labelling regulations.

Phytosteryl Isostearyl Dimer Dilinoleate

[redacted]: ACUTE ORAL TOXICITY STUDY IN THE RAT - ACUTE TOXIC CLASS METHOD

TABLE 1
MORTALITY DATA

Dose Level mg/kg	Sex	Number of Animals Treated	Deaths During Day of Dosing (Hour)				Deaths During Period After Dosing (Days)								Deaths
			½	1	2	4	1	2	3	4	5	6	7	8-14	
2000	Female	3	0	0	0	0	0	0	0	0	0	0	0	0	0/3
	Male	3	0	0	0	0	0	0	0	0	0	0	0	0	0/3

Phytosteryl Isostearyl Dimer Dilinoleate

[redacted]: ACUTE ORAL TOXICITY STUDY IN THE RAT - ACUTE TOXIC CLASS METHOD

TABLE 2
INDIVIDUAL CLINICAL OBSERVATIONS

Dose Level mg/kg	Animal Number and Sex	Effects Noted After Dosing (Hours)				Effects Noted During Period After Dosing (Days)													
		½	1	2	4	1	2	3	4	5	6	7	8	9	10	11	12	13	14
2000	1-0 Female	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1-1 Female	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1-2 Female	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

0 = no signs of systemic toxicity

Phytosteryl Isostearyl Dimer Dilinoleate

[redacted]: ACUTE ORAL TOXICITY STUDY IN THE RAT - ACUTE TOXIC CLASS METHOD

TABLE 3
INDIVIDUAL CLINICAL OBSERVATIONS

Dose Level mg/kg	Animal Number and Sex	Effects Noted After Dosing (Hours)				Effects Noted During Period After Dosing (Days)													
		½	1	2	4	1	2	3	4	5	6	7	8	9	10	11	12	13	14
2000	2-0 Male	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2-1 Male	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2-2 Male	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

0 = no signs of systemic toxicity

Phytosteryl Isostearyl Dimer Dilinoleate

[redacted]: ACUTE ORAL TOXICITY STUDY IN THE RAT - ACUTE TOXIC CLASS METHOD

TABLE 4

INDIVIDUAL BODYWEIGHTS AND WEEKLY BODYWEIGHT CHANGES

Dose Level mg/kg	Animal Number and Sex	Bodyweight (g) at Day			Bodyweight Gain (g) During Week	
		0	7	14	1	2
2000	1-0 Female	209	230	248	21	18
	1-1 Female	206	241	265	35	24
	1-2 Female	225	245	260	20	15

Phytosteryl Isostearyl Dimer Dilinoleate

[redacted]: ACUTE ORAL TOXICITY STUDY IN THE RAT - ACUTE TOXIC CLASS METHOD

TABLE 5

INDIVIDUAL BODYWEIGHTS AND WEEKLY BODYWEIGHT CHANGES

Dose Level mg/kg	Animal Number and Sex	Bodyweight (g) at Day			Bodyweight Gain (g) During Week	
		0	7	14	1	2
2000	2-0 Male	232	305	364	73	59
	2-1 Male	235	310	363	75	53
	2-2 Male	231	292	346	61	54

Phytosteryl Isostearyl Dimer Dilinoleate

[redacted]: ACUTE ORAL TOXICITY STUDY IN THE RAT - ACUTE TOXIC CLASS METHOD

TABLE 6

INDIVIDUAL NECROPSY FINDINGS

Dose Level mg/kg	Animal Number and Sex	Macroscopic Observations
2000	1-0 Female	No abnormalities detected
	1-1 Female	No abnormalities detected
	1-2 Female	No abnormalities detected

Phytosteryl Isostearyl Dimer Dilinoleate

[redacted]: ACUTE ORAL TOXICITY STUDY IN THE RAT - ACUTE TOXIC CLASS METHOD

TABLE 6

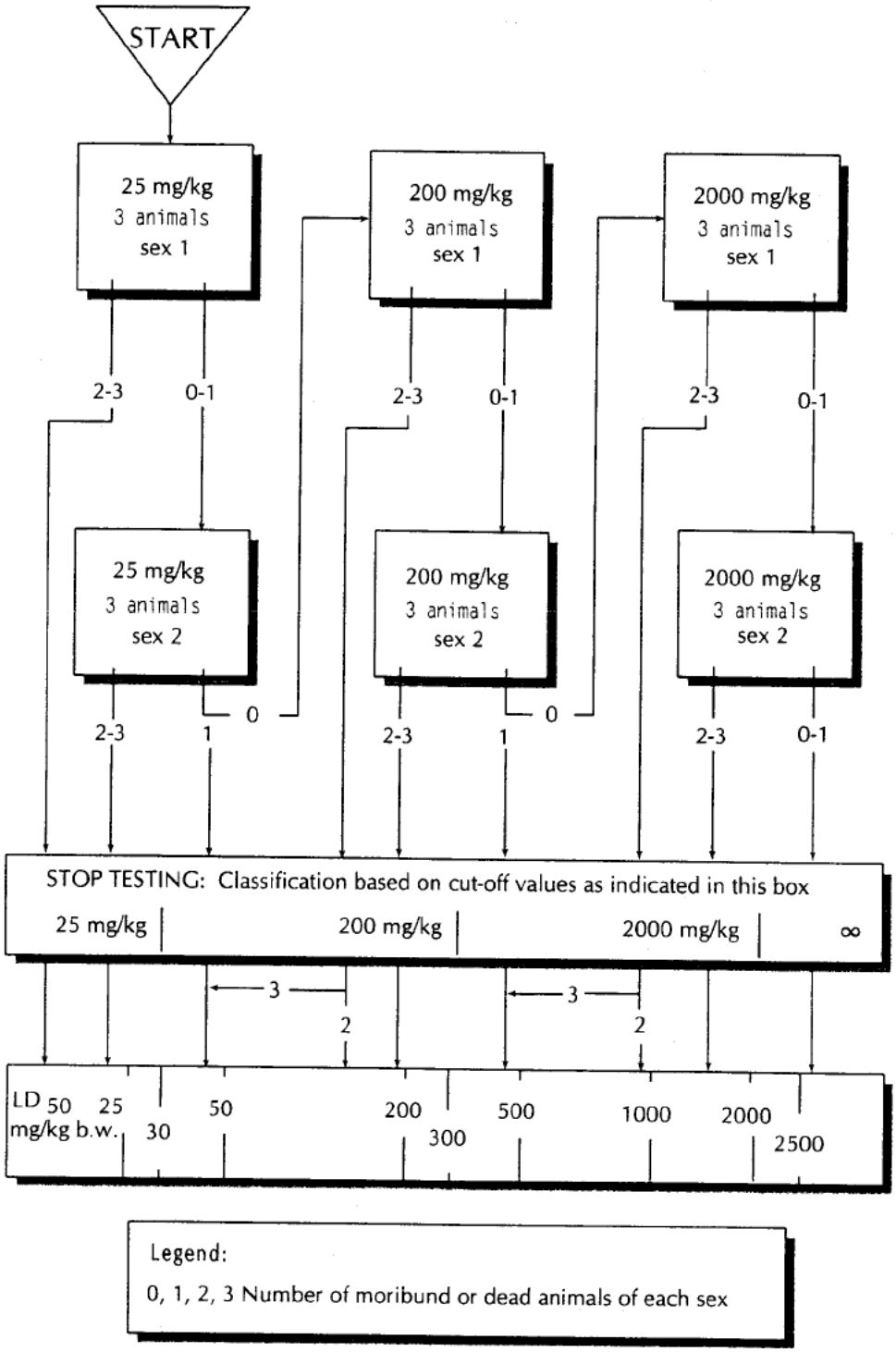
INDIVIDUAL NECROPSY FINDINGS

Dose Level mg/kg	Animal Number and Sex	Macroscopic Observations
2000	2-0 Male	No abnormalities detected
	2-1 Male	No abnormalities detected
	2-2 Male	No abnormalities detected

APPENDICES

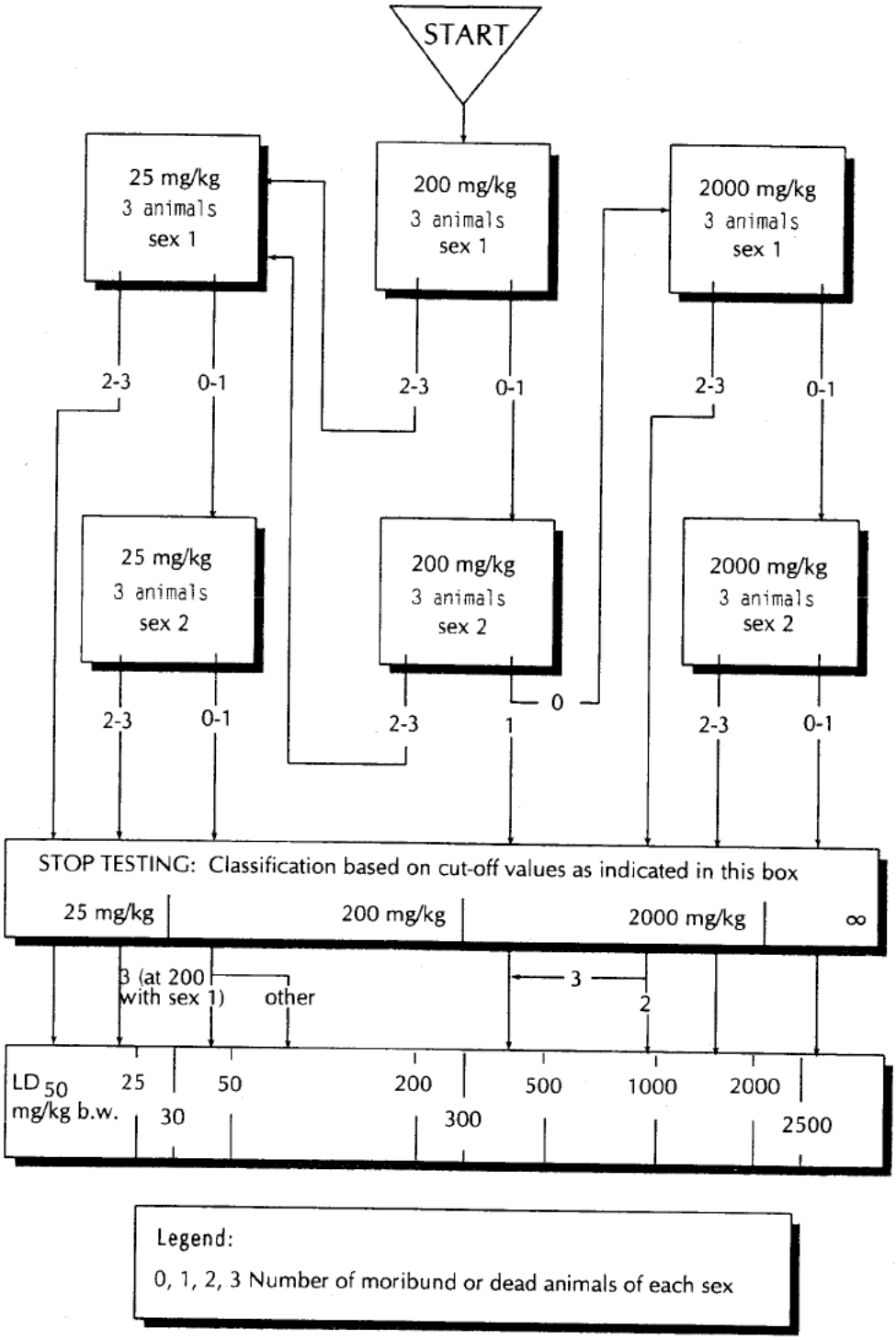
APPENDIX Ia

TEST PROCEDURE WITH A STARTING DOSE OF 25 mg/kg BODYWEIGHT



APPENDIX Ib

TEST PROCEDURE WITH A STARTING DOSE OF 200 mg/kg BODYWEIGHT

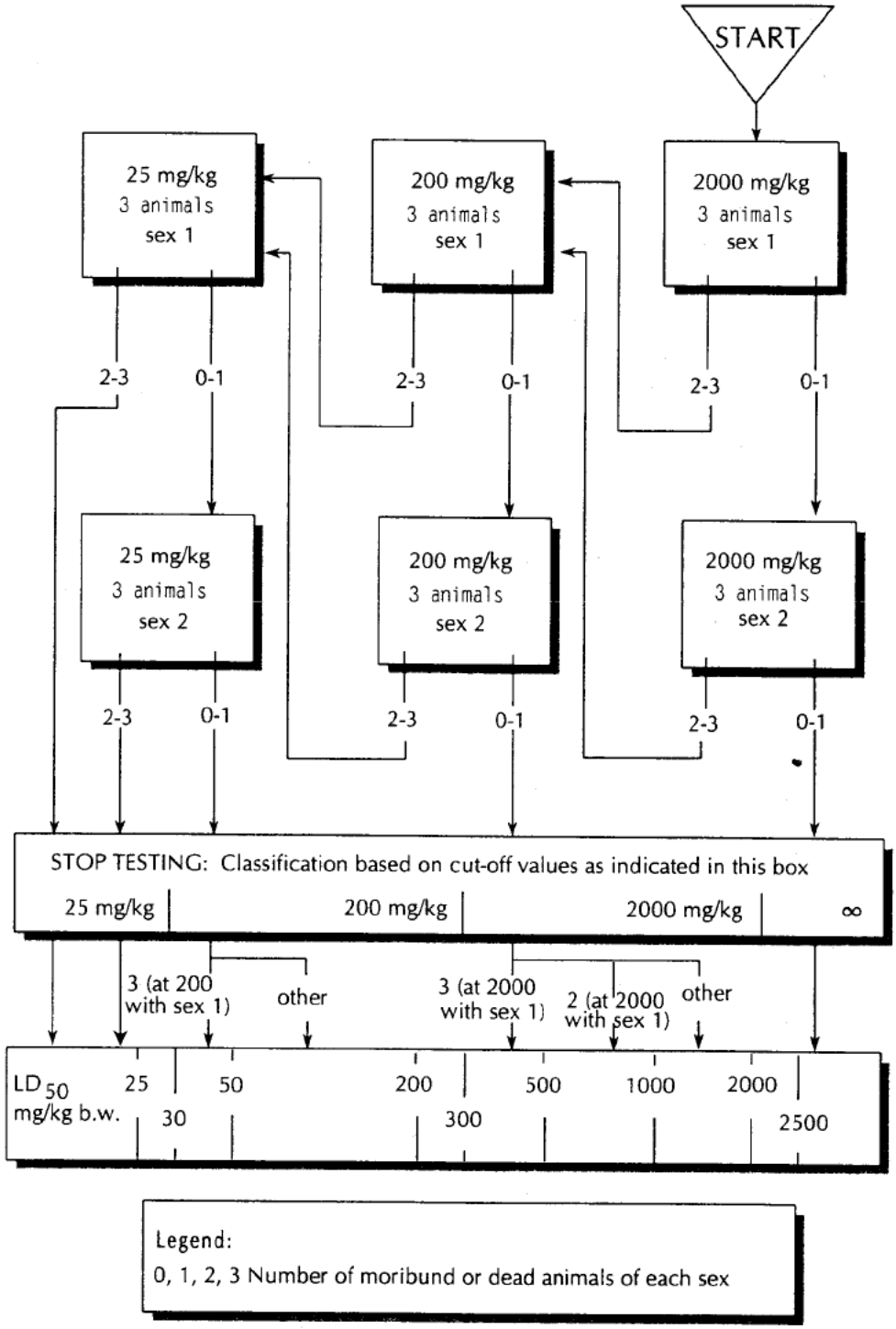


Legend:

0, 1, 2, 3 Number of moribund or dead animals of each sex

APPENDIX Ic

TEST PROCEDURE WITH A STARTING DOSE OF 2000 mg/kg BODYWEIGHT



APPENDIX II

THE DEPARTMENT OF HEALTH OF THE GOVERNMENT OF THE UNITED KINGDOM

GOOD LABORATORY PRACTICE

STATEMENT OF COMPLIANCE
IN ACCORDANCE WITH DIRECTIVE 88/320 EEC

LABORATORY	TEST TYPE
SafePharm Laboratories Ltd. Shardlow Business Park London Road Shardlow Derbyshire DE72 2GD	Analytical Chemistry Environmental Fate Environmental Toxicity Mutagenicity Phys/Chem Tests Toxicology

DATE OF INSPECTION

23rd March 1998

A general inspection for compliance with the Principles of Good Laboratory Practice was carried out at the above laboratory as part of UK GLP Compliance Programme.

At the time of the inspection no deviations were found of sufficient magnitude to affect the validity of non-clinical studies performed at these facilities.

21st July 1998

UK GLP Monitoring Authority

Ensemble, un pas pour l'humanité.

[redacted]

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

[redacted]

[redacted]

Acute eye irritation study in the rabbit (OECD 405)

Baugy, November 17, 2004

[redacted]

TESTING FACILITY:
Centre de Recherches Biologiques (CERB)
Chemin de Montifault
18800 Baugy
France

TESTING FACILITY'S APPROVAL

Scientific and Managing Director:
S. Richard, Pharm.D, Ph.D
Registered Toxicologist

25/11/04
Date

Signature

Head of Short-Term Toxicology Studies
and Study Director:
L. Baudet, INSA Engineer

17/11/2004
Date

Signature

Responsible for Quality Assurance:
S. Bidoli-Beutin, Quality Engineer

19/11/04
Date

Signature

STUDY DIRECTOR CERTIFICATE

◊ [redacted] Acute eye irritation study in the rabbit.

