Safety Assessment of Phenyl-Substituted Methicones as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	August 18, 2023
Panel Meeting Date:	September 11-12, 2023

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.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel member involved in this assessment: Daniel C. Liebler, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume. This safety assessment was prepared by Preethi Raj, M.Sc., Senior Scientific Analyst/Writer, CIR.

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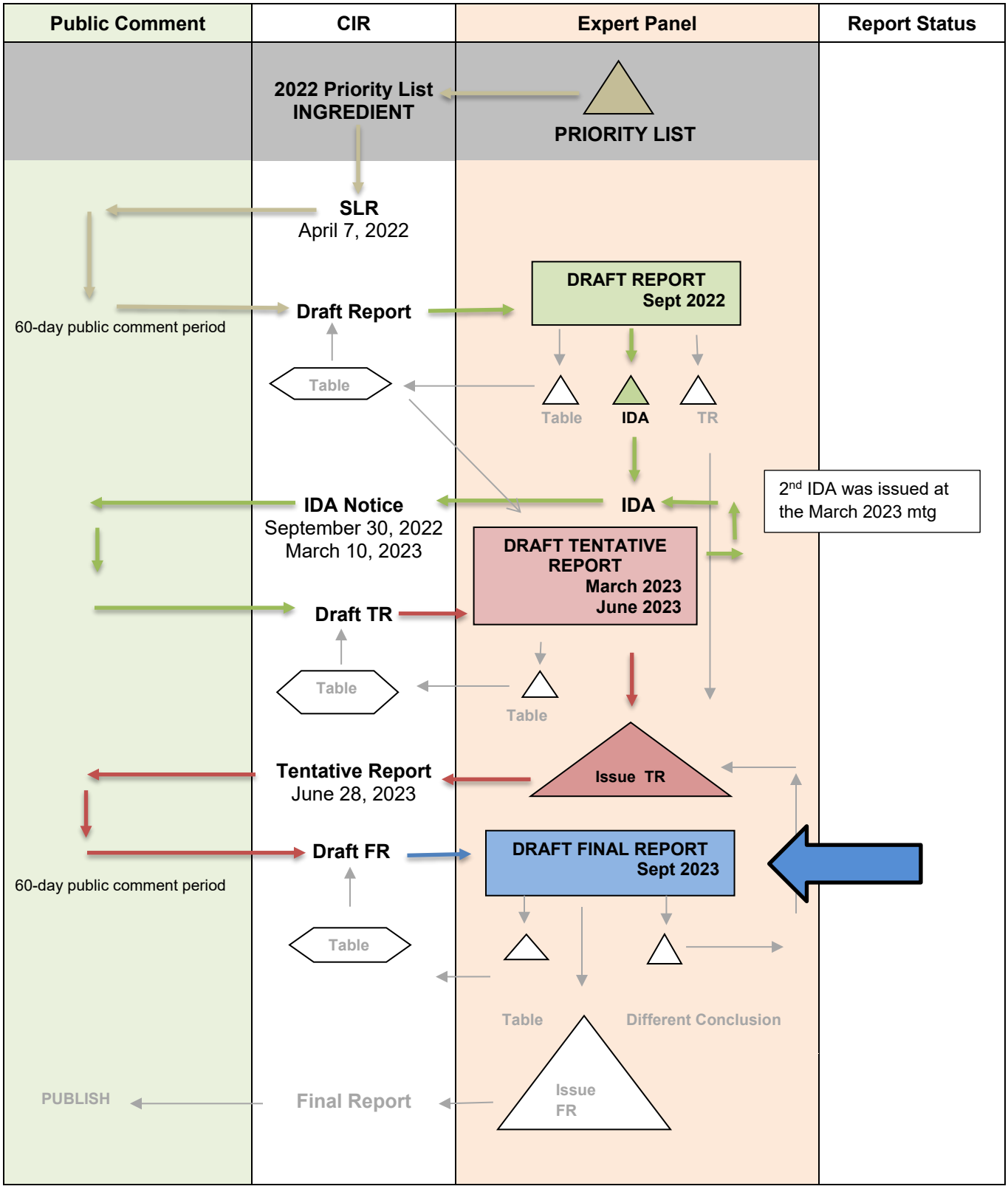
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Phenyl-Substituted Methicones

MEETING September 2023



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Preethi S. Raj, M.Sc.
Senior Scientific Analyst/Writer, CIR
Date: August 18, 2023
Subject: Safety Assessment of Phenyl-Substituted Methicones as Used in Cosmetics

Enclosed is a Draft Final Report of the Safety Assessment of Phenyl-Substituted Methicones as Used in Cosmetics (identified as *report_PhenylSubMethicones_092023* in the pdf). This is the fourth time the Panel is seeing a safety assessment of these 7 cosmetic ingredients. At the June 2023 meeting, a Draft Tentative Report was presented to the Panel; the Panel concluded that these ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment, with the exception that the available data are insufficient to make a determination of safety for use of these ingredients in products that may be incidentally inhaled.