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

◊ [redacted]

I declare that the following report constitutes a true and faithful account of the procedures adopted and the results obtained in the performance of this study. The study conducted by Centre de Recherches Biologiques was performed according to the criteria of Good Laboratory Practice.

L. Baudet
Study Director

Date

Signature

QUALITY ASSURANCE STATEMENT

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

- [redacted]: Acute eye irritation study in the rabbit (OECD 405).
- [redacted]

- **STUDY PLAN AUDIT**

Audit performed on 23 June 2004 by Mrs F. Paulien.
Findings were reported to Study Director and Management on 23 June 2004.

- **AMENDMENT AUDIT**

No amendment was issued for this study.

- **IN STUDY AUDIT**

The Quality Assurance Unit ensures the strict application of the centre's current procedures.

At or about the time that the study part was in progress, audits were made on general procedures and facilities once a month during critical phases in accordance with SOP 9.02 independently of the type of studies.

Findings were reported to Study Director and Management.

No specified audit of critical phases was carried out for this study.

QUALITY ASSURANCE STATEMENT

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

- [redacted] Acute eye irritation study in the rabbit (OECD 405).
- [redacted]

- **RAW DATA AND REPORT AUDIT**

Audit performed on 19 October 2004 by Mrs C. Bertrand.
Findings were reported to Study Director and Management on 19 October 2004.

- **CONCLUSION**

This study was undertaken in accordance with study plan.
The data in the present report are in accordance with raw data.

Mrs. S. Bidoli-Beutin
Quality Engineer
Responsible for Quality Assurance

19/11/04
Date

Signature

[redacted]

Contents

[redacted]

List of Tables

SUMMARY

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

At the request of [redacted] any irritant property and/or degree of corrosion of the test substance [redacted] was evaluated following a single ocular instillation in the rabbit in accordance with requirements of OECD Guideline No. 405 (April 24, 2002).

Three animals were used for the study.

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

0.1 mL of [redacted] was introduced into the conjunctival sac of the left eye of each of the animals. The untreated right eye served as a control.

The application of the test substance did not induce colouring of the application site and did not interfere with grading of any eye lesion.

Any conjunctival, iris and corneal lesion was evaluated approximately one hour, 24 hours, 48 hours and 72 hours after instillation of [redacted]

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

Mean indices were calculated from results obtained for each rabbit at times 1, 24, 48 and 72 hours.

Results obtained were as follows:
A slight redness (score 1) was noted in all animals at time 1 hour.

Table 1: Total score/tissue/time/animal

Treatment	Animal number	Conjunctivae 1h	Conjunctivae 24h/48h/72h	Iris 1h/24h/48h/72h	Cornea 1h/24h/48h/72h
[redacted]	20040372	2	0	0	0
Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	20040373	2	0	0	0
	20040374	2	0	0	0

Table 2: Total score/time/animal

Treatment	Animal number	1h	24h	48h	72h
[redacted]	20040372	2	0	0	0
	20040373	2	0	0	0
Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	20040374	2	0	0	0

Table 3: Group mean total score/time

Treatment	1h	24h	48h	72h
Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	2	0	0	0

Under the experimental conditions adopted and according with the modified Kay and Calandra interpretation of eye irritation test, [redacted] was practically non-irritant (class 2) for the eye of the rabbit.

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

PART I
EXPERIMENTAL STUDY PLAN

1.1 AIM

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

The aim of the study was to determine any irritant property of [redacted] following a single ocular instillation in the rabbit. Ocular irritation and/or corrosion following instillation of [redacted] in the eye of the rabbit was evaluated by grading of any ocular irritation reaction seen, using a predetermined scoring system.

1.2 GLP COMPLIANCE STATEMENT

The study took place according to the criteria of Good Laboratory Practice (GLP), published by:

- The French Ministry of Social Affairs and National Solidarity, State Secretariat for Health: Guidelines concerning Good Laboratory Practice (GLP) dated March 14, 2000, Official Text Reference MESP0020869A.
- Directive 99/11/ EEC concerning Good Laboratory Practice (GLP).
- OECD principles on GLP OECD Health and Safety publication ENV/MC/CHEM (98) 17 (as revised in 1997).
- The Food and Drug Administration: GLP 21 CFR Part 58 Regulation dated December 22, 1978 and corresponding Amendments.
- Good Laboratory Practice Guidelines: "notification No. 424 of the Pharmaceutical Affairs Bureau of the Japanese Ministry of Health and Welfare".

Approval for the site of experimentation: No. B 18-023-01.

1.3 DEVIATIONS FROM STUDY PLAN

Deviation n ° 1, Testing facility's approval: Th. Vierling signature was removed from the signatories' lists of the study report.
Reason: As Th. Vierling signature is not formally compulsory according to GLP, it was removed from the signatories' lists of the study report during his absence.

Deviation n ° 2, Report: The signed study plan was not included in the report.
Reason: At the Sponsor's request.

Deviation n ° 3, Report: The address of our Scientific Representative in the UK for linguistic review (J. Fowler) is now as follows: P.O. Box 274 Loughton IG10 4WB UK

There were no other study plan deviations during the course of the study.

These deviations are considered to have had no detrimental effect on the results of the study.

With the exception of the points reported above, the study took place in accordance with the study plan No. [redacted]

1.4 STUDY DATES

- Date of start of the experimental period: 23.Aug.2004
- Date of end of the experimental period: 02.Sep.2004

1.5 ETHICS

The standard study plan relating to this study has been approved by the CERB Internal Ethics Committee.

1.6 DIRECTIVE COMPLIANCE STATEMENT

The study plan applied, in accordance with requirements of OECD Guideline No. 405 (April 24, 2002) enabled full evaluation of the reversible or irreversible nature of any effects seen.

1.7 TEST SUBSTANCE

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

On 7 June 2004, we received one sample of [redacted]. Immediately upon receipt, [redacted] was registered, then stored at ambient temperature in accordance with the Sponsor's instructions. The complete description of the chemical and physical properties of [redacted] including stability, is the responsibility of the Sponsor. The Sponsor did not supply the certificate of analysis of the test substance.

Appearance: Off white paste.

1.8 INITIAL CONSIDERATIONS

In the interest of animal welfare substances meeting any of the following criteria should not be tested in animals for eye irritation:

1) Substances of demonstrated corrosive action as well as strongly acidic or alkaline substances (pH $\leqslant$ 2 or $\geqslant$ 11.5), which most likely have corrosive properties.

2) Substances which have produced severe skin irritation (with a mean score of 2.5 or more in at least one animal, as assessed at the four time points 1 h, 24 h, 48 h and 72 h), since it is presumed that the test substance was also produced severe effects if tested on the eye. In the absence of any skin irritation data, a preliminary skin irritation test should be undertaken in one animal prior to implementation of any study of effect on the eye.

1.9 MATERIAL

1.9.1 Animals

Species: Rabbit.

Breed: New Zealand Albino.

Choice of species: The rabbit is chosen because of its acceptance as a predictor of irritant/corrosive effects of chemicals in man and the recognition by regulatory authorities that this species is suitable for eye irritation studies.

Sex: Female.

Origin: CEGAV breeding establishment - Les Hautes Nöes, 61350 Saint Mars d'Egrenne, France.

Date of delivery: 26 May 2004

Identification: Animals were individually identified by an ear clip.

Body weight: Between 3.2 kg and 3.4 kg at the start of the experiment.

Acclimatisation: For at least 5 days before the treatment, in the area where the experiment took place.

Housing: Animals were housed individually in cages of standard size. Excreta were removed by unrolling plasticised brown paper, previously placed under cages. These cages were placed in an air-conditioned (17- 21 ° C) animal house kept at between 45 % and 65 % relative humidity in which non-recycled filtered air is changed approximately ten times per hour. The artificial day/night cycle was 12 hours light and 12 hours darkness with light on at 7.30 a.m.

Feeding: SDS/DIETEX STANRAB (P) SQC feed was available *ad libitum*. The criteria for acceptable levels of contaminants in the feed supply was within the limits of the analytical specifications established by the diet manufacturer. A certificate of analysis concerning this feed product is included in Appendix A, page 26.

Drinking water: Drinking water was available *ad libitum* in polycarbonate feeder bottles with a stainless steel nipple. A specimen of water is obtained every 6 months and sent to the Laboratoire Départemental d'Analyse du Cher - 216 rue Louis Mallet, 18014 Bourges Cedex, France - for analysis. The criteria for acceptable levels of contaminants in the water supply was within the limits of the analytical specifications. The certificates of analysis are included in Appendix B, page 29.

1.10 EXPERIMENTAL STUDY PLAN

1.10.1 Study design

Three animals were required for the complete test. Animals were selected on the basis of their general conditions.

Exposure of one animal: A single animal test was considered in order to anticipate marked effects.

Exposure of two additional animals: After instillation of the test substance in the first animal, an assessment of the initial local pain reaction was made. Providing severe effects were not observed in the first treated animal, two additional animals were subsequently treated in an identical manner.

1.10.2 Choice of doses

As required by the guideline, 0.1 mL of [redacted] was instilled.

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

1.10.3 Dose adjustment

The dose was expressed in mL of [redacted] as instilled. The standard amount applied was not adjusted to body weight.

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

1.10.4 Form of administration

The test substance was instilled undiluted.

1.10.5 Method of administration

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

0.1 mL of [redacted] was introduced into the conjunctival sac of the left eye of each of the animals. The conjunctival sac was opened by gently pulling the lower lid away from the eyeball. Eyelids were held closed for approximately 1 second in order to avoid any loss of [redacted] The non-treated right eye was used as control. Following treatment, animals were kept for approximately one hour in a restraint cage, in order to prevent rubbing of the eye. The day of instillation was taken as the first study day D1.

Timing, frequency and duration of administration

[redacted] was instilled once only.

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

1.10.6 Experimental procedure

Weighing

Individual body weights were taken at the beginning and at the end of the experiment.

The results are presented in table 2.5, page 24.

Examination of the eye

Lesions of the conjunctiva, iris and cornea were monitored by direct examination.
One hour, 24 hours, 48 hours and 72 hours approximately after the instillation of [redacted] all possible conjunctival, iris or corneal lesions were evaluated on the left eye of each animal.
Ocular lesions were graded using the following scoring system in accordance with the OECD Guideline No. 405 (see table 1.1, page 17):

Calculation of ocular primary irritation indices

Grading of irritancy potential using the Kay and Calandra scheme:

The numerical values corresponding to each animal, tissue and day are recorded. The data relating to the conjunctivae was designated the letters A (redness), B (chemosis) and C (lacrimation), those relating to the iris designated the letter D and those relating to the cornea designated the letter E (degree of opacity) and F (area of opacity). For each tissue the total score was calculated as follow:

Score for conjunctivae = (A + B + C) x 2

Score for iris = D x 5

Score cornea = (E x F) x 5

Using the numerical data obtained, a modified version of the system described by Kay and Calandra was used to classify the ocular irritation potential of the test material. This was achieved by adding together the total scores for the cornea, iris and conjunctivae for each of the 1, 24, 48 and 72-hour observations for each rabbit. The group means of the total scores for each observation was calculated. The highest of these group means (the maximum mean score) together with the persistence of the reactions were allowed classification of the eye irritancy potential of the test material using the table 1.2, page 18.

Table 1.1: Scoring system of ocular lesions

OCULAR REACTIONS	OBSERVATIONS	SCORE
	CONJUNCTIVAE	
Chemosis (Swelling refers to lids and/or nictitating membranes)	No swelling	0
	Any swelling above normal (includes nictitating membranes)	1
	Obvious swelling with partial eversion of the lids	2
	Swelling with lids about half-closed	3
	Swelling with lids more than half-closed	4
Lacrimation	No lacrimation	0
	Slight lacrimation (slight secretions normally present at the medical angle should not be taken into account)	1
	Lacrimation with the moistening of the eyelids and of fur around eyelids	2
	Lacrimation with moistening of eyelids and of fur over large areas around eye	3
Redness (refers to palpebral and bulbar conjunctiva, not to cornea and iris)	Blood vessels normal	0
	Some blood vessels definitely hyperaemic (injected)	1
	Diffuse, crimson colour, individual vessels not easily discernible	2
	Diffuse breefy red	3
	IRIS	
	Normal	0
	Markedly deepened rugae, congestion, swelling, moderate circumcorneal hyperamia or injection, any of these or combination of any thereof, iris still reacting to light (sluggish reaction is positive)	1
	No reaction to light, haemorrhage, gross destruction (any or all of these)	2
	CORNEA*	
Opacity (degrees of density, most dense area is taken for reading)	No ulceration or opacity	0
	Scattered or diffuse areas of opacity (other than slight dulling of normal lustre), details of iris clearly visible	1
	Easily discernible translucent areas, details of iris slightly obscured	2
	Nacreous area, no details of iris visible, size of pupil barely discernible	3
	Opaque cornea, iris not discernible through the opacity	4
Area of cornea involved	A quarter (or less) but not zero	1
	Greater than one quarter but less than half	2
	Greater than half but less than three-quarters	3
	Greater than three-quarters, up to whole area	4

* The zone with the most severe lesions only is described. The assessment of the area of cornea involved is described as an exponent of the degree of opacification, on the result data sheet.

Criteria of classification

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

[redacted] was classified on the basis of results obtained, in accordance with the modified Kay and Calandra interpretation of eye irritation test (see table 1.2, page 18).

Table 1.2: Modified Kay and Calandra interpretation of eye irritation test

Maximum mean score		Persistence of score	Description rating	Class
0.0 to 0.5	Group mean total score at 24 hours = 0 Group mean total score at 24 hours > 0		Non-irritant Practically non-irritant	(1) (2)
0.5 to 2.5	Group mean total score at 24 hours = 0 Group mean total score at 24 hours > 0		Practically non-irritant Minimal irritant	(2) (3)
2.5 to 15	Group mean total score at 48 hours = 0 Group mean total score at 48 hours > 0		Minimal irritant Mild irritant	(3) (4)
15 to 25	Group mean total score at 72 hours = 0 Group mean total score at 72 hours > 0		Mild irritant Moderate irritant	(4) (5)
25 to 50		More than half of the individual total scores at 7 days 10 or less	Moderate irritant	(5)
	Group mean total score at 7 days 20 or less	More than half of the individual total scores at 7 days > 10 but no individual total score at 7 days > 30	Moderate irritant	(5)
		More than half of the individual total scores at 7 days > 10 and any individual score at 7 days > 30	Severe irritant	(6)
	Group mean total score at 7 days > 20		Severe irritant	(6)
50 to 80		More than half of the individual total scores at 7 days 30 or less	Severe irritant	(6)
	Group mean total score at 7 days 40 or less	More than half of the individual total scores at 7 day > 30 but no individual total scores at 7 days > 60	Severe irritant	(6)
		More than half of the individual total scores at 7 days > 30 and individual total score at 7 days > 60	Very severe irritant	(7)
	Group mean total score at 7 days > 40		Very severe irritant	(7)
80 to 100		More than half of the individual total scores a 7 days 60 or less	Very severe irritant	(7)
	Group mean total score at 7 days 80 or less	More than half of the individual total scores at 7 days > 60 but no individual total score at 7 days > 100	Very severe irritant	(7)
		More than half of the individual total scores at 7 days > 60 and individual total score a 7 days > 100	Extremely severe irritant	(8)
	Group mean total score at 7 days > 80		Extremely severe irritant	(8)
100 to 110	Group mean total score at 7 days 80 or less Group mean total score at 7 days > 80		Very severe irritant Extremely severe irritant	(7) (8)

Termination of study

Animals were euthanased by an overdose of sodium pentobarbital injected by the intravenous route. No necropsy was performed at the end of the study.

1.11 PRESENTATION AND ANALYSIS OF RESULTS

1.11.1 Presentation of results

The following results are presented:

- body weights at start and termination of the experiment
- toxic effects other than ocular irritation
- individual observations of treated eyes in tabular form
- narrative description of the degree and nature of irritation,
- primary irritation index
- description of other ocular lesions or signs of toxicity
- classification of Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

1.11.2 Analysis of results

All data were recorded as and when obtained using forms identified by the study number. Data were presented tabulated by animal number and time, nature, severity and duration of effects.

1.12 QUALITY ASSURANCE

The Quality Assurance Unit confirms that operating procedures governing studies are strictly applied, by periodic in-study audits. These audits are undertaken at random over the course of the year according to the CERB procedure No. 9.02. The experimental report in English and data were audited by Quality Assurance, in accordance with the standard procedures of the Centre.

1.13 ARCHIVES

The study plan, raw data, correspondence and the report will be stored for 5 years at CERB - 18800 Baugy, France, starting from the date of the final report.

No sample of test substance will be archived at CERB in the context of this study.

At the end of this period, CERB will contact the Sponsor in order to determine by joint agreement, either:

- continued storage of records
- return of records to the Sponsor
- destruction of records

After the issue of the final report, all remaining test substance will be sent to Laboservice, route de la Centrale, 69702, Givors Cedex, where it will be destroyed by incineration, under the responsibility of CERB.

PART II
EXPERIMENTAL RESULTS

2.1 OCCULAR TOLERENCE

Individuals findings are presented in table 2.1, page 22.

The application of the test substance did not induce colouring of the application site and did not interfere with grading of any eye lesion.

Any conjunctival, iris and corneal lesion was evaluated approximately one hour, 24 hours, 48 hours and 72 hours after instillation of [redacted] Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate
A slight redness (score 1) was noted in all animals at time 1 hour.

Mean indices were calculated from results obtained for each rabbit at times 1, 24, 48 and 72 hours.

Results are presented in table 2.2, page 23, table 2.3, page 23 and table 2.4, page 23.

2.2 CONCLUSION

Under the experimental conditions adopted and according with the modified Kay and Calandra interpretation of eye irritation test, [redacted] was practically non-irritant (class 2) for the eye of the rabbit.

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

Table 2.1: Acute eye lesions - Individual scores - [redacted]

Observations (range of scores; normal score)	Time	Animal serial number		
		1	2	3
Chemosis (0-4; 0)	1 hour	0	0	0
	24 hours	0	0	0
	48 hours	0	0	0
	72 hours	0	0	0
Lacrimation (0-3; 0)	1 hour	0	0	0
	24 hours	0	0	0
	48 hours	0	0	0
	72 hours	0	0	0
Redness (0-3; 0)	1 hour	**1**	**1**	**1**
	24 hours	0	0	0
	48 hours	0	0	0
	72 hours	0	0	0
Iris (0-2; 0)	1 hour	0	0	0
	24 hours	0	0	0
	48 hours	0	0	0
	72 hours	0	0	0
Cornea opacity (0-4; 0)	1 hour	0	0	0
	24 hours	0	0	0
	48 hours	0	0	0
	72 hours	0	0	0
Aera of cornea involved (0-4; 0)	1 hour	0	0	0
	24 hours	0	0	0
	48 hours	0	0	0
	72 hours	0	0	0

Individual data presented as a score attributed to each sign.
Correspondence between animal serial and identification numbers:
1:20040372 2:20040373 3:20040374
Emboldened numbers indicate values different from normal
Electronic signature: approved by Stephanie Spiga on 10-SEP-2004 at 09:16:28.846

[redacted]

Table 2.2: Total score/tissue/time/animal

Treatment	Animal number	Conjunctivae 1h	Conjunctivae 24h/48h/72h	Iris 1h/24h/48h/72h	Cornea 1h/24h/48h/72h
[redacted] Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	20040372	2	0	0	0
	20040373	2	0	0	0
	20040374	2	0	0	0

Table 2.3: Total score/time/animal

Treatment	Animal number	1h	24h	48h	72h
[redacted] Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	20040372	2	0	0	0
	20040373	2	0	0	0
	20040374	2	0	0	0

Table 2.4: Group mean total score/time

Treatment	1h	24h	48h	72h
[redacted] Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	2	0	0	0

Table 2.5: Body weight (individual values)

Treatment	Animal number	day 1	day 4
[redacted]	20040372	3.370	3.408
	20040373	3.375	3.465
	20040374	3.282	3.287

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

Results expressed in Kg

APPENDICES

Appendix A

CERTIFICATE OF ANALYSIS OF FEED

[redacted]

[redacted]

Special Diets Services

Special Quality Control Certificate of Analysis

PRODUCT: STANRAB (P) SQC — BATCH NO: 3522

PREMIX BATCH NO: 13389 — DATE OF MANUFACTURE: 02-DEC-03

Nutrient	Found Analysis		Contaminant	Found Analysis		Limit of Detection
Moisture	10.0	%	Fluoride	2	mg/kg	1.0 mg/kg
Crude Fat	3.7	%	Nitrate as NaNO3	522	mg/kg	2.0 mg/kg
Crude Protein	16.9	%	Nitrite as NaNO2	Non Detected	mg/kg	1.0 mg/kg
Crude Fibre	14.8	%	Lead	1.00	mg/kg	0.25 mg/kg
Ash	6.7	%	Arsenic	Non Detected	mg/kg	0.2 mg/kg
Calcium	0.85	%	Cadmium	0.11	mg/kg	0.05 mg/kg
Phosphorus	0.87	%	Mercury	Non Detected	mg/kg	0.01 mg/kg
Sodium	0.37	%	Selenium	0.05	mg/kg	0.05 mg/kg
Chloride	0.74	%				
Potassium	1.00	%				
Magnesium	0.24	%	Total Aflatoxins	Non Detected	mcg/kg	1 mcg/kg each of B1,B2,G1,G2
Iron	211	mg/kg				
Copper	12	mg/kg	Total P.C.B	Non Detected	mcg/kg	10.0 mcg/kg
Manganese	70	mg/kg	Total D.D.T	Non Detected	mcg/kg	10.0 mcg/kg
Zinc	53	mg/kg	Dieldrin	Non Detected	mcg/kg	10.0 mcg/kg
			Lindane	Non Detected	mcg/kg	10.0 mcg/kg
			Heptachlor	Non Detected	mcg/kg	10.0 mcg/kg
			Malathion	Non Detected	mcg/kg	20.0 mcg/kg
Vitamin A	7.4	iu/g	Total Viable Organisms x 1000	6.90	per grm	1000/g
Vitamin E	81	mg/kg				
Vitamin C		mg/kg	Mesophilic Spores x 100	Non Detected	per grm	100/g
			Salmonellae Species	Non Detected	per grm	Absent in 20 grm
			Entero Bacteriaceae	Non Detected	per grm	Absent in 20 grm
			Escherichia Coli	Non Detected	per grm	Absent in 20 grm
			Fungal Units	40	per grm	Absent in 20 grm
			Antibiotic Activity	Non Detected		

Signed .....

Dated 21.01.04

Special Diets Services
P.O. Box 705, Witham
Essex. CM8 3AD. England
Tel: +44 (0) 1376 511260
Fax: +44 (0) 1376 511247

8 March 2004

Dear Customer

PRODUCT SHELF LIFE

Research diets produced by SDS carry a nine months shelf life. This is calculated by adding nine months to the date of manufacture and subtracting one day.

The manufacture and expiry dates are printed on the ticket number attached to the bag.

Denise A. Pyman

Denise A. Pyman (Mrs.)
QUALITY MANAGER

Dietex International Ltd
trading as SDS

Company Number 4225846
Registered in England and Wales

Appendix B

CERTIFICATES OF ANALYSIS OF WATER

Laboratoire Départemental d'Analyses
216 rue Louis Mallet - 18014 BOURGES
Tél : 02.48.21.15.31 - Fax : 02.48.50.82.52

ANALYSIS N° : 04072101011803

DATE OF CREATION AT THE DOSSIER : 04/09/03
DATE OF ARRIVAL AT THE LABORATORY : 04/07/21 11:15 AM
EDITION'S DATE : 04/09/03
Time : 10:15:43

Name	: CERB
Location	: BAUGY

CERB
CHEMIN DE MONTIFAULT

18800 BAUGY

Collector	: LE CLIENT
Name	: DISTRIBUTION
Sampling site	: SITE N°1 = SITE GENERAL
Location	: BAUGY

WATER ANALYSIS RESULTS

BORDEREAU : 1 | DATE OF WATER SAMPLING : 04/07/21 | TIME : 08:45

Parameters	Results	Standard	Unity	Méthods	Date .anal
Physicochemistry					
Ammonia solution (mg/l)	<0.07		mg/l	NF T 90-015-2	04/07/22
Chloride ions (mg/l)	17.0		mg/l	NF T 90-014	04/07/21
Conductivité à 25°C	306		µS/cm	NF EN 27888	04/07/21
Iron (µg/l)	<10		µg/l	RODIER	04/07/21
Nitrate (mg/l)	9	<50	mg/l	NF EN ISO 13395	04/07/21
Nitrite (mg/l)	<0.01	<0.1	mg/l	NF EN 26777	04/07/21
Oxygen yielded by potassium permanganate (mg/l 02	0.5		mg/l O2	NF EN ISO 8467	04/07/21
pH	7.7		unitépH	NF T 90-008	04/07/21
Sulfate ions (mg/l)	22.0		mg/l	NF T 90-040	04/07/22
Alkalinity (in french degrees)	10.0		°F	NF EN ISO 9963-1	04/07/21
Hardness (in french degrees)	13		°F	NF T 90-003	04/07/21
Turbidity (U Jackson)	0.2	<1	FNU	NF EN ISO 27027	04/07/21

Observations : conductivité lue à 21.7 °C et corrigée à 25°C
pH pris à une T=21.3 °C
Compte tenu du milieu utilisé, seuls les clostridiums perfringens seront détectés dans l'analyse des bactéries sulfito-reducteurs

* As indicated by decree 89-3 and the followings

Applied 6/09/04

CENTRE DE RECH... S.A. Cap. 648 ... Chemin de ... Tél. : ... N° SIR...

Responsible,

Christelle LESPRIT

Certificated by the French Health Ministry Page 1/1

Laboratoire Départemental d'Analyses

215 rue Louis Mallet - 18014 BOURGES
Tél : 02.48.21.15.31 - Fax : 02.48.50.62.62

ANALYSIS N° : 04072101012101

DATE OF CREATION AT THE DOSSIER : 04/07/21
DATE OF ARRIVAL AT THE LABORATORY : 04/07/21 11:15 AM
EDITION'S DATE : 04/07/26
Time : 11:18:10

Name	: CERB
Location	: BAUGY

CERB
CHEMIN DE MONTIFAULT

18600 BAUGY

Collector	: LE CLIENT
Name	: DISTRIBUTION
Sampling site	: SITE N° A
Location	: BAUGY

WATER ANALYSIS RESULTS

BORDEREAU : 1 | DATE OF WATER SAMPLING : 04/07/21 | TIME : 08:41

Parameters	Results	Standard	Unity	Methods	Date .anal
Bacteriology					
Aerobic viable bacteria 22°C/ml	6		n/ml	EN ISO 6222	04/07/26
Aerobic viable bacteria 37°C/ml	4		n/ml	EN ISO 6222	04/07/23
Bact.et spores sulfito-rédu/100 ml	0		n/100ml	NF EN 26461-2	04/07/23
Coliform organisms/100 ml	0		n/100ml	NF EN ISO 9308-1	04/07/23
Enterococcus /100 ml-MS	0	0	n/100ml	NF EN ISO 7899-2	04/07/23
Escherichia-coli /100ml	0	0	n/100ml	NF EN ISO 9308-1	04/07/23

Observations : Compte tenu du milieu utilisé, seuls les clostridiums perfringens seront détectés dans l'analyse des bactéries sulfito-reducteurs

* As indicated by decree 89-3 and the followings

Applied 30/07/07

Responsible,

Christelle LESPRIT

Certificated by the French Health Ministry Page 1/1

[redacted]

Consumer Product Testing Co.

EST. 1975

FINAL REPORT

CLIENT: Creative Strategy, Inc.
High Park Nihonbashi Bldg. 4F
2-45-4 Nihonbashi-Hamacho
Chuo-ku, Tokyo 103-0007, Japan

SPONSOR: [redacted]

TEST: The MatTek Corporation EpiOcular™ Tissue Model *In Vitro* Toxicity Testing System

TEST ARTICLE: [redacted]

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

EXPERIMENT REFERENCE NO.: [redacted]

12/30/05

Steven Nitka
Vice President
Laboratory Director

70 New Dutch Lane • Fairfield, New Jersey 07004-2514 • (973) 808-7111 • Fax (973) 808-7234

[redacted]

Consumer Product Testing Co.

EST. 1975

QUALITY ASSURANCE UNIT STATEMENT

Study No.: [redacted]

The objective of the Quality Assurance Unit (QAU) is to monitor the conduct and reporting of nonclinical laboratory studies. This study has been performed under Good Laboratory Practice principles (including government regulations to the extent applicable) and in accordance with standard operating procedures and applicable standard protocols. The QAU maintains copies of study protocols and standard operating procedures and has inspected this study on the date listed below. The findings of this inspection may have been reported to management and the Study Director.

Date of data inspection: December 27, 2005

Quality Assurance:

Christine Hendricks 12/30/05
Signature/Date

'0 New Dutch Lane • Fairfield, New Jersey 07004-2514 • (973) 808-7111 • Fax (973) 808-7234
Clinical • Toxicology • Analytical Chemistry • Microbiology

Objective:

To evaluate the test article for irritancy potential utilizing the MatTek Corporation EpiOcular *in vitro* toxicity testing system.

Introduction:

"MatTek's patented EpiOcular corneal Model consists of normal, human-derived epidermal keratinocytes which have been cultured to form a stratified, squamous epithelium similar to that found in the cornea. The epidermal cells, which are cultured on specially prepared cell culture inserts using serum free medium, differentiate to form a multilayered structure which closely parallels the corneal epithelium . . . " This system " . . . provides a predictive, morphologically relevant *in vitro* means to assess ocular irritancy."[1]

EpiOcular, when used with the recommended cell metabolism assay, can quickly provide toxicological profiles. The procedure utilizes a water-soluble, yellow, tetrazolium salt (MTT {3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide}), which is reduced by succinate dehydrogenase in the mitochondria of viable cells to a purple, insoluble formazan derivative. Substances which damage this mitochondrial enzyme inhibit the reduction of the tetrazolium salt. The amount of MTT reduced by a culture is therefore proportional to the number of viable cells.

Test Article: [redacted]

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

Method:

The test article is not water soluble. As per MatTek's protocol, it was therefore dosed as received. After the appropriate tissue preparation, 100 microliters of the test article and the negative control (distilled water) were added to the Millicells containing the EpiOcular samples. The six (6) well plates containing the dosed EpiOcular samples were then incubated at 37°C, five (5)% carbon dioxide and $\geq$ 90% humidity.

[1]MatTek Corporation, 200 Homer Avenue, Ashland, Massachusetts 01721

Method (continued):

After the appropriate exposure period, each insert was individually removed from its plate and rinsed with phosphate buffered saline (PBS) to remove any residual material. Each was then rinsed a second and third time. Following the 3 rinses, each Millicell was submerged in 5 milliliters of assay media for 10 minutes, at room temperature. This final soak removed any residual, absorbed article. After the 10 minutes, excess liquid was shaken off and each EpiOcular tissue was placed into 300 microliters of MTT solution. The EpiOcular samples were then returned to the incubator.

After the three (3) hour MTT exposure, each insert was removed and gently rinsed with PBS to remove any residual MTT solution. Excess PBS was shaken from each of the inserts, which were then blotted on the bottom on paper towels. The inserts were then each placed into one (1) well of a 24 well extraction plate. Each insert was then immersed in two (2) milliliters of extraction, at room temperature, overnight. After the extraction procedure, the liquid within each insert was decanted back into the well from which it was taken. The remaining extractant solution was then agitated and a 200 microliter aliquot of each extract was removed for evaluation. A Dynatech MR 4000 Automatic Microplate Reader was used to determine the absorbance of each extract at 570nm. With the absorbance of the negative control (distilled water) defined as 100%, the percent absorbencies of the test article was determined. The percentages listed below directly correlate with the cell metabolism in the EpiOcular samples.

Results:

Article **(% & Exposure)**	**System**	**Percent Viability**	**Percent Inhibition**
[redacted] Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate			
(100% - 20 min.)	EpiOcular	77	23
(100% - 1 hr.)	EpiOcular	80	20
(100% - 4 hr.)	EpiOcular	81	19

When possible, using a semi-log scale, the percent viabilities for the article were plotted on the linear y axis versus the dosing time on the log x axis. By interpolation, the time at which the percent viability would be 50% was determined (ET-50). As a general guideline (provided by MatTek) the following equation can be used to estimate the rabbit Draize eye score:

Draize = -4.74 + 101.7/(ET-50)^0.5

Based on the literature (Kay, J.H. and Calandra, J.C., "Interpretation of eye irritation tests," *J. Soc. Cosmetic Chem.*, 13, 281-289 (1962)), the ocular irritancy estimated potential has been categorized by MatTek into the following groups, based on the Draize score:

Draize Score	Irritancy Classification	Example	EpiOcular ET-50 (min)
0-15	Non-irritating, Minimal	PEG-75 Lanolin, Tween 20	>256 – 26.5
15.1 – 25	Mild	3% Sodium Dodecyl Sulfate	<26.5 – 11.7
25.1 – 50	Moderate	5% Triton X-100	<11.7 – 3.45
50.1 – 110	Severe, Extreme	5% Benzalkonium Chloride	<3.45

Discussion:

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

Under the conditions of this test, the [redacted] article elicited *in vitro* results which indicate that its ET-50 is greater than 256 minutes. Therefore, at 100%, the test article's estimated Draize ocular irritation score is 0 with a "non-irritating" irritancy classification.

Conclusion:

Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate

Under the conditions of this test, the results indicate that the [redacted] test article, at 100%, has a "non-irritating" classification.

Professional personnel involved:

Steven Nitka, B.S.	-	Vice President Laboratory Director (Study Director)
Lillian Vazquez, B.S.	-	Laboratory Supervisor
Melissa Fiuza, B.S.	-	Technician
Christine Hendricks	-	Senior Quality Assurance Associate

[redacted]

SafePharm Laboratories

Dimer Dilinoleyl Dimer Dilinoleate

[redacted]

ACUTE EYE IRRITATION IN THE RABBIT

[redacted]

AUTHOR: A Sanders

[redacted]

ISSUED BY:

Safepharm Laboratories Limited
P.O. Box No. 45
DERBY
DE1 2BT
U.K.

Telephone: (01332) 792896

Facsimile: (01332) 799018

QUALITY ASSURANCE REPORT

This study type is classed as short-term. The standard test method for this study type ("General Study Plan" in OECD terminology) was reviewed for compliance once only on initial production. Inspection of the routine and repetitive procedures that constitute the study is carried out as a continuous process designed to encompass the major phases at or about the time this study was in progress.

This report has been audited by Safepharm Quality Assurance Unit, and is considered to be an accurate account of the data generated and of the procedures followed.