Additionally at the June meeting, the Panel reviewed data received in response to the second IDA that was issued at its March 2023 meeting, including correspondence from the Silicones, Environmental, Health, and Safety Center (SEHSC) aw well as a CAS number review for Phenyl Trimethicone conducted by the Council. The Panel acknowledged that although the SEHSC stated the data they submitted are representative of Phenyl Trimethicone, the test article in those studies is associated with CAS No. 70131-69-0, which is no longer connected to Phenyl Trimethicone in the wINCI *Dictionary*. Therefore, it was unclear to the Panel as to whether data submitted by the SEHSC were applicable, and determined to exclude those data based on that uncertainty.

Furthermore, the Panel agreed that data on the particle size distribution and concentrations of use for these ingredients in products which may be incidentally inhaled, as well as short-term intermittent-exposure inhalation data, remain lacking. Accordingly, in June, the Panel identified the following data needs for these ingredients:

- Clarification of the identity and chemical nomenclature for the test article referred to as Phenyl Trimethicone in the SEHSC data submission
- Additional respiratory toxicity data at, or above, the reported maximum concentration of use in inhaled exposures near the face (Phenyl Trimethicone is reported to be used at up to 7.5% in aerosol sprays)
    - Preferably, the protocol should be similar to the short-term inhalation toxicity study described in the original report (i.e., a 4-wk study in which rats were exposed twice daily to a 30-s burst of an aerosol containing 3% Phenyl Trimethicone, followed by a 15-min chamber exposure).

Subsequently, the SEHSC has informed CIR that upon being made aware that CAS No. 70131-69-0 is no longer associated in the *Dictionary* with the INCI name Phenyl Trimethicone, the data submitted with CAS No. 70131-69-0 are not appropriate for inclusion in the report (*SEHSCclarification_PhenylSubMethicones_092023*).

Also included in this package, for your review, are a flow chart (*flow_PhenylSubMethicones_092023*), literature search strategy (*search_PhenylSubMethicones_092023*), ingredient data profile (*dataprofile_PhenylSubMethicones_092023*), ingredient history (*history_PhenylSubMethicones_092023*), and transcripts from the previous meeting (*transcripts_PhenylSubMethicones_092023*). Previous reports that the Panel has published on the safety of Phenyl Trimethicone, and meeting minutes associated with these reports, are also included in this package for your review (*originalreport_PhenylSubMethicones_092023*; *rereview2006_PhenylSubMethicones_092023*; *originalminutes_PhenylSubMethicones_092023*).

The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report, and provide the editorial changes that should be made in the Discussion in response to receipt of the clarification from SEHSC. The Panel should then issue a Final Report.

American Chemistry Council | SEHSC Silicones Environmental, Health, and Safety Center

August 15, 2023

Bart Heldreth, Ph.D.
Executive Director
Cosmetic Ingredient Review
1620 L St., NW
Suite 1200
Washington, D.C. 20026

Re: SEHSC Data Submission on CAS RN 70131-69-0

Dear Dr. Heldreth,

The Silicones Environmental, Health, and Safety Center (SEHSC)[1] of the American Chemistry Council hereby submits this letter on behalf of its member companies to inform CIR that the information submitted on Phenyl Trimethicone was for the material associated with CAS RN 70131-69-0. PCPC provided a copy of their April 28, 2023, Memo to the CIR on their Phenyl Trimethicone CAS Number Review to SEHSC. Now that our members are aware that CAS RN 70131-69-0 is no longer associated with the INCI name Phenyl Trimethicone, the members would like to confirm that the data on CAS RN 70131-69-0, submitted by SEHSC on behalf of its members, is not appropriate for the Phenyl Trimethicone report.

If you have any questions regarding, please contact me at (202) 249-6196 or tracy_guerrero@americanchemistry.com.

Sincerely,

Tracy Guerrero

Tracy Guerrero
Director

[1] SEHSC is a not-for-profit trade sector group whose mission is to promote the safe use of silicones through product stewardship and environmental, health, and safety research. The Center is comprised of North American silicone chemical producers and importers.