In each case, the outcome of QA evaluation is reported to the Study Director and Management on the day of evaluation. Audits of study documentation, and process inspections appropriate to the type and schedule of this study were as follows:

	14 January 2000	Standard Test Method Compliance Audit
	14 September 2000	Test Material Preparation
	13 September 2000	Animal Preparation
	13 September 2000	Dosing
	12 September 2000	Assessment of Response
§	31 October 2000	Draft Report Audit
§	Date of QA Signature	Final Report Audit

§ Evaluation specific to this study

..... DATE: ..... 2 MAR 2001 .....

For Safepharm Quality Assurance Unit*

***Authorised QA Signatures:**

Head of Department:	JR Pateman CBiol MIBiol DipRQA
Deputy Head of Department:	JM Crowther MIScT
Senior Audit Staff:	JV Johnson BSc; G Wren ONC; RJ Gilbert BSc

GLP COMPLIANCE STATEMENT

The work described was performed in compliance with UK GLP standards (Schedule 1, Good Laboratory Practice Regulations 1999 (SI 1999/3106)). These Regulations are in accordance with GLP standards published as OECD Principles on Good Laboratory Practice (revised 1997, ENV/MC/CHEM(98)17); and are in accordance with, and implement, the requirements of Directives 87/18/EEC (as amended by Directive 1999/11/EC) and 88/320/EEC (as amended by Directive 1999/12/EC).

These international standards are acceptable to the United States Environmental Protection Agency and Food and Drug Administration, and fulfil the requirements of 40 CFR Part 160, 40 CFR Part 792 and 21 CFR Part 58 (as amended).

This report fully and accurately reflects the procedures used and data generated.

..... DATE: 01 MAR 2001

A Sanders
Study Director

CONTENTS

[redacted]

ACUTE EYE IRRITATION IN THE RABBIT

SUMMARY

Introduction. The study was performed to assess the irritancy potential of the test material to the eye of the New Zealand White rabbit. The method was designed to meet the requirements of the following:

- OECD Guidelines for the Testing of Chemicals No. 405 "Acute Eye Irritation/Corrosion" (adopted 24 February 1987)
- Commission Directive 92/69/EEC Method B5 Acute Toxicity (Eye Irritation)
- Japanese Ministry of Health and Welfare, 1992

Result. A single application of the test material to the non-irrigated eye of three rabbits produced moderate conjunctival irritation. Treated eyes appeared normal at the 48-hour observation

Conclusion. The test material produced a maximum group mean score of 9.3 and was classified as a minimal irritant (Class 3 on a 1 to 8 scale) to the rabbit eye according to a modified Kay and Calandra classification system.

The test material did not meet the criteria for classification as irritant according to EU labelling regulations Commission Directive 93/21/EEC.

[redacted]

ACUTE EYE IRRITATION IN THE RABBIT

1. INTRODUCTION

The study was performed to assess the irritancy potential of the test material following a single application to the rabbit eye. The method was designed to meet the requirements of the following:

- OECD Guidelines for the Testing of Chemicals No. 405 "Acute Eye Irritation/Corrosion" (adopted 24 February 1987)
- Commission Directive 92/69/EEC Method B5 Acute Toxicity (Eye Irritation)
- Japanese Ministry of Health and Welfare, 1992

The albino rabbit has been shown to be a suitable model for this type of study and is recommended in the test method. The results of the study are believed to be of value in predicting the likely eye irritancy potential of the test material to man.

The study was performed between 16 October 2000 and 22 October 2000.

2. TEST MATERIAL

2.1 Description, Identification and Storage Conditions

Sponsor's identification	:	[redacted]
Description	:	pale yellow viscous liquid
Batch number	:	[redacted]
Date received	:	25 August 2000
Storage conditions	:	room temperature in the dark

Data relating to the identity, purity and stability of the test material are the responsibility of the Sponsor.

2.2 Preparation of Test Material

For the purpose of the study the test material was used as supplied.

The absorption of the test material was not determined.

2.3 Measurement of pH

The pH of a 10% v/v aqueous preparation of the test material was determined prior to commencement of the study and found to be approximately 8.0.

3. METHODS

3.1 Animals and Animal Husbandry

Three New Zealand White rabbits were supplied by David Percival Ltd, Moston, Sandbach, Cheshire, UK. At the start of the study the animals weighed 2.91 to 3.21 kg and were twelve to sixteen weeks old. After an acclimatisation period of at least five days each animal was given a number unique within the study which was written with a black indelible marker-pen on the inner surface of the ear and on the cage label.

The animals were individually housed in suspended metal cages. Free access to mains drinking water and food (STANRAB SQC Rabbit Diet, Special Diets Services Ltd, Witham, Essex, UK) was allowed throughout the study. The diet and drinking water were considered not to contain any contaminant of a level that might have affected the purpose or integrity of the study.

The temperature and relative humidity were set to achieve limits of 17 to 23°C and 30 to 70% respectively. Any occasional deviations from these targets were considered not to have affected the purpose or integrity of the study. The rate of air exchange was at least fifteen changes per hour and the lighting was controlled by a time switch to give twelve hours continuous light (06:00 to 18:00) and twelve hours darkness.

3.2 Procedure

Immediately before the start of the test, both eyes of the provisionally selected test rabbits were examined for evidence of ocular irritation or defect with the aid of a light source from a standard ophthalmoscope. Only animals free of ocular damage were used.

Initially, a single rabbit was treated. A volume of 0.1 ml of the test material, was placed into the conjunctival sac of the right eye, formed by gently pulling the lower lid away from the eyeball. The upper and lower eyelids were held together for about one second immediately after treatment, to prevent loss of the test material, and then released. The left eye remained untreated and was used for control purposes.

After consideration of the ocular responses produced in the first treated animal, two additional animals were treated.

Assessment of ocular damage/irritation was made approximately 1 hour and 24, 48 and 72 hours following treatment, according to the numerical evaluation given in Appendix 1, (from Draize J H (1977) "Dermal and Eye Toxicity Tests" In: Principles and Procedures for Evaluating the Toxicity of Household Substances, National Academy of Sciences, Washington DC p.48 to 49).

Any other ocular effects were also noted. Examination of the eye was facilitated by the use of the light source from a standard ophthalmoscope.

3.3 Interpretation of Results

The numerical values corresponding to each animal, tissue and observation time were recorded. The data relating to the conjunctivae were designated by the letters A (redness), B (chemosis) and C (discharge), those relating to the iris designated by the letter D and those relating to the cornea by the letters E (degree of opacity) and F (area of opacity). For each tissue the score was calculated as follows:

Score for conjunctivae = $(A + B + C) \times 2$

Score for iris = $D \times 5$

Score for cornea = $(E \times F) \times 5$

Using the numerical data obtained a modified version of the system described by Kay J H and Calandra J C, J. Soc. Cosmet. Chem., 1962 13 281-289 (see Appendix 2) was used to classify the ocular irritancy potential of the test material. This was achieved by adding together the scores for the cornea, iris and conjunctivae for each time point for each rabbit. The group means of the total scores for each observation were calculated. The highest of these group means (the maximum group mean score) together with the persistence of the reactions enabled classification of the eye irritancy potential of the test material.

If evidence of irreversible ocular damage is noted, the test material will be classified as corrosive to the eye.

4. ARCHIVES

Unless instructed otherwise by the Sponsor, all original data and the final report will be retained in the Safepharm archives for five years, after which instructions will be sought as to further retention or disposal.

5. RESULTS

Individual and group mean scores for ocular irritation are given in Table 1 and Table 2.

No corneal or iridial effects were noted during the study.

Moderate conjunctival irritation was noted in all treated eyes one hour after treatment with minimal conjunctival irritation at the 24-hour observation.

Treated eyes appeared normal at the 48-hour observation.

6. CONCLUSION

The test material produced a maximum group mean score of 9.3 and was classified as a MINIMAL IRRITANT (CLASS 3 ON A 1 TO 8 SCALE) to the rabbit eye according to a modified Kay and Calandra classification system.

The test material did not meet the criteria for classification as irritant according to EU labelling regulations Commission Directive 93/21/EEC.

[redacted]: ACUTE EYE IRRITATION IN THE RABBIT

Table 1 Individual Scores and Individual Total Scores for Ocular Irritation

Rabbit Number and Sex (Bodyweight kg)	221 Female (3.21)				200 Female (3.14)				201 Female (2.91)			
Time After Treatment	1 hour	24 hours	48 hours	72 hours	1 hour	24 hours	48 hours	72 hours	1 hour	24 hours	48 hours	72 hours
CORNEA												
E = Degree of Opacity	0	0	0	0	0	0	0	0	0	0	0	0
F = Area of Opacity	0	0	0	0	0	0	0	0	0	0	0	0
Score (E x F) x 5	0	0	0	0	0	0	0	0	0	0	0	0
IRIS												
D	0	0	0	0	0	0	0	0	0	0	0	0
Score (D x 5)	0	0	0	0	0	0	0	0	0	0	0	0
CONJUNCTIVAE												
A = Redness	2	1	0	0	2	1	0	0	2	1	0	0
B = Chemosis	1	1	0	0	1	0	0	0	1	0	0	0
C = Discharge	2	1	0	0	1	0	0	0	2	1	0	0
Score (A + B + C) x 2	10	6	0	0	8	2	0	0	10	4	0	0
Total Score	10	6	0	0	8	2	0	0	10	4	0	0

[redacted]: ACUTE EYE IRRITATION IN THE RABBIT

Table 2 Individual Total Scores And Group Mean Scores For Ocular Irritation

Rabbit Number and Sex	Individual Total Scores At:			
	1 Hour	24 Hours	48 Hours	72 Hours
221 Female	10	6	0	0
200 Female	8	2	0	0
201 Female	10	4	0	0
Group Total	28	12	0	0
Group Mean Score	9.3	4.0	0.0	0.0

Appendix 1 Draize Scale for Scoring Ocular Irritation

1. CONJUNCTIVAE

(A) Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)

Vessels normal	0
Vessels definitely injected above normal	1
More diffuse, deeper crimson red, individual vessels not easily discernible	2
Diffuse beefy red	3

(B) Chemosis

No swelling	0
Any swelling above normal (includes nictitating membrane)	1
Obvious swelling with partial eversion of lids	2
Swelling with lids about half closed	3
Swelling with lids half closed to completely closed	4

(C) Discharge

No discharge	0
Any amount different from normal (does not include small amounts observed in inner canthus of normal animals)	1
Discharge with moistening of the lids and hairs just adjacent to lids	2
Discharge with moistening of the lids and hairs a considerable area around the eye	3

THE TOTAL SCORE = (A + B + C) x 2 **MAXIMUM TOTAL = 20**

2. IRIS

(D) Values

Normal	0
Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof) iris still reacting to light (sluggish reaction is positive)	1
No reaction to light, haemorrhage, gross destruction (any or all of these)	2

THE TOTAL SCORE = D x 5 **MAXIMUM TOTAL = 10**

3. CORNEA

(E) Degree of Opacity (most dense area used)

No opacity	0
Scattered or diffuse areas, details of iris clearly visible	1
Easily discernible translucent areas, details of iris slightly obscured	2
Opalescent areas, no details of iris visible, size of pupil barely discernible	3
Opaque, iris not discernible through the opacity	4

(F) Area of Cornea Involved

One quarter (or less) but not zero	1
Greater than one quarter but less than half	2
Greater than half but less than three quarters	3
Greater than three quarters, up to whole area	4

THE TOTAL SCORE = (E x F) x 5 **MAXIMUM TOTAL = 80**

MAXIMUM TOTAL SCORE POSSIBLE = 110

[redacted]: ACUTE EYE IRRITATION IN THE RABBIT

Appendix 2 Modified Kay and Calandra Interpretation of Eye Irritation Test

MAXIMUM MEAN SCORE		PERSISTENCE OF SCORE	DESCRIPTION RATING (AND CLASS)	
0.0 to 0.5	Group mean total score at 24 hours = 0		Non-irritant	(1)
	Group mean total score at 24 hours > 0		Practically non-irritant	(2)
0.5 to 2.5	Group mean total score at 24 hours = 0		Practically non-irritant	(2)
	Group mean total score at 24 hours > 0		Minimal irritant	(3)
2.5 to 15	Group mean total score at 48 hours = 0		Minimal irritant	(3)
	Group mean total score at 48 hours > 0		Mild irritant	(4)
15 to 25	Group mean total score at 72 hours = 0		Mild irritant	(4)
	Group mean total score at 72 hours > 0		Moderate irritant	(5)
25 to 50	Group mean total score at 7 days 20 or less	More than half of the individual total scores at 7 days 10 or less	Moderate irritant	(5)
		More than half of the individual total scores at 7 days > 10 but no individual total score at 7 days > 30	Moderate irritant	(5)
		More than half of the individual total scores at 7 days > 10 and any individual score at 7 days > 30	Severe irritant	(6)
	Group mean total score at 7 days > 20		Severe irritant	(6)
50 to 80	Group mean total score at 7 days 40 or less	More than half of the individual total scores at 7 days 30 or less	Severe irritant	(6)
		More than half of the individual total scores at 7 days > 30 but no individual total scores at 7 days > 60	Severe irritant	(6)
		More than half of the individual total scores at 7 days > 30 and individual total score at 7 days > 60	Very severe irritant	(7)
	Group mean total score at 7 days > 40		Very severe irritant	(7)
80 to 100	Group mean total score at 7 days 80 or less	More than half of the individual total scores at 7 days 60 or less	Very severe irritant	(7)
		More than half of the individual total scores at 7 days > 60 but no individual total score at 7 days > 100	Very severe irritant	(7)
		More than half of the individual total scores at 7 days > 60 and individual total score at 7 days > 100	Extremely severe irritant	(8)
	Group mean total score at 7 days > 80		Extremely severe irritant	(8)
100 to 110	Group mean total score at 7 days 80 or less		Very severe irritant	(7)
	Group mean total score at 7 days > 80		Extremely severe irritant	(8)

Appendix 3 Statement of GLP Compliance in Accordance with Directive 88/320/EEC

THE DEPARTMENT OF HEALTH OF THE GOVERNMENT OF THE UNITED KINGDOM

GOOD LABORATORY PRACTICE

STATEMENT OF COMPLIANCE IN ACCORDANCE WITH DIRECTIVE 88/320 EEC

LABORATORY

SafePharm Laboratories Ltd
Shardlow Business Park
London Road
Shardlow
Derbyshire
DE72 2GD

TEST TYPE

Analytical Chemistry
Environmental Fate
Environmental Toxicity
Mutagenicity
Phys/Chem Tests
Toxicology

DATE OF INSPECTION
28 February 2000

A general inspection for compliance with the Principles of Good Laboratory Practice was carried out at the above laboratory as part of UK GLP Compliance Programme.

At the time of the inspection no deviations were found of sufficient magnitude to affect the validity of non-clinical studies performed at these facilities.

Roger G. Alexander
26/4/00

Dr. Roger G. Alexander
Head. UK GLP Monitoring Authority

[redacted]

Consumer Product Testing Co.

EST. 1975

FINAL REPORT

CLIENT: Creative Strategy, Inc.
High Park Nihonbashi Bldg. 4F
2-45-4 Nihonbashi-Hamacho
Chuo-ku, Tokyo 103-0007, Japan

SPONSOR: [redacted]

TEST: The MatTek Corporation EpiOcular™ Tissue Model *In Vitro* Toxicity Testing System

TEST ARTICLE: [redacted]

Dimer Dilinoleyl Dimer Dilinoleate

EXPERIMENT REFERENCE NO.: [redacted]

12/30/05

Steven Nitka
Vice President
Laboratory Director

70 New Dutch Lane • Fairfield, New Jersey 07004-2514 • (973) 808-7111 • Fax (973) 808-7234

[redacted]

Consumer Product Testing Co.

EST. 1975

QUALITY ASSURANCE UNIT STATEMENT

Study No.: [redacted]

The objective of the Quality Assurance Unit (QAU) is to monitor the conduct and reporting of nonclinical laboratory studies. This study has been performed under Good Laboratory Practice principles (including government regulations to the extent applicable) and in accordance with standard operating procedures and applicable standard protocols. The QAU maintains copies of study protocols and standard operating procedures and has inspected this study on the date listed below. The findings of this inspection may have been reported to management and the Study Director.

Date of data inspection: December 27, 2005

Quality Assurance:

Christine Hendricks 12/30/05
Signature/Date

0 New Dutch Lane • Fairfield, New Jersey 07004-2514 • (973) 808-7111 • Fax (973) 808-7234
Clinical • Toxicology • Analytical Chemistry • Microbiology

Objective:

To evaluate the test article for irritancy potential utilizing the MatTek Corporation EpiOcular *in vitro* toxicity testing system.

Introduction:

"MatTek's patented EpiOcular corneal Model consists of normal, human-derived epidermal keratinocytes which have been cultured to form a stratified, squamous epithelium similar to that found in the cornea. The epidermal cells, which are cultured on specially prepared cell culture inserts using serum free medium, differentiate to form a multilayered structure which closely parallels the corneal epithelium . . . " This system " . . . provides a predictive, morphologically relevant *in vitro* means to assess ocular irritancy."[1]

EpiOcular, when used with the recommended cell metabolism assay, can quickly provide toxicological profiles. The procedure utilizes a water-soluble, yellow, tetrazolium salt (MTT {3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide}), which is reduced by succinate dehydrogenase in the mitochondria of viable cells to a purple, insoluble formazan derivative. Substances which damage this mitochondrial enzyme inhibit the reduction of the tetrazolium salt. The amount of MTT reduced by a culture is therefore proportional to the number of viable cells.

Test Article: [redacted]

Dimer Dilinoleyl Dimer Dilinoleate

Method:

The test article is not water soluble. As per MatTek's protocol, it was therefore dosed as received. After the appropriate tissue preparation, 100 microliters of the test article and the negative control (distilled water) were added to the Millicells containing the EpiOcular samples. The six (6) well plates containing the dosed EpiOcular samples were then incubated at 37°C, five (5)% carbon dioxide and ≥ 90% humidity.

[1]MatTek Corporation, 200 Homer Avenue, Ashland, Massachusetts 01721

Method (continued):

After the appropriate exposure period, each insert was individually removed from its plate and rinsed with phosphate buffered saline (PBS) to remove any residual material. Each was then rinsed a second and third time. Following the 3 rinses, each Millicell was submerged in 5 milliliters of assay media for 10 minutes, at room temperature. This final soak removed any residual, absorbed article. After the 10 minutes, excess liquid was shaken off and each EpiOcular tissue was placed into 300 microliters of MTT solution. The EpiOcular samples were then returned to the incubator.

After the three (3) hour MTT exposure, each insert was removed and gently rinsed with PBS to remove any residual MTT solution. Excess PBS was shaken from each of the inserts, which were then blotted on the bottom on paper towels. The inserts were then each placed into one (1) well of a 24 well extraction plate. Each insert was then immersed in two (2) milliliters of extraction, at room temperature, overnight. After the extraction procedure, the liquid within each insert was decanted back into the well from which it was taken. The remaining extractant solution was then agitated and a 200 microliter aliquot of each extract was removed for evaluation. A Dynatech MR 4000 Automatic Microplate Reader was used to determine the absorbance of each extract at 570nm. With the absorbance of the negative control (distilled water) defined as 100%, the percent absorbencies of the test article was determined. The percentages listed below directly correlate with the cell metabolism in the EpiOcular samples.

Results:

Article (% & Exposure)	System	**Percent Viability**	**Percent Inhibition**
[redacted] Dimer Dilinoleyl Dimer Dilinoleate			
(100% - 20 min.)	EpiOcular	63	37
(100% - 1 hr.)	EpiOcular	58	42
(100% - 4 hr.)	EpiOcular	57	43

When possible, using a semi-log scale, the percent viabilities for the article were plotted on the linear y axis versus the dosing time on the log x axis. By interpolation, the time at which the percent viability would be 50% was determined (ET-50). As a general guideline (provided by MatTek) the following equation can be used to estimate the rabbit Draize eye score:

Draize = -4.74 + 101.7/(ET-50)^0.5

Based on the literature (Kay, J.H. and Calandra, J.C., "Interpretation of eye irritation tests," *J. Soc. Cosmetic Chem.*, 13, 281-289 (1962)), the ocular irritancy estimated potential has been categorized by MatTek into the following groups, based on the Draize score:

Draize Score	Irritancy Classification	Example	EpiOcular ET-50 (min)
0-15	Non-irritating, Minimal	PEG-75 Lanolin, Tween 20	>256 – 26.5
15.1 – 25	Mild	3% Sodium Dodecyl Sulfate	<26.5 – 11.7
25.1 – 50	Moderate	5% Triton X-100	<11.7 – 3.45
50.1 – 110	Severe, Extreme	5% Benzalkonium Chloride	<3.45

Discussion:

Dimer Dilinoleyl Dimer Dilinoleate

Under the conditions of this test, the [redacted] article elicited *in vitro* results which indicate that its ET-50 is greater than 256 minutes. Therefore, at 100%, the test article's estimated Draize ocular irritation score is 0 with a "non-irritating" irritancy classification.

Conclusion:

Dimer Dilinoleyl Dimer Dilinoleate

Under the conditions of this test, the results indicate that the [redacted] test article, at 100%, has a "non-irritating" classification.

Professional personnel involved:

Steven Nitka, B.S.	-	Vice President Laboratory Director (Study Director)
Lillian Vazquez, B.S.	-	Laboratory Supervisor
Melissa Fiuza, B.S.	-	Technician
Christine Hendricks	-	Senior Quality Assurance Associate

[redacted]

[redacted] [redacted]

Dimer Dilinoleyl Dimer Dilinoleate

Eye Irritation Assessment of [redacted] by the Short Time Exposure *In Vitro* Test Method (STE-Method)

[redacted]

November 23, 2021

[redacted] [redacted]

Dimer Dilinoleyl Dimer Dilinoleate

Eye Irritation Assessment of [redacted]
by the Short Time Exposure In Vitro Test Method (STE-method)

1. Summary

Cytotoxicity testing of the test subject against the short time exposure in vitro test method (STE method), an alternative test for eye irritation, was performed on [redacted]

After exposure to 5% and 0.05% solutions of [redacted], the cell viability (CV) was found to be 93.1% and 89.5%, respectively, and the predictive model was evaluated as non-classified (not classified as an eye irritant) in the UN GHS category.

2. Purpose

Dimer Dilinoleyl Dimer Dilinoleate

To evaluate the eye irritation potential of [redacted] by the STE-method.

3. Study dates

Experimental Start Date: Nobember 5, 2021
Experimental Completion Date: Nobember 16, 2021

4. Test material

Test article: [redacted] Dimer Dilinoleyl Dimer Dilinoleate
Manufacturer: [redacted]
Lot. No.: [redacted]
Description: Liquid

Positive control: Sodium lauryl sulphate (SLS, CAS No. 151-21-3)
Manufacturer: FUJIFILM Wako Pure Chemical Corporation
Lot. No.: LEH9543
Description: Solid

5. Test system

Cell type: Epithelial cell line from rabbit cornea purchased from ATCC®
Medium: 50–100 unit/mL penicillin and 50–100 μg/mL streptomycin (FUJIFILM Wako Pure Chemical Corporation) were added to Eagle's minimum essential medium (FUJIFILM Wako Pure Chemical Corporation) containing 10% foetal bovine serum.

6. Other reagents

Reagent name	CAS No.	Lot. No.	Manufacturer
Dulbecco's phosphate-buffered saline	—	—	FUJIFILM Wako Pure Chemical Corporation
Normal saline	—	K1A82	Otsuka Pharmaceutical Co., Ltd.
DMSO	67-68-5	TPG3220	Sigma-Aldrich Co. LLC
Mineral oil	8042-47-5	A2797	Sigma-Aldrich Co. LLC
3-(4,5-Dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium	298-93-1	2339839	Thermo Fisher Scientific K.K.

[redacted] [redacted]

bromide (MTT)			
Isopropanol	67-63-0	DLN0933	FUJIFILM Wako Pure Chemical Corporation
Hydrochloric acid	7647-01-0	V5R6666	Nacalai Tesque

7. Test method

Tests were performed according to the OECD Test Guideline No. 491 STE-Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage.

7-1. Selection of the sample solvent

The sample solvent was determined to be mineral oil for the test article according to the following flow diagram:

When 5% (w/w) solution is prepared with saline, does it dissolve or is it suspended uniformly?
YES → Saline
↓ NO

When 5% (w/w) solution is prepared with 5% DMSO in saline, does it dissolve or is it suspended uniformly?
YES → 5% DMSO in saline
↓ NO

When 5% (w/w) solution is prepared with mineral oil, does it dissolve or is it suspended uniformly?
YES → Mineral oil
↓ NO

Without testing

7-2. Pre-culture of cells (Study Day 1)

SIRC were treated with trypsin-EDTA, which was then removed by centrifugation, and the cell counts were seeded into a 96-well plate in 3.0×10^3 cells/well/200 µL medium (when exposed on day five) or at a cell density of 6.0×10^3 cells/well/200 µL medium (when exposed on day four).

7-3. Test substance exposure and measurement of cell viability (day four or five)

7-3-1. Preparation of test substance

The test substance was dissolved or suspended uniformly in the selected solvent at 5% (w/w) concentration and further diluted serially to a 0.05% concentration.

7-3-2. Preparation of positive control (0.01% SLS in saline)

SLS (1% (w/w)) in saline was prepared and diluted to form a 0.01% (v/v) solution.

7-3-3. Preparation of the MTT solution

[redacted]

First, 0.5 mg MTT/mL of cellular medium was prepared and filtered through a 0.22 μM filter. Then, it was stored in darkness until use.

7-3-4. Test sample exposure and measurement of CV

The corrugated 96-well plate medium was removed on an aspirator and exposed to SIRC for 5 min in 200 μL of test article solutions, positive controls, and test vehicle (vehicle control). After exposure, the test article solutions were removed, washed three times with 200 μL of phosphate-buffered saline (-), and the MTT-containing medium was added at 200 μL/well and allowed to stand for 2 h in a carbonate incubator (37°C, 5% CO_2, 100% humidity). The MTT-containing medium was removed, and 200 μL of MTT extract was added and left at room temperature for 1 h. The 570 nm absorbance (OD570) of the extracts was measured using a microplate reader.

8. Cell viability calculations and predictive models

8-1. Calculation of CV

CV was calculated from OD570 of the test samples according to the equation below. Incidentally, it was subjected to three-well/sample in each experiment, and the mean OD570 of the three wells was used to calculate CV.

$$CV\% = \frac{\text{OD570 (Test Sample) - OD570 Blanks}}{\text{OD570 (Vehicle Control) - OD570 Blanks}} \times 100$$

If the CV of the test sample-treated group was negative, the survival rate was set to zero.

8-2. Judgment

Three independent exposure experiments were performed according to the above procedure, and the mean of three CVs was used for the final determination. Based on the results of CV at 5% and 0.05% concentrations, eye irritation ranking was performed according to figure 1.

Cell viability		**UN GHS category**
5% Concentration	**0.05% Concentration**	
> 70%	> 70%	No category
≤ 70%	> 70%	No prediction can be made
≤ 70%	≤ 70%	Category1

Figure 1. UN GHS eye irritation category predicted in STE method

[redacted] [redacted]

9. Results and discussion Dimer Dilinoleyl Dimer Dilinoleate

CVs at 5% and 0.05% levels in [redacted] and positive control groups are shown in the table below. From the predicted model of Fig. 1, [redacted] were predicted to be "No category" as eye irritants based on the UN GHS classification. Dimer Dilinoleyl Dimer Dilinoleate

		CV (%)			CV mean of three trials (%)	Standard deviation
Dimer Dilinoleyl Dimer Dilinoleate [redacted] [redacted]	5% Concentration	104.4	92.0	83.0	93.1	10.7
	0.05% Concentration	90.1	96.6	81.9	89.5	7.3
Positive control sodium lauryl sulphate	0.01% Concentration	51.7	40.1	17.9	36.5	17.1

10. Study criteria

The results of this study were approved because the following conditions were met:

a. The OD570 of the operation target group was ≥ 0.3 after blank subtraction.
b. The CV was ≥ 80% in the vehicle control group relative to the manipulated control group.
c. The CV of the positive control group was 21.1%–62.3%.
d. The standard deviation of CV in three independent experiments was < 15%.

* [redacted]

[redacted]

SafePharm Laboratories

Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate

[redacted]

ACUTE EYE IRRITATION IN THE RABBIT

[redacted]

AUTHOR: A Sanders

[redacted]

TEST FACILITY:

Safepharm Laboratories Limited
P.O. Box No. 45
DERBY
DE1 2BT
U.K.

Telephone: (01332) 792896

Facsimile: (01332) 799018

QUALITY ASSURANCE REPORT

This study type is classed as short-term. The standard test method for this study type ("General Study Plan" in OECD terminology) was reviewed for compliance once only on initial production. Inspection of the routine and repetitive procedures that constitute the study is carried out as a continuous process designed to encompass the major phases at or about the time this study was in progress.

This report has been audited by Safepharm Quality Assurance Unit, and is considered to be an accurate account of the data generated and of the procedures followed.

In each case, the outcome of QA evaluation is reported to the Study Director and Management on the day of evaluation. Audits of study documentation, and process inspections appropriate to the type and schedule of this study were as follows:

	28 March 2002	Standard Test Method Compliance Audit
	17 June 2002	Test Material Preparation
	17 June 2002	Animal Preparation
	17 June 2002	Dosing
	05 June 2002	Assessment of Response
§	31 July 2002	Draft Report Audit
§	Date of QA Signature	Final Report Audit

§ Evaluation specific to this study

..... G. Wren ..... DATE: 14 OCT 2002 .....

For Safepharm Quality Assurance Unit*

***Authorised QA Signatures:**

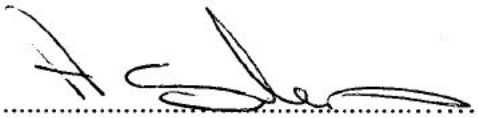
Head of Department:	JR Pateman CBiol MIBiol DipRQA FRQA
Deputy Head of Department:	JM Crowther MIScT MRQA
Senior Audit Staff:	JV Johnson BSc MRQA; G Wren ONC MRQA; R Hurst MRQA

GLP COMPLIANCE STATEMENT

The work described was performed in compliance with UK GLP standards (Schedule 1, Good Laboratory Practice Regulations 1999 (SI 1999/3106)). These Regulations are in accordance with GLP standards published as OECD Principles on Good Laboratory Practice (revised 1997, ENV/MC/CHEM(98)17); and are in accordance with, and implement, the requirements of Directives 87/18/EEC (as amended by Directive 1999/11/EC) and 88/320/EEC (as amended by Directive 1999/12/EC).

These international standards are acceptable to the Regulatory agencies of the following countries: Australia, Austria, Belgium, Canada, the Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Republic of Korea, Luxembourg, Mexico, The Netherlands, New Zealand, Norway, Poland, Portugal, Slovenia, Spain, Sweden, Switzerland, Turkey, the United Kingdom, and the United States of America.

This report fully and accurately reflects the procedures used and data generated.



..... DATE: 10 OCT 2002

A Sanders
Study Director

CONTENTS

[redacted]

ACUTE EYE IRRITATION IN THE RABBIT

SUMMARY

Introduction. The study was performed to assess the irritancy potential of the test material to the eye of the New Zealand White rabbit. The method was designed to meet the requirements of the following:

- OECD Guidelines for the Testing of Chemicals No. 405 "Acute Eye Irritation/Corrosion" (adopted 24 February 1987)
- Commission Directive 92/69/EEC Method B5 Acute Toxicity (Eye Irritation)

Result. A single application of the test material to the non-irrigated eye of three rabbits produced moderate conjunctival irritation. All treated eyes appeared normal at the 48-hour observation.

Conclusion. The test material produced a maximum group mean score of 10.0 and was classified as a minimal irritant (Class 3 on a 1 to 8 scale) to the rabbit eye according to a modified Kay and Calandra classification system.

The test material did not meet the criteria for classification as irritant according to EU labelling regulations Commission Directive 93/21/EEC.

[redacted]

ACUTE EYE IRRITATION IN THE RABBIT

1. INTRODUCTION

The study was performed to assess the irritancy potential of the test material following a single application to the rabbit eye. The method was designed to meet the requirements of the following:

- OECD Guidelines for the Testing of Chemicals No. 405 "Acute Eye Irritation/Corrosion" (adopted 24 February 1987)
- Commission Directive 92/69/EEC Method B5 Acute Toxicity (Eye Irritation)

The albino rabbit has been shown to be a suitable model for this type of study and is recommended in the test method. The results of the study are believed to be of value in predicting the likely eye irritancy potential of the test material to man.

The study was performed between 18 June 2002 and 30 June 2002.

2. TEST MATERIAL

2.1 Description, Identification and Storage Conditions

Sponsor's identification	:	[redacted]
Description	:	pale yellow/brown paste
Batch number	:	[redacted]
Date received	:	05 June 2002
Storage conditions	:	room temperature in the dark

Data relating to the identity, purity and stability of the test material are the responsibility of the Sponsor.

2.2 Preparation of Test Material

For the purpose of the study the test material was used as supplied.

The absorption of the test material was not determined.

2.3 Measurement of pH

The pH of test material was determined prior to commencement of the study and found to be as follows:

Preparation	pH Measurement
10% w/w aqueous preparation of the test material	approximately 5.0

3. METHODS

3.1 Animals and Animal Husbandry

Three New Zealand White rabbits were supplied by David Percival Ltd, Moston, Sandbach, Cheshire, UK. At the start of the study the animals were in the weight range of 2.0 to 3.5 kg and were twelve to twenty weeks old. After an acclimatisation period of at least five days each animal was given a number unique within the study which was written with a black indelible marker-pen on the inner surface of the ear and on the cage label.

The animals were individually housed in suspended metal cages. Free access to mains drinking water and food (Certified Rabbit Diet (Code 5322) supplied by PMI Nutrition International, Nottingham, UK) was allowed throughout the study. The diet and drinking water were considered not to contain any contaminant of a level that might have affected the purpose or integrity of the study.

The temperature and relative humidity were set to achieve limits of 17 to 23°C and 30 to 70% respectively. Any occasional deviations from these targets were considered not to have affected the purpose or integrity of the study. The rate of air exchange was at least fifteen changes per hour and the lighting was controlled by a time switch to give twelve hours continuous light (06:00 to 18:00) and twelve hours darkness.

The animals were provided with environmental enrichment items which were considered not to contain any contaminant of a level that might have affected the purpose or integrity of the study.

3.2 Procedure

Immediately before the start of the test, both eyes of the provisionally selected test rabbits were examined for evidence of ocular irritation or defect with the aid of a light source from a standard ophthalmoscope. Only animals free of ocular damage were used.

Initially, a single rabbit was treated. A volume of 0.1 ml of the test material was placed into the conjunctival sac of the right eye, formed by gently pulling the lower lid away from the eyeball. The upper and lower eyelids were held together for about one second immediately after treatment, to prevent loss of the test material, and then released. The left eye remained untreated and was used for control purposes. Immediately after administration of the test material, an assessment of the initial pain reaction was made according to the six point scale shown in Appendix 1.

After consideration of the ocular responses produced in the first treated animal, two additional animals were treated.