700 2nd Street NE, Washington, DC 20002 | (202) 249.7000

CIR History of:

Phenyl-Substituted Methicones

July 2021; January 2022

-Concentration of use data submitted by Council

January 2022

-FDA frequency of use data obtained

April 2022

- SLR posted on the CIR website; received SLR comments

Data received, by date:

April 12, 2022:

78-82% Phenyl Trimethicone, 18-22% Polysilicone-11

- Acute oral toxicity study of rats
- Primary skin irritation test of rabbits
- Primary ocular irritation test of rabbits

100% Trimethylsiloxyphenyl Dimethicone; HRIPT in 51 subjects

April, 2022:

- 3 SIOPTs
  - 0.06% Diphenyl Dimethicone in a lip color (20 subjects)
  - 0.5% Diphenylsiloxy Phenyl Trimethicone in an ampoule (20 subjects)
  - 10% Phenyl Trimethicone in a mousse foundation (21 subjects)
- 2 cumulative irritation assays
  - 3.2363% Phenyl Trimethicone in a SPF cream (25 subjects)
  - 2% Trimethylsiloxyphenylphenyl Dimethicone in a serum (28 subjects)
- 3 HRIPTs
  - 0.5% Diphenylsiloxy Phenyl Trimethicone in an ampoule (112 subjects)
  - 3% Trimethylsiloxyphenyl Dimethicone in a cream (103 subjects)
  - 5% Trimethylsiloxyphenyl Dimethicone in a shine gloss (18 subjects)
- 7.5% Phenyl Trimethicone; Photocontact allergenicity assay of a lotion (27 subjects)
- 26.18% Phenyl Trimethicone; Maximization assay of a concealer (26 subjects)
- 2% Trimethylsiloxyphenyl Dimethicone; Photo-allergenicity test of a serum (26 subjects)

May 18, 2022:

- 15% Diphenyl Dimethicone; LLNA in CBA mice
- 15% Diphenyl Dimethicone; 13-wk, repeated dose oral toxicity study in rats
- 4 HRIPTs:
  - 2% Diphenyl Dimethicone; Modified Marzulli-Maibach (111 subjects)
  - 0.2% Phenyl Methicone; Marzulli-Maibach (107 subjects)
  - 28.67% Phenyl Trimethicone (203 subjects)
  - 38.006% Trimethylsiloxyphenyl Dimethicone (205 subjects)

May 20, 2022:

- 100% Diphenyl Dimethicone: Buehler test in guinea pigs; 24-h primary dermal irritation test in rabbits

- 100% Diphenylsiloxy Phenyl Trimethicone ; LLNA in mice; primary dermal irritation test in rabbits

September 2022

-A Draft Report was presented to the Panel. The Panel issued an IDA with the following data needs:
- Method of manufacture and impurities (specific to cosmetic ingredients) for all ingredients
- Molecular weight ranges for all ingredients

Data received, by date:

November 14, 2022

- Anonymous. 2022. Method of manufacture and molecular weight – Diphenyl Dimethicone
- Anonymous. 2022. Method of manufacture and molecular weight – Phenyl Trimethicone

November 21, 2022

- Anonymous. 2022. Impurities and molecular weight – Diphenyl Dimethicone and Diphenylsiloxy Phenyl Trimethicone
- Anonymous. 2022. General manufacturing process of Diphenyl Dimethicone
- Anonymous. 2022. General manufacturing process of Diphenylsiloxy Phenyl Trimethicone

November 29, 2022

- Anonymous. 2019. Clinical safety evaluation repeated insult patch test (lip balm containing 11% Diphenylsiloxy Phenyl Trimethicone).
- Anonymous. 2011. Clinical safety evaluation repeated insult patch test (product containing 20% Phenyl Trimethicone).

January 13, 2023

- Anonymous. 2023. Phenyl Trimethicone (process flow diagram, impurities, molecular weight)

February 14, 2023

Wave 2 data submission received from the Silicones, Environmental, Health, and Safety Center (SEHSC):

- data1: SEHSC Data Call-In Results: an Excel spreadsheet containing toxicity study summaries for Phenyl Trimethicone (identified as test substance or phenyl silsesquioxanes) and Trimethylsiloxyphenyl Dimethicone