Assessment of ocular damage/irritation was made approximately 1 hour and 24, 48 and 72 hours following treatment, according to the numerical evaluation given in Appendix 2, (from Draize J H (1977) "Dermal and Eye Toxicity Tests" In: Principles and Procedures for Evaluating the Toxicity of Household Substances, National Academy of Sciences, Washington DC p.48 to 49).

Any other ocular effects were also noted. Examination of the eye was facilitated by the use of the light source from a standard ophthalmoscope.

3.3 Interpretation of Results

The numerical values corresponding to each animal, tissue and observation time were recorded. The data relating to the conjunctivae were designated by the letters A (redness), B (chemosis) and C (discharge), those relating to the iris designated by the letter D and those relating to the cornea by the letters E (degree of opacity) and F (area of cornea involved). For each tissue the score was calculated as follows:

Score for conjunctivae	=	(A + B + C) x 2
Score for iris	=	D x 5
Score for cornea	=	(E x F) x 5

Using the numerical data obtained a modified version of the system described by Kay J H and Calandra J C, J. Soc. Cosmet. Chem., 1962 13 281-289 (see Appendix 3) was used to classify the ocular irritancy potential of the test material. This was achieved by adding together the scores for the cornea, iris and conjunctivae for each time point for each rabbit. The group means of the total scores for each observation were calculated. The highest of these group means (the maximum group mean score) together with the persistence of the reactions enabled classification of the eye irritancy potential of the test material.

If evidence of irreversible ocular damage is noted, the test material will be classified as corrosive to the eye.

4. ARCHIVES

Unless instructed otherwise by the Sponsor, all original data and the final report will be retained in the Safepharm archives for five years, after which instructions will be sought as to further retention or disposal.

5. RESULTS

Individual and group mean scores for ocular irritation are given in Table 1 and Table 2.

No corneal or iridial effects were noted during the study.

Moderate conjunctival irritation was noted in all treated eyes one hour after treatment with minimal conjunctival irritation at the 24-hour observation.

All treated eyes appeared normal at the 48-hour observation.

6. CONCLUSION

The test material produced a maximum group mean score of 10.0 and was classified as a MINIMAL IRRITANT (CLASS 3 ON A 1 TO 8 SCALE) to the rabbit eye according to a modified Kay and Calandra classification system.

The test material did not meet the criteria for classification as irritant according to EU labelling regulations Commission Directive 93/21/EEC.

[redacted]: ACUTE EYE IRRITATION IN THE RABBIT

Table 1 Individual Scores and Individual Total Scores for Ocular Irritation

Rabbit Number and Sex	IPR = 1				IPR = 1				IPR = 1			
	17 Male				160 Male				161 Male			
Time After Treatment	1 Hour	24 Hours	48 Hours	72 Hours	1 Hour	24 Hours	48 Hours	72 Hours	1 Hour	24 Hours	48 Hours	72 Hours
CORNEA												
E = Degree of Opacity	0	0	0	0	0	0	0	0	0	0	0	0
F = Area of Cornea Involved	0	0	0	0	0	0	0	0	0	0	0	0
Score (E x F) x 5	0	0	0	0	0	0	0	0	0	0	0	0
IRIS												
D	0	0	0	0	0	0	0	0	0	0	0	0
Score (D x 5)	0	0	0	0	0	0	0	0	0	0	0	0
CONJUNCTIVAE												
A = Redness	2	1	0	0	2	1	0	0	2	1	0	0
B = Chemosis	1	0	0	0	1	0	0	0	1	0	0	0
C = Discharge	2	1	0	0	2	1	0	0	2	1	0	0
Score (A + B + C) x 2	10	4	0	0	10	4	0	0	10	4	0	0
Total Score	10	4	0	0	10	4	0	0	10	4	0	0

IPR = Initial pain reaction

[redacted]: ACUTE EYE IRRITATION IN THE RABBIT

Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate

Table 2 Individual Total Scores And Group Mean Scores For Ocular Irritation

Rabbit Number and Sex	Individual Total Scores At:			
	1 Hour	24 Hours	48 Hours	72 Hours
17 Male	10	4	0	0
160 Male	10	4	0	0
161 Male	10	4	0	0
Group Total	30	12	0	0
Group Mean Score	10.0	4.0	0.0	0.0

[redacted]: ACUTE EYE IRRITATION IN THE RABBIT

Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate

Appendix 1 Initial Pain Reaction

When the material is instilled in the eye there may be an initial local pain reaction. The reaction will be graded as follows:

Class	Reaction by Animal	Descriptive Rating
0	No response	No initial pain
1	A few blinks only, normal within one or two minutes	Practically no initial pain
2	Rabbit blinks and tries to open eye, but reflex closes it	Slight initial pain
3	Rabbit holds eye shut and puts pressure on lids, may rub eye with paw	Moderate initial pain
4	Rabbit holds eye shut vigorously, may squeal	Severe initial pain
5	Rabbit holds eye shut vigorously, may squeal, claw at eye, jump and try to escape	Very severe initial pain

There is often no correlation between the initial pain and the subsequent eye irritation.

[redacted]: ACUTE EYE IRRITATION IN THE RABBIT

Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate

Appendix 2 Draize Scale for Scoring Ocular Irritation

1. CONJUNCTIVAE

(A) Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)

Vessels normal	0
Vessels definitely injected above normal	1
More diffuse, deeper crimson red, individual vessels not easily discernible	2
Diffuse beefy red	3

(B) Chemosis

No swelling	0
Any swelling above normal (includes nictitating membrane)	1
Obvious swelling with partial eversion of lids	2
Swelling with lids about half closed	3
Swelling with lids half closed to completely closed	4

(C) Discharge

No discharge	0
Any amount different from normal (does not include small amounts observed in inner canthus of normal animals)	1
Discharge with moistening of the lids and hairs just adjacent to lids	2
Discharge with moistening of the lids and hairs a considerable area around the eye	3

THE TOTAL SCORE = (A + B + C) x 2 **MAXIMUM TOTAL = 20**

2. IRIS

(D) Values

Normal	0
Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof) iris still reacting to light (sluggish reaction is positive)	1
No reaction to light, haemorrhage, gross destruction (any or all of these)	2

THE TOTAL SCORE = D x 5 **MAXIMUM TOTAL = 10**

3. CORNEA

(E) Degree of Opacity (most dense area used)

No opacity	0
Scattered or diffuse areas, details of iris clearly visible	1
Easily discernible translucent areas, details of iris slightly obscured	2
Opalescent areas, no details of iris visible, size of pupil barely discernible	3
Opaque, iris not discernible through the opacity	4

(F) Area of Cornea Involved

One quarter (or less) but not zero	1
Greater than one quarter but less than half	2
Greater than half but less than three quarters	3
Greater than three quarters, up to whole area	4

THE TOTAL SCORE = (E x F) x 5 **MAXIMUM TOTAL = 80**

MAXIMUM TOTAL SCORE POSSIBLE = 110

[redacted]: ACUTE EYE IRRITATION IN THE RABBIT

Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate

Appendix 3 Modified Kay and Calandra Interpretation of Eye Irritation Test

MAXIMUM MEAN SCORE		PERSISTENCE OF SCORE	DESCRIPTION RATING (AND CLASS)	
0.0 to 0.5	Group mean total score at 24 hours = 0		Non-irritant	(1)
	Group mean total score at 24 hours > 0		Practically non-irritant	(2)
0.5 to 2.5	Group mean total score at 24 hours = 0		Practically non-irritant	(2)
	Group mean total score at 24 hours > 0		Minimal irritant	(3)
2.5 to 15	Group mean total score at 48 hours = 0		Minimal irritant	(3)
	Group mean total score at 48 hours > 0		Mild irritant	(4)
15 to 25	Group mean total score at 72 hours = 0		Mild irritant	(4)
	Group mean total score at 72 hours > 0		Moderate irritant	(5)
25 to 50	Group mean total score at 7 days 20 or less	More than half of the individual total scores at 7 days 10 or less	Moderate irritant	(5)
		More than half of the individual total scores at 7 days > 10 but no individual total score at 7 days > 30	Moderate irritant	(5)
		More than half of the individual total scores at 7 days > 10 and any individual score at 7 days > 30	Severe irritant	(6)
	Group mean total score at 7 days > 20		Severe irritant	(6)
50 to 80	Group mean total score at 7 days 40 or less	More than half of the individual total scores at 7 days 30 or less	Severe irritant	(6)
		More than half of the individual total scores at 7 days > 30 but no individual total scores at 7 days > 60	Severe irritant	(6)
		More than half of the individual total scores at 7 days > 30 and individual total score at 7 days > 60	Very severe irritant	(7)
	Group mean total score at 7 days > 40		Very severe irritant	(7)
80 to 100	Group mean total score at 7 days 80 or less	More than half of the individual total scores at 7 days 60 or less	Very severe irritant	(7)
		More than half of the individual total scores at 7 days > 60 but no individual total score at 7 days > 100	Very severe irritant	(7)
		More than half of the individual total scores at 7 days > 60 and individual total score at 7 days > 100	Extremely severe irritant	(8)
	Group mean total score at 7 days > 80		Extremely severe irritant	(8)
100 to 110	Group mean total score at 7 days 80 or less		Very severe irritant	(7)
	Group mean total score at 7 days > 80		Extremely severe irritant	(8)

Appendix 4 Statement of GLP Compliance in Accordance with Directive 88/320/EEC

THE DEPARTMENT OF HEALTH OF THE GOVERNMENT OF THE UNITED KINGDOM

GOOD LABORATORY PRACTICE

STATEMENT OF COMPLIANCE
IN ACCORDANCE WITH DIRECTIVE 88/320 EEC

LABORATORY

SafePharm Laboratories Ltd
Shardlow Business Park
London Road
Shardlow
Derbyshire
DE72 2GD

TEST TYPE

Analytical Chemistry
Environmental Fate
Environmental Toxicity
Mutagenicity
Phys/Chem Tests
Toxicology

DATE OF INSPECTION
28 February 2000

A general inspection for compliance with the Principles of Good Laboratory Practice was carried out at the above laboratory as part of UK GLP Compliance Programme.

At the time of the inspection no deviations were found of sufficient magnitude to affect the validity of non-clinical studies performed at these facilities.

Roger G. Alexander
26/4/00

Dr. Roger G. Alexander
Head, UK GLP Monitoring Authority

[redacted]

SAFEPHARM LABORATORIES LTD

[redacted]

Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate

ACUTE EYE IRRITATION IN THE RABBIT

SPL PROJECT NUMBER: 274/079

I verify that this is an exact copy of the original report which is located in the Archives of Safepharm Laboratories Ltd., Derby, UK.

..... DATE: 15 OCT 2002

A Sanders
Study Director

[redacted]

Phytosteryl Isostearyl Dimer Dilinoleate

[redacted]

ACUTE EYE IRRITATION

TEST IN THE RABBIT

[redacted]

AUTHOR: A Sanders

[redacted]

ISSUED BY:

Safepharm Laboratories Limited
P.O. Box No. 45
DERBY
DE1 2BT
UK

Telephone: DERBY (01332) 792896

Facsimile: (01332) 799018

[redacted]

[redacted]

QUALITY ASSURANCE REPORT

The routine inspection of short term studies at Safepharm is carried out as a continuous process designed to encompass all major phases of each study type once per month. Inspection findings are reported to Management/Study Directors on the day of inspection in each case. The standard test method for each study type ("Standardised Study Plan" in OECD terminology) is inspected for compliance once only on initial issue of the document.

This report has been audited by Safepharm Quality Assurance Unit. It is considered to be an accurate account of the data generated and of the procedures followed.

Inspection and audit occasions relevant to this study are as follows:

23 November 1998	Standard Test Method Compliance Audit
31 January 2000	Test Material Preparation
05 January 2000	Animal Preparation
05 January 2000	Dosing
05, 25 January 2000	Assessment of Response
05 February 2000	Draft Report Audit
Date of QA Signature	Final Report Audit

..... DATE: 22 FEB 2000

For Safepharm Quality Assurance Unit*

---

*Authorised QA Signatures:

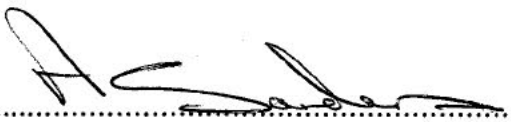
Head of Department: JR Pateman CBiol MIBiol DipRQA
Deputy Head of Department: JM Crowther MIScT
Senior Audit Staff: JV Johnson BSc; G Wren ONC; RJ Gilbert BSc

GLP COMPLIANCE STATEMENT

I, the undersigned, hereby declare that the objectives laid down in the protocol were achieved and as nothing occurred to adversely affect the quality or integrity of the study, I consider the data generated to be valid. This report fully and accurately reflects the procedures used and data generated.

The work described was performed in compliance with UK GLP standards (Schedule 1, Good Laboratory Practice Regulations 1999 (SI 1999/3106)). These Regulations are in accordance with GLP standards published as OECD Principles on Good Laboratory Practice (revised 1997, ENV/MC/CHEM(98)17); and are in accordance with, and implement, the requirements of Directives 87/18/EEC (as amended by Directive 1999/11/EC) and 88/320/EEC (as amended by Directive 1999/12/EC).

These international standards are acceptable to the United States Environmental Protection Agency and Food and Drug Administration, and fulfil the requirements of 40 CFR Part 160, 40 CFR Part 792 and 21 CFR Part 58 (as amended).



..... DATE: 21 FEB 2000

A Sanders
Study Director
for Safepharm Laboratories

CONTENTS

SUMMARY

STUDY SPONSOR : [redacted]

STUDY TITLE : ACUTE EYE IRRITATION TEST IN THE RABBIT

TEST MATERIAL : [redacted]

Phytosteryl Isostearyl Dimer Dilinoleate

1. A study was performed to assess the irritancy potential of the test material to the eye of the New Zealand White rabbit. The method used followed that described in the OECD Guidelines for Testing of Chemicals No. 405 "Acute Eye Irritation/Corrosion" (adopted 24 February 1987) and Method B5 of Commission Directive 92/69/EEC (which constitutes Annex V of Council Directive 67/548/EEC).

   The results may be used as a basis for classification and labelling under Annex VI of Council Directive 67/548/EEC (as adapted to technical progress by Commission Directive 93/21/EEC) relating to the classification, packaging and labelling of dangerous substances.

2. A single instillation of the test material to the non-irrigated eye of three rabbits produced minimal to moderate conjunctival irritation. Two treated eyes appeared normal at the 24-hour observation and the remaining treated eye appeared normal at the 48-hour observation.

3. The test material produced a maximum group mean score of 6.7 and was classified as a minimal irritant (Class 3 on a 1 to 8 scale) to the rabbit eye according to a modified Kay and Calandra classification system.

   The test material did not meet the criteria for classification as irritant according to EU labelling regulations. No symbol and risk phrase are required.

Phytosteryl Isostearyl Dimer Dilinoleate

[redacted]

ACUTE EYE IRRITATION
TEST IN THE RABBIT

1. INTRODUCTION

The study was performed to assess the irritancy potential of the test material following a single instillation to the rabbit eye. The method used followed the recommendations of the OECD Guidelines for Testing of Chemicals No. 405 "Acute Eye Irritation/Corrosion" (adopted 24 February 1987) and Method B5 of Commission Directive 92/69/EEC (which constitutes Annex V of Council Directive 67/548/EEC).

The results may be used as a basis for classification and labelling under Annex VI of Council Directive 67/548/EEC (as adapted to technical progress by Commission Directive 93/21/EEC) relating to the classification, packaging and labelling of dangerous substances.

The test system was chosen because the rabbit has been shown to be a suitable model for this type of study and is recommended in the test method. The results of the study are believed to be of value in predicting the likely eye irritancy potential of the test material to man.

The study was performed between 04 January 2000 and 09 January 2000.

2. TEST MATERIAL AND EXPERIMENTAL PREPARATION

2.1 Description, Identification and Storage Conditions

Sponsor's identification	:	[redacted]
Batch number	:	[redacted]
Date received	:	22 November 1999
Description	:	yellow turbid viscous liquid
Storage conditions	:	room temperature in the dark

Data relating to the identity, purity and stability of the test material are the responsibility of the Sponsor.

2.2 Experimental Preparation

For the purpose of this study the test material was used as supplied.

3. METHODS

3.1 Animals and Animal Husbandry

Three New Zealand White rabbits, supplied by David Percival Ltd, Moston, Sandbach, Cheshire, UK, were used. At the start of the study the animals weighed 2.75 to 3.25 kg and were twelve to sixteen weeks old. After a minimum acclimatisation period of five days each animal was given a number unique within the study which was written with a black indelible marker-pen on the inner surface of the ear and on the cage label.

The animals were individually housed in suspended metal cages. Free access to mains drinking water and food (STANRAB SQC Rabbit Diet, Special Diets Services Ltd, Witham, Essex, UK) was allowed throughout the study.

The temperature and relative humidity were set to achieve limits of 17 to 23°C and 30 to 70% respectively. Occasional deviations from these targets were considered not to have affected the purpose or integrity of the study. The rate of air exchange was approximately fifteen changes per hour and the lighting was controlled by a time switch to give twelve hours continuous light and twelve hours darkness.

3.2 Procedure

Immediately before the start of the test, both eyes of the provisionally selected test rabbits were examined for evidence of ocular irritation or defect with the aid of a light source from a standard ophthalmoscope. Animals showing evidence of ocular lesions were rejected and replaced.

One rabbit was initially treated. A volume of 0.1 ml of the test material was instilled into the conjunctival sac of the right eye, formed by gently pulling the lower lid away from the eyeball. The upper and lower eyelids were held together for about one second immediately after instillation, to prevent loss of the test material, and then released. The left eye remained untreated and was used for control purposes. Immediately after administration of the test material, an assessment of the initial pain reaction was made.

After consideration of the ocular responses produced in the first treated animal, two additional animals were treated.

Assessment of ocular damage/irritation was made approximately 1 hour and 24, 48 and 72 hours following treatment, according to the numerical evaluation given in Appendix I, (from Draize J H (1977) "Dermal and Eye Toxicity Tests" In: Principles and Procedures for Evaluating the Toxicity of Household Substances, National Academy of Sciences, Washington DC p.48 to 49).

Any other ocular effects were also noted. Examination of the eye was facilitated by the use of the light source from a standard ophthalmoscope.

3.3 Interpretation of Results

3.3.1 Classification According to a Modified Version of the Kay and Calandra System

The numerical values corresponding to each animal, tissue and observation time were recorded. The data relating to the conjunctivae were designated by the letters A (redness), B (chemosis) and C (discharge), those relating to the iris designated by the letter D and those relating to the cornea by the letters E (degree of opacity) and F (area of opacity). For each tissue the score was calculated as follows:

Score for conjunctivae	=	(A + B + C) x 2
Score for iris	=	D x 5
Score for cornea	=	(E x F) x 5

Using the numerical data obtained a modified version of the system described by Kay J H and Calandra J C, J. Soc. Cosmet. Chem., 1962 13 281-289 (see Appendix II) was used to classify the ocular irritancy potential of the test material. This was achieved by adding together the scores for the cornea, iris and conjunctivae for each time point for each rabbit. The group means of the total scores for each observation were calculated. The highest of these group means (the maximum group mean score) together with the persistence of the reactions enabled classification of the eye irritancy potential of the test material.

If any rabbit shows irreversible ocular damage the test material will be classified as corrosive to the eye.

3.3.2 Interpretation According to Annex VI of Council Directive 67/548/EEC, Relating to the Classification, Packaging and Labelling of Dangerous Substances

The results were interpreted according to Commission Directive 93/21/EEC which adapts Council Directive 67/548/EEC on the regulations relating to the classification, packaging and labelling of dangerous substances, as follows:

Interpretation According to Annex VI Section 3.2.6, Irritant

Substances and preparations shall be classified as irritant and assigned the symbol "Xi", the indication of danger "irritant" and the appropriate risk phrase in accordance with the following criteria:

R 36 "IRRITATING TO EYES"

- Substances and preparations which, when applied to the eye of the animal, cause significant ocular lesions which occur within 72 hours after exposure and which persist for at least 24 hours.

Ocular lesions are significant if the mean scores of the eye irritation test cited in Annex V have any of the following values:

- cornea opacity equal to or greater than 2 but less than 3.
- iris lesion equal to or greater than 1 but not greater than 1.5.
- redness of the conjunctivae equal to or greater than 2.5.
- oedema of the conjunctivae (chemosis) equal to or greater than 2.

Or, in the case where the Annex V test has been completed using three animals, if the lesions on two or more animals are equivalent to any of the above values except that for iris lesion, the value should be equal to or greater than 1 but less than 2, and for redness of the conjunctivae the value should be equal to or greater than 2.5.

In both cases all scores at each of the reading times (24, 48 and 72 hours) for an effect should be used in calculating the respective mean values.

- Substances or preparations which cause significant ocular lesions, based on practical experience in humans.

- Organic peroxides except where evidence to the contrary is available.

R 41 "RISK OF SERIOUS DAMAGE TO EYES"

- Substances and preparations which, when applied to the eye of the animal cause severe ocular lesions which occur within 72 hours after exposure and which persist for at least 24 hours.

Ocular lesions are severe if the means of the scores of the eye irritation test in Annex V have any of the following values:

- cornea opacity equal to or greater than 3.

- iris lesion greater than 1.5.

The same shall be the case where the test has been completed using three animals if these lesions, on two or more animals, have any of the following values:

- cornea opacity equal to or greater than 3.

- iris lesion equal to 2.

In both cases all scores at each of the reading times (24, 48 and 72 hours) for an effect should be used in calculating the respective mean values.

Ocular lesions are also severe when they are still present at the end of the observation time.

Ocular lesions are also severe if the substance or preparation causes irreversible colouration of the eyes.

- Substances and preparations which cause severe ocular lesions, based on practical experience in humans.

4. ARCHIVES

Unless instructed otherwise by the Sponsor, all original data and the final report will be retained in the Safepharm archives for a period of five years. After this period, the Sponsor's instructions will be sought.

5. RESULTS

Individual and group mean scores for ocular irritation are given in Tables 1 and 2. The individual mean scores as required for the EU labelling regulations are presented in Table 3.

No corneal or iridial effects were noted during the study.

Moderate conjunctival irritation was noted in one treated eye with minimal conjunctival irritation in two treated eyes one hour after treatment. Minimal conjunctival irritation was noted in one treated eye at the 24-hour observation.

Two treated eyes appeared normal at the 24-hour observation and the remaining treated eye appeared normal at the 48-hour observation.

6. CONCLUSION Phytosteryl Isostearyl Dimer Dilinoleate

The test material, [redacted] produced a maximum group mean score of 6.7 and was classified as a MINIMAL IRRITANT (CLASS 3 ON A 1 TO 8 SCALE) to the rabbit eye according to a modified Kay and Calandra classification system.

The test material did not produce positive criteria in any rabbit according to the EU labelling regulations. No symbol and risk phrase are therefore required.

[redacted]: ACUTE EYE IRRITATION TEST IN THE RABBIT

TABLE 1

INDIVIDUAL SCORES AND INDIVIDUAL TOTAL SCORES FOR OCULAR IRRITATION

Rabbit Number and Sex (Bodyweight kg)	IPR = 1				IPR = 1				IPR = 1			
	6 Female (2.75)				99 Female (3.25)				98 Female (2.87)			
Time After Treatment	1 hr	24 hr	48 hr	72 hr	1 hr	24 hr	48 hr	72 hr	1 hr	24 hr	48 hr	72 hr
CORNEA												
E = Degree of Opacity	0	0	0	0	0	0	0	0	0	0	0	0
F = Area of Opacity	0	0	0	0	0	0	0	0	0	0	0	0
Score (E x F) x 5	0	0	0	0	0	0	0	0	0	0	0	0
IRIS												
D	0	0	0	0	0	0	0	0	0	0	0	0
Score (D x 5)	0	0	0	0	0	0	0	0	0	0	0	0
CONJUNCTIVAE												
A = Redness	2	1	0	0	1	0	0	0	1	0	0	0
B = Chemosis	1	0	0	0	1	0	0	0	0	0	0	0
C = Discharge	2	1	0	0	1	0	0	0	1	0	0	0
Score (A + B + C) x 2	10	4	0	0	6	0	0	0	4	0	0	0
Total Score	10	4	0	0	6	0	0	0	4	0	0	0

Key: hr = hour(s) IPR = initial pain reaction

Phytosteryl Isostearyl Dimer Dilinoleate

[redacted]: ACUTE EYE IRRITATION TEST IN THE RABBIT

TABLE 2

INDIVIDUAL TOTAL SCORES AND GROUP MEAN SCORES FOR OCULAR IRRITATION

Rabbit Number and Sex	Individual Total Scores At:			
	1 Hour	24 Hours	48 Hours	72 Hours
6 Female	10	4	0	0
99 Female	6	0	0	0
98 Female	4	0	0	0
Group Total	20	4	0	0
Group Mean Score	6.7	1.3	0.0	0.0

[redacted]: ACUTE EYE IRRITATION TEST IN THE RABBIT

TABLE 3

INDIVIDUAL AND MEAN SCORES FOR CORNEA, IRIS AND CONJUNCTIVAE REQUIRED FOR EU LABELLING REGULATIONS

Rabbit Number and Sex (Bodyweight kg)	Time After Treatment	Corneal Opacity	Iridial Inflammation	Conjunctival Redness	Conjunctival Chemosis
6 Female	24 Hours	0	0	1	0
	48 Hours	0	0	0	0
(2.75)	72 Hours	0	0	0	0
Total		0	0	1	0
Mean		0.0	0.0	0.3	0.0
99 Female	24 Hours	0	0	0	0
	48 Hours	0	0	0	0
(3.25)	72 Hours	0	0	0	0
Total		0	0	0	0
Mean		0.0	0.0	0.0	0.0
98 Female	24 Hours	0	0	0	0
	48 Hours	0	0	0	0
(2.87)	72 Hours	0	0	0	0
Total		0	0	0	0
Mean		0.0	0.0	0.0	0.0

APPENDICES

APPENDIX I

DRAIZE SCALE FOR SCORING OCULAR IRRITATION

1. CONJUNCTIVAE

(A) Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)

Vessels normal	0
Vessels definitely injected above normal	1
More diffuse, deeper crimson red, individual vessels not easily discernible	2
Diffuse beefy red	3

(B) Chemosis

No swelling	0
Any swelling above normal (includes nictitating membrane)	1
Obvious swelling with partial eversion of lids	2
Swelling with lids about half closed	3
Swelling with lids half closed to completely closed	4

(C) Discharge

No discharge	0
Any amount different from normal (does not include small amounts observed in inner canthus of normal animals)	1
Discharge with moistening of the lids and hairs just adjacent to lids	2
Discharge with moistening of the lids and hairs a considerable area around the eye	3

THE TOTAL SCORE = (A + B + C) x 2 **MAXIMUM TOTAL = 20**

2. IRIS

(D) Values

Normal	0
Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof) iris still reacting to light (sluggish reaction is positive)	1
No reaction to light, haemorrhage, gross destruction (any or all of these)	2

THE TOTAL SCORE = D x 5 **MAXIMUM TOTAL = 10**

3. CORNEA

(E) Degree of Opacity (most dense area used)

No opacity	0
Scattered or diffuse areas, details of iris clearly visible	1
Easily discernible translucent areas, details of iris slightly obscured	2
Opalescent areas, no details of iris visible, size of pupil barely discernible	3
Opaque, iris not discernible through the opacity	4

(F) Area of Cornea Involved

One quarter (or less) but not zero	1
Greater than one quarter but less than half	2
Greater than half but less than three quarters	3
Greater than three quarters, up to whole area	4

THE TOTAL SCORE = (E x F) x 5 **MAXIMUM TOTAL = 80**

MAXIMUM TOTAL SCORE POSSIBLE = 110

APPENDIX II

MODIFIED KAY AND CALANDRA INTERPRETATION OF EYE IRRITATION TEST

MAXIMUM MEAN SCORE		PERSISTENCE OF SCORE	DESCRIPTION RATING (AND CLASS)	
0.0 to 0.5	Group mean total score at 24 hours = 0		Non-irritant	(1)
	Group mean total score at 24 hours > 0		Practically non-irritant	(2)
0.5 to 2.5	Group mean total score at 24 hours = 0		Practically non-irritant	(2)
	Group mean total score at 24 hours > 0		Minimal irritant	(3)
2.5 to 15	Group mean total score at 48 hours = 0		Minimal irritant	(3)
	Group mean total score at 48 hours > 0		Mild irritant	(4)
15 to 25	Group mean total score at 72 hours = 0		Mild irritant	(4)
	Group mean total score at 72 hours > 0		Moderate irritant	(5)
25 to 50	Group mean total score at 7 days 20 or less	More than half of the individual total scores at 7 days 10 or less	Moderate irritant	(5)
		More than half of the individual total scores at 7 days > 10 but no individual total score at 7 days > 30	Moderate irritant	(5)
		More than half of the individual total scores at 7 days > 10 and any individual score at 7 days > 30	Severe irritant	(6)
	Group mean total score at 7 days > 20		Severe irritant	(6)
50 to 80	Group mean total score at 7 days 40 or less	More than half of the individual total scores at 7 days 30 or less	Severe irritant	(6)
		More than half of the individual total scores at 7 days > 30 but no individual total scores at 7 days > 60	Severe irritant	(6)
		More than half of the individual total scores at 7 days > 30 and individual total score at 7 days > 60	Very severe irritant	(7)
	Group mean total score at 7 days > 40		Very severe irritant	(7)
80 to 100	Group mean total score at 7 days 80 or less	More than half of the individual total scores at 7 days 60 or less	Very severe irritant	(7)
		More than half of the individual total scores at 7 days > 60 but no individual total score at 7 days > 100	Very severe irritant	(7)
		More than half of the individual total scores at 7 days > 60 and individual total score at 7 days > 100	Extremely severe irritant	(8)
	Group mean total score at 7 days > 80		Extremely severe irritant	(8)
100 to 110	Group mean total score at 7 days 80 or less		Very severe irritant	(7)
	Group mean total score at 7 days > 80		Extremely severe irritant	(8)

APPENDIX III

THE DEPARTMENT OF HEALTH OF THE GOVERNMENT OF THE UNITED KINGDOM

GOOD LABORATORY PRACTICE

STATEMENT OF COMPLIANCE
IN ACCORDANCE WITH DIRECTIVE 88/320 EEC

LABORATORY	TEST TYPE
SafePharm Laboratories Ltd. Shardlow Business Park London Road Shardlow Derbyshire DE72 2GD	Analytical Chemistry Environmental Fate Environmental Toxicity Mutagenicity Phys/Chem Tests Toxicology

DATE OF INSPECTION

23rd March 1998

A general inspection for compliance with the Principles of Good Laboratory Practice was carried out at the above laboratory as part of UK GLP Compliance Programme.

At the time of the inspection no deviations were found of sufficient magnitude to affect the validity of non-clinical studies performed at these facilities.

21st July 1998

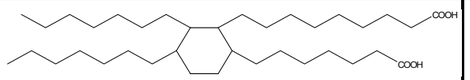
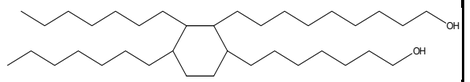
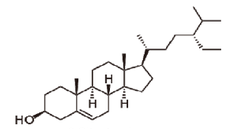
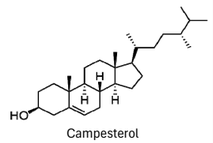
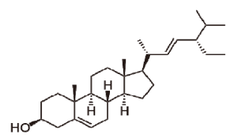
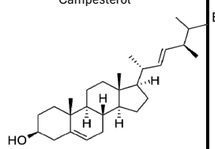
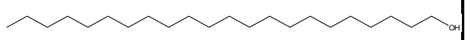
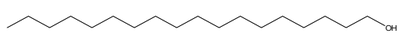
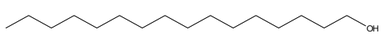
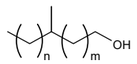
UK GLP Monitoring Authority

The information of dimer dilinoleate ingredients

INCI	Chemical structure	UV spectra	Method of Manufacture	Impurities	Safety data (Test guideline (Test conditions), Test concentration, Test date, Results)	Reference
Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	R3－OCO－R1(－COO－R2－OCO－R1)n－COO－R3 R1; Dimer Acid residue R2; Dimer Diol residue R3; Phytosterol, Behenyl Alcohol, Isostearyl Alcohol residue	Almost no UV absorption (Data attached)	Raw materials→Reaction→Purification →Filtration→Packaging	Hevy metal: 20ppm Max. Arsenic: 2ppm Max.	Acute Oral Toxicity: OECD TG423, 100%, 2004.05.05, LD50>2000mg/kg Primary Skin Irritation: OECD TG404, 100%, 2004.05.05, NON IRRITANT Skin Sensitizetion: OECD TG406, 25%, 2004.03.30, NON-SENSITIZER Eye Irritation: OECD TG405, 100%, 2004.11.27, PRACTICALLY NON IRRITANT Eye Irritation: Eye irritation study using EpiOcular corneal model, 100%, 2005.12.30, NON IRRITANT Mutagenicity: OECD TG471, 100%, 2004.06.11, NEGATIVE Genotoxicity: Chromosome aberration test using mammalian cell culture, 100%, 2010.10.11, NEGATIVE Human 24hr Closed Patch: 45 subjects, 100%, 2004.02.26, NEGATIVE RIPT (Repeated Insult Patch Test): 42 subjects, 100%, 2024.11.05, NEGATIVE	Unpublished data
Bis-Behenyl/Phytosteryl Dimer Dilinoleate	$R_2－OCO－R_1－COO－R_2$ R1 : Dimer acid residue R2 : Phytosterol residue or Behenyl alcohol residue	Almost no UV absorption (Data attached)	Raw materials→Reaction→Purification →Filtration→Packaging	Hevy metal: 20ppm Max. Arsenic: 2ppm Max.	Mutagenicity: Ames Test, 100%, 2019.03.05, NEGATIVE	Unpublished data
Dimer Dilinoleyl Dimer Dilinoleate	$HO\text{-}R1\text{-}(OCO\text{-}R2\text{-}COO\text{-}R1)_n\ OH$ R1 : Dimer diol residue	Almost no UV absorption (Data attached)	Raw materials→Reaction→Purification →Filtration→Packaging	Hevy metal: 20ppm Max. Arsenic: 2ppm Max.	Acute Oral Toxicity: OECD TG423, 100%, 2001.03.02, LD50>2500mg/kg Primary Skin Irritation: OECD TG404, 100%, 2001.03.02, MILD IRRITANT Skin Sensitizetion: OECD TG406, 100%, 2001.03.02, NON-SENSITIZER Eye Irritation: OECD TG405, 100%, 2001.03.02, MINIMAL IRRITANT Eye Irritation: Eye irritation study using EpiOcular corneal model, 100%, 2005.12.30, NON IRRITANT Eye Irritation: OECD TG491, 100%, 2021.11.16, NO CATEGORY Mutagenicity: OECD TG471, 100%, 2001.01.01, NEGATIVE Human Closed Patch: 42 subjects, 100%, 2001.02.16, NEGATIVE	Unpublished data
Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate	$R_2－OCO－R_1－COO－R_2$ R1 : Dimer acid residue R2 : Phytosterol residue, Behenyl alcohol residue, Stearyl alcohol residue, Cetryl alcohol residue or Isostearyl alcohol residue	Almost no UV absorption (Data attached)	Raw materials→Reaction→Purification →Filtration→Packaging	Hevy metal: 20ppm Max. Arsenic: 2ppm Max.	Acute Oral Toxicity: OECD TG423, 100%, 2003.05.27, LD50>2500mg/kg Primary Skin Irritation: OECD TG404, 100%, 2002.08.30, NON IRRITANT Cumulative skin irritation study using guinea pigs: 100%, 2004.05.10, NON IRRITANT Skin Sensitizetion: OECD TG406, 100%, 2002.10.16, NON-SENSITIZER Eye Irritation: OECD TG405, 100%, 2002.10.14, MINIMAL IRRITANT Mutagenicity: OECD TG471, 100%, 2003.05.01, NEGATIVE Genotoxicity: Chromosome aberration test using mammalian cell culture, 100%, 2004.05.10, NEGATIVE Human 24hr Closed Patch: 45 subjects, 100%, 2002.10.31, NEGATIVE	Unpublished data
Phytosteryl Isostearyl Dimer Dilinoleate	$R_2－OCO－R_1－COO－R_2$ R1 : Dimer acid residue R2 : Phytosterol residue or Isostearyl alcohol residue	Almost no UV absorption (Data attached)	Raw materials→Reaction→Purification →Filtration→Packaging	Hevy metal: 20ppm Max. Arsenic: 2ppm Max.	Acute Oral Toxicity: OECD TG423, 100%, 2000.02.22, LD50> 2000 mg/kg Primary Skin Irritation: OECD TG404, 100%, 2000.02.22, MILD IRRITANT Cumulative skin irritation study using guinea pigs: 100%, 2000.06.27, PRACTICALLY NON IRRITANT Skin Sensitizetion: OECD TG406, 100%, 2000.02.22, NON-SENSITIZER Eye Irritation: OECD TG405, 100%, 2000.02.22, MINIMAL IRRITANT Mutagenicity: OECD TG471, 100%, 2000.07.25, NEGATIVE Genotoxicity: Chromosome aberration test using mammalian cell culture, 100%, 2001.02.28, NEGATIVE Human 24hr Closed Patch: 45 subjects, 100%, 1999.12.21, NEGATIVE	Unpublished data