Separate files for toxicity studies testing Trimethylsiloxyphenyl Dimethicone

- data2: Acute dermal toxicity study using Sprague-Dawley rats
- data3: Acute oral toxicity study using CD rats
- data4: Short-term oral toxicity study using rats
- data5: Acute dermal irritation study using New Zealand albino rabbits, guinea pig maximization test using Dunkin-Hartley guinea pigs, acute ocular irritation study using New Zealand albino rabbits

March 2023: A Draft Tentative Report was presented to the Panel. The Panel considered the Wave 2 data submission from the SEHSC. As part of this submission, data were submitted for Phenyl Trimethicone, based

on the CAS number (70131-69-0, which according to the wINCI Dictionary is one of the CAS numbers for Phenyl Trimethicone). However, the test article was referred to as phenyl silsesquioxanes, or simply as the generic terms test material or test substance. It was unclear to the Panel as to whether any of those submitted data actually refer to Phenyl Trimethicone, and if they are applicable to this safety assessment. The Panel noted that phenyl silsesquioxanes is not a cosmetic ingredient and it has a cage-like structure, whereas the phenyl-substituted methicones are linear. In particular, the Panel noted an acute inhalation toxicity study in which rats were exposed whole body to an aerosol of 0.5 and 5 mg/l phenyl silsesquioxanes for 4 h, and the resulting LC50 was 0.5 mg/l. Accordingly, the Panel issued an IDA, with the following data needs:

• Clarification of the identity and chemical nomenclature for test substances referred to in the SEHSC data submission
• Applicability of these data for use in this assessment
• Additional respiratory toxicity data at, or above, the reported maximum concentration of use in inhaled exposures near the face (Phenyl Trimethicone is reported to be used at up to 7.5% in aerosol sprays)
    o Preferably, the protocol should be similar to the short-term inhalation study of rats exposed to an aerosol containing 3% Phenyl Trimethicone that is described in the original report (30-s burst, followed by a 15-min exposure within a chamber)

Following the Panel's issue of the IDA, several clarifications/files were received from the SEHSC:

- the identity of 'phenyl silsesquioxanes' was confirmed to be Phenyl Trimethicone (no error in naming)
- it was confirmed that no data was available for a short-term oral toxicity study testing Phenyl Trimethicone, mentioned in the data summary spreadsheet
- the complete file for a 4-wk oral toxicity study testing Trimethylsiloxyphenyl Dimethicone in rats
- concentrations at which Phenyl Trimethicone was tested in an Ames test and mouse lymphoma assay, as described in the data summary spreadsheet
- The redacted file for an Ames test in which Trimethylsiloxyphenyl Dimethicone was tested

June 2023: A Draft Tentative Report was presented to the Panel. The Panel reviewed information received from the SEHSC on the test article referred to as Phenyl Trimethicone (and phenyl silsequioxanes), as well as a CAS number review conducted by Council, and considered this data to be equivocal. Additionally, the Panel received information on the unreported use of these ingredients in dry shampoos, leading the them to believe that data on the safety of these ingredients being used in products which may be incidentally inhaled is lacking. Thus, the Panel concluded that these ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment, with the exception that the available data are insufficient to make a determination of safety for use of these ingredients in products that may be incidentally inhaled. Accordingly, the Panel identified the additional data needs as:

- Clarification of the identity and chemical nomenclature for the test article referred to as Phenyl Trimethicone in the SEHSC data submission
- Additional respiratory toxicity data at, or above, the reported maximum concentration of use in inhaled exposures near the face (Phenyl Trimethicone is reported to be used at up to 7.5% in aerosol sprays)
    - Preferably, the protocol should be similar to the short-term inhalation toxicity study described in the original report (rats were exposed to a 30-s burst, followed by a 15-min chamber exposure to an aerosol containing 3% Phenyl Trimethicone).

September 2023

A Draft Final Report is being presented to the Panel.

Phenyl-Substituted Methicones Data Profile* – September 11-12, 2023 – Preethi Raj																														
				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 Absorption	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
Diphenyl Dimethicone	X	X	X					X	X		X									X	X		X	X			X		
Diphenylsiloxy Phenyl Trimethicone	X	X	X		X		X	X			X			X	X					X	X		X	X			X		
Diphenylsiloxy Phenyl/Propyl Trimethicone	X																													
Phenyl Dimethicone	X																													
Phenyl Methicone	X											X									X			X			X		
Phenyl Trimethicone	X	OX	X		O	X	O	OX		O		O	O	OX	O					OX	OX		O	OX	X		OX		
Trimethylsiloxyphenyl Dimethicone	X						X	X			X				X					X	X		X	X	X		X		