General information of dimer dilinoleate	Refer to the appendix for the representative structures of each raw material.		The ester of dimer acid and alcohol can be synthesized by directly esterifying dimer acid and alcohol at high temperatures (180-240° C) while removing the water produced in the reaction. Additionally, the reaction temperature can be lowered by using acid or alkaline catalysts. The catalysts are removed after the reaction by neutralizing with an acid or alkali wash. Antioxidants may be added to the resulting ester to improve its stability.	Heavy metals are regulated to be 20 ppm Max, and arsenic is regulated to be 2 ppm Max. Additionally, trace amounts of free alcohol, free fatty acids, and salts of free fatty acids derived from raw materials may be present. The safety information regarding Phytosterol , Behenyl alcohol, Stearyl alcohol, Cetryl alcohol and Isostearyl alcohol is available in the CIR report(Ref.1, Ref.2.). The safety information regarding Dimer acid is available in the CIR report(Ref3.). Additionally, for safety information on dimer derivatives, there is the following CIR report.(Ref.4)		Ref.1 : Safety Assessment of Phytosterols as Used in Cosmetics Ref.2 : Final Report on the Safety Assessment of Cetearyl Alcohol, Cetyl Alcohol, Isostearyl Alcohol, Myristyl Alcohol, and Behenyl Alcohol Ref.3 : Safety Assessment of Fatty Acids & Fatty Acid Salts as Used in Cosmetics Ref.4 : Amended Safety Assessment of Dialkyl Dimer Dilinoleates as Used in Cosmetics

Appendix

	Representative structure	M.W.
Dimer acid (Hydrogenated dimer dilinoleic acid)		568
Dimer diol (Hydrogenated dimer dilinoleyl alcohol)		536
Phytosterol	 β-Sitosterol  Campesterol  Stigmasterol  Brassicasterol	β－Sitosterol：414.7 Stigmasterol：412.7 Campesterol：400.7 Brassicasterol：398.7 Average：about 409
Behenyl alcohol		326.6
Stearyl alcohol		270.5
Cetryl alcohol		242.4
Isostearyl alcohol	 n+m=14	270.5

Ocular irritation studies

INCI	Safety data (Test guideline (Test conditions), Test concentration, Test date, Results, Summary)	Reference
Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	1. OECD TG405, 100%, 2004.11.27, PRACTICALLY NON IRRITANT In the test using three rabbits in accordance with OECD TG405, mild redness was observed in all cases after 1 hour, but no further reactions were observed after 72 hours of observation, and the substance was therefore determined to be non-irritating. 2. Eye irritation study using EpiOcular corneal model, 100%, 2005.12.30, NON IRRITANT Based on the literature (Kay, J.H., "Interpretation of eye irritation tests," J. Soc. Cosmetic Chem., 13, 281-289 (1962), the eye irritation test was performed using the EpiOcular corneal model. As a result, the substance was determined to be non-irritating because the ET-50 (incubation time at which cell viability reaches 50%) was greater than 256 minutes.	Attached test report : O-1(TG405), O-2(EpiOcular) (Unpublished data)
Dimer Dilinoleyl Dimer Dilinoleate	3. OECD TG405, 100%, 2001.03.02, MINIMAL IRRITANT In the study using three rabbits in accordance with OECD TG405, moderate conjunctival irritation was observed in all cases after 1 hour, but no reaction was observed after 48 hours, so the substance was judged to be minimally irritating. 4. Eye irritation study using EpiOcular corneal model, 100%, 2005.12.30, NON IRRITANT Based on the literature (Kay, J.H., "Interpretation of eye irritation tests," J. Soc. Cosmetic Chem., 13, 281-289 (1962), the eye irritation test was performed using the EpiOcular corneal model. As a result, the substance was determined to be non-irritating because the ET-50 (incubation time at which cell viability reaches 50%) was greater than 256 minutes. 5. OECD TG491, 100%, 2021.11.16, NO CATEGORY In the eye irritation test conducted in accordance with OECD TG 491, cell viability exceeded the standard value of 70% at all test concentrations, and the substance was therefore determined to be not categorized as an eye irritant.	Attached test report : O-3(TG405), O-4(EpiOcular), O-5(TG491) (Unpublished data)
Phytosteryl/Isostearyl/Cetyl/Stearyl/ Behenyl Dimer Dilinoleate	6. OECD TG405, 100%, 2002.10.14, MINIMAL IRRITANT In the study using three rabbits in accordance with OECD TG405, moderate conjunctival irritation was observed in all cases after 1 hour, but no reaction was observed after 48 hours, so the substance was judged to be minimally irritating.	Attached test report : O-6(TG405) (Unpublished data)
Phytosteryl Isostearyl Dimer Dilinoleate	7. OECD TG405, 100%, 2000.02.22, MINIMAL IRRITANT In the study using three rabbits in accordance with OECD TG405, moderate conjunctival irritation was observed in one rabbit after 1 hour and minimal conjunctival irritation was observed in two rabbits; however, all reactions disappeared in two rabbits after 24 hours and in the remaining rabbit after 48 hours, and therefore the substance was judged to be minimally irritating.	Attached test report : O-7(TG405) (Unpublished data)

Acute Oral Toxicity studies

INCI	Safety data (Test guideline (Test conditions), Test concentration, Test date, Results)	Reference
Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	1. Acute Oral Toxicity: OECD TG423, 100%, 2004.05.05, LD50>2000mg/kg	Attached test report : A-1(TG423) (Unpublished data)
Dimer Dilinoleyl Dimer Dilinoleate	2. Acute Oral Toxicity: OECD TG423, 100%, 2001.03.02, LD50>2500mg/kg	Attached test report : A-2(TG423) (Unpublished data)
Phytosteryl/Isostearyl/Cetyl/Stearyl/ Behenyl Dimer Dilinoleate	3. Acute Oral Toxicity: OECD TG423, 100%, 2003.05.27, LD50>2500mg/kg	Attached test report : A-3(TG423) (Unpublished data)
Phytosteryl Isostearyl Dimer Dilinoleate	4. Acute Oral Toxicity: OECD TG423, 100%, 2000.02.22, LD50> 2000 mg/kg	Attached test report : A-4(TG423) (Unpublished data)

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: November 14, 2025

SUBJECT: Dimer Dilinoleate Ingredients – Structure Clarification for Previously Submitted Information

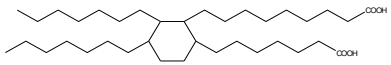
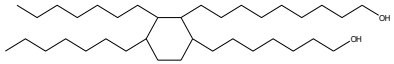
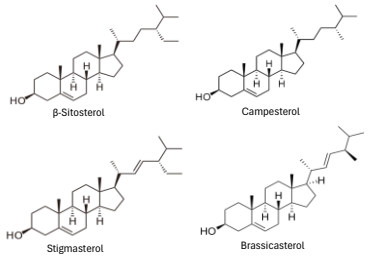
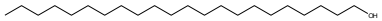
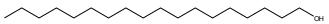
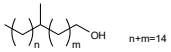
The structure for Dimer Dilinoleyl Dimer Dilinoleate was not clear on p.212 of the Dimer Dilinoleates Panel book for the December 4-5, 2025 meeting, and the definition of R2 was missing. The attached clarifies the structure and defines R2.

The information of dimer dilinoleate ingredients

INCI	Chemical structure	UV spectra	Method of Manufacture	Impurities	Safety data (Test guideline (Test conditions), Test concentration, Test date, Results)	Reference
Bis-Behenyl/Isostearyl/Phytosteryl Dimer Dilinoleyl Dimer Dilinoleate	R3−OCO−R1(−COO−R2−OCO−R1)n−COO−R3 R1; Dimer Acid residue R2; Dimer Diol residue R3; Phytosterol, Behenyl Alcohol, Isostearyl Alcohol residue	Almost no UV absorption (Data attached)	Raw materials→Reaction→Purification →Filtration→Packaging	Hevy metal: 20ppm Max. Arsenic: 2ppm Max.	Acute Oral Toxicity: OECD TG423, 100%, 2004.05.05, LD50>2000mg/kg Primary Skin Irritation: OECD TG404, 100%, 2004.05.05, NON IRRITANT Skin Sensitizetion: OECD TG406, 25%, 2004.03.30, NON-SENSITIZER Eye Irritation: OECD TG405, 100%, 2004.11.27, PRACTICALLY NON IRRITANT Eye Irritation: Eye irritation study using EpiOcular corneal model, 100%, 2005.12.30, NON IRRITANT Mutagenicity: OECD TG471, 100%, 2004.06.11, NEGATIVE Genotoxicity: Chromosome aberration test using mammalian cell culture, 100%, 2010.10.11, NEGATIVE Human 24hr Closed Patch: 45 subjects, 100%, 2004.02.26, NEGATIVE RIPT (Repeated Insult Patch Test): 42 subjects, 100%, 2024.11.05, NEGATIVE	Unpublished data
Bis-Behenyl/Phytosteryl Dimer Dilinoleate	$R_2-OCO-R_1-COO-R_2$ R1 : Dimer acid residue R2 : Phytosterol residue or Behenyl alcohol residue	Almost no UV absorption (Data attached)	Raw materials→Reaction→Purification →Filtration→Packaging	Hevy metal: 20ppm Max. Arsenic: 2ppm Max.	Mutagenicity: Ames Test, 100%, 2019.03.05, NEGATIVE	Unpublished data
Dimer Dilinoleyl Dimer Dilinoleate	HO−R1 (−OCO−R2−COO−R1) n−OH R1 : Dimer diol residue R2 : Dimer acid residue	Almost no UV absorption (Data attached)	Raw materials→Reaction→Purification →Filtration→Packaging	Hevy metal: 20ppm Max. Arsenic: 2ppm Max.	Acute Oral Toxicity: OECD TG423, 100%, 2001.03.02, LD50>2500mg/kg Primary Skin Irritation: OECD TG404, 100%, 2001.03.02, MILD IRRITANT Skin Sensitizetion: OECD TG406, 100%, 2001.03.02, NON-SENSITIZER Eye Irritation: OECD TG405, 100%, 2001.03.02, MINIMAL IRRITANT Eye Irritation: Eye irritation study using EpiOcular corneal model, 100%, 2005.12.30, NON IRRITANT Eye Irritation: OECD TG491, 100%, 2021.11.16, NO CATEGORY Mutagenicity: OECD TG471, 100%, 2001.01.01, NEGATIVE Human Closed Patch: 42 subjects, 100%, 2001.02.16, NEGATIVE	Unpublished data
Phytosteryl/Isostearyl/Cetyl/Stearyl/Behenyl Dimer Dilinoleate	$R_2-OCO-R_1-COO-R_2$ R1 : Dimer acid residue R2 : Phytosterol residue, Behenyl alcohol residue, Stearyl alcohol residue, Cetryl alcohol residue or Isostearyl alcohol residue	Almost no UV absorption (Data attached)	Raw materials→Reaction→Purification →Filtration→Packaging	Hevy metal: 20ppm Max. Arsenic: 2ppm Max.	Acute Oral Toxicity: OECD TG423, 100%, 2003.05.27, LD50>2500mg/kg Primary Skin Irritation: OECD TG404, 100%, 2002.08.30, NON IRRITANT Cumulative skin irritation study using guinea pigs: 100%, 2004.05.10, NON IRRITANT Skin Sensitizetion: OECD TG406, 100%, 2002.10.16, NON-SENSITIZER Eye Irritation: OECD TG405, 100%, 2002.10.14, MINIMAL IRRITANT Mutagenicity: OECD TG471, 100%, 2003.05.01, NEGATIVE Genotoxicity: Chromosome aberration test using mammalian cell culture, 100%, 2004.05.10, NEGATIVE Human 24hr Closed Patch: 45 subjects, 100%, 2002.10.31, NEGATIVE	Unpublished data
Phytosteryl Isostearyl Dimer Dilinoleate	$R_2-OCO-R_1-COO-R_2$ R1 : Dimer acid residue R2 : Phytosterol residue or Isostearyl alcohol residue	Almost no UV absorption (Data attached)	Raw materials→Reaction→Purification →Filtration→Packaging	Hevy metal: 20ppm Max. Arsenic: 2ppm Max.	Acute Oral Toxicity: OECD TG423, 100%, 2000.02.22, LD50> 2000 mg/kg Primary Skin Irritation: OECD TG404, 100%, 2000.02.22, MILD IRRITANT Cumulative skin irritation study using guinea pigs: 100%, 2000.06.27, PRACTICALLY NON IRRITANT Skin Sensitizetion: OECD TG406, 100%, 2000.02.22, NON-SENSITIZER Eye Irritation: OECD TG405, 100%, 2000.02.22, MINIMAL IRRITANT Mutagenicity: OECD TG471, 100%, 2000.07.25, NEGATIVE Genotoxicity: Chromosome aberration test using mammalian cell culture, 100%, 2001.02.28, NEGATIVE Human 24hr Closed Patch: 45 subjects, 100%, 1999.12.21, NEGATIVE	Unpublished data

General information of dimer dilinoleate	Refer to the appendix for the representative structures of each raw material.		The ester of dimer acid and alcohol can be synthesized by directly esterifying dimer acid and alcohol at high temperatures (180-240° C) while removing the water produced in the reaction. Additionally, the reaction temperature can be lowered by using acid or alkaline catalysts. The catalysts are removed after the reaction by neutralizing with an acid or alkali wash. Antioxidants may be added to the resulting ester to improve its stability.	Heavy metals are regulated to be 20 ppm Max, and arsenic is regulated to be 2 ppm Max. Additionally, trace amounts of free alcohol, free fatty acids, and salts of free fatty acids derived from raw materials may be present. The safety information regarding Phytosterol , Behenyl alcohol, Stearyl alcohol, Cetryl alcohol and Isostearyl alcohol is available in the CIR report(Ref.1, Ref.2.). The safety information regarding Dimer acid is available in the CIR report(Ref3.). Additionally, for safety information on dimer derivatives, there is the following CIR report.(Ref.4)		Ref.1 : Safety Assessment of Phytosterols as Used in Cosmetics Ref.2 : Final Report on the Safety Assessment of Cetearyl Alcohol, Cetyl Alcohol, Isostearyl Alcohol, Myristyl Alcohol, and Behenyl Alcohol Ref.3 : Safety Assessment of Fatty Acids & Fatty Acid Salts as Used in Cosmetics Ref.4 : Amended Safety Assessment of Dialkyl Dimer Dilinoleates as Used in Cosmetics

Appendix

	Representative structure	M.W.
Dimer acid (Hydrogenated dimer dilinoleic acid)		568
Dimer diol (Hydrogenated dimer dilinoleyl alcohol)		536
Phytosterol	 β-Sitosterol Campesterol Stigmasterol Brassicasterol	β-Sitosterol：414.7 Stigmasterol：412.7 Campesterol：400.7 Brassicasterol：398.7 Average : about 409
Behenyl alcohol		326.6
Stearyl alcohol		270.5
Cetryl alcohol		242.4
Isostearyl alcohol	 n+m=14	270.5