* "X" indicates that data were available in a category for the ingredient; "O" indicates that data from the original assessment were available

[Phenyl-Substituted Methicones – 7 ingredients]

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
Diphenyl Dimethicone	68083-14-7	NR	NR	NR	NR	✓*	NR	NR	✓*	✓*	NR	NR	NR	NR	NR	NR	✓*
Diphenylsiloxy Phenyl/Propyl Trimethicone	NR	NR	NR	NR	NR	NR	NR	NR	✓*	NR	NR	NR	NR	NR	NR	NR	✓*
Diphenylsiloxy Phenyl Trimethicone	352230-22-9	NR	NR	NR	NR	NR	NR	NR	✓*	✓	NR	NR	NR	✓	NR	NR	✓*
Phenyl Dimethicone	9005-12-3	NR	NR	NR	NR	✓*	NR	NR	✓*	NR	NR	NR	NR	NR	NR	NR	✓*
Phenyl Methicone	31230-04-03 63148-58-3	✓*	NR	NR	NR	✓*	NR	NR	✓*	NR	NR	NR	NR	NR	NR	NR	✓*
Phenyl Trimethicone	NR	NR	NR	NR	NR	✓*	NR	NR	✓*	✓	NR	NR	NR	NR	NR	NR	✓*
Trimethylsiloxyphenyl Dimethicone	73138-88-2	✓*	NR	NR	NR	NR	NR	NR	✓*	NR	NR	NR	NR	NR	NR	NR	✓*

Search Strategy

[*total # of hits / # hits that were useful*]

Pubmed (as of 07/23/2023)
((((((((((((((diphenyl dimethicone) OR (68083-14-7)) OR (diphenylsiloxy phenyl/propyl trimethicone)) OR (diphenylsiloxy phenyl trimethicone)) OR (352230-22-9)) OR (Hydrogen Diphenyl Dimethicone)) OR (68037-60-5)) OR (Phenyl Dimethicone)) OR (9005-12-3)) OR (Phenyl Methicone)) OR (31230-04-03)) OR (63148-58-3)) OR (Phenyl Trimethicone)) OR (Triphenyl Trimethicone)) OR (Trimethylsiloxyphenyl Dimethicone)) OR (73138-88-2) – 272/2

((diphenyl dimethicone) OR (68083-14-7)) AND (toxicity) – 0/0
diphenylsiloxy phenyl/propyl trimethicone AND toxicity – 0/0
((diphenylsiloxy phenyl trimethicone) OR (352230-22-9)) AND (toxicity)- 0/0
((Hydrogen Diphenyl Dimethicone) OR (68037-60-5)) AND (toxicity) -0/0
((Phenyl Dimethicone) OR (9005-12-3)) AND (toxicity) – 0/0
((Phenyl Methicone) OR (31230-04-03)) AND (toxicity) – 40/0
(phenyl trimethicone) AND (toxicity) -0/0
(triphenyl trimethicone) AND (toxicity)- 0/0
((73138-88-2) OR (Trimethylsiloxyphenyl Dimethicone)) AND (toxicity) – 19/0

Google Search
diphenyl dimethicone acute oral toxicity – 13/0
diphenyl dimethicone short term oral toxicity – 46/2
diphenyl dimethicone subchronic oral toxicity – 55/0
diphenyl dimethicone chronic oral toxicity – 62/0
diphenyl dimethicone dermal toxicity – 37/0
diphenyl dimethicone acute dermal toxicity – 55/0
diphenyl dimethicone short term dermal toxicity- 45/0
diphenyl dimethicone subchronic dermal toxicity- 27/0

diphenyl dimethicone chronic dermal toxicity – 38/0
diphenyl dimethicone inhalation toxicity – 43/0
diphenyl dimethicone acute inhalation toxicity- 25/0
diphenyl dimethicone short term inhalation toxicity – 37/0
diphenyl dimethicone subchronic inhalation toxicity – 45/0
diphenyl dimethicone chronic inhalation toxicity- 11/0
diphenyl dimethicone developmental toxicity- 48/0
diphenyl dimethicone reproductive toxicity – 38/0
diphenyl dimethicone dermal sensitization – 33/0
diphenyl dimethicone genotoxicity -80/1
diphenyl dimethicone mutagenicity – 99/0
diphenyl dimethicone carcinogenicity- 112/0

diphenylsiloxy phenyl trimethicone acute oral toxicity – 12/0
diphenylsiloxy phenyl trimethicone short term oral toxicity – 29/0
diphenylsiloxy phenyl trimethicone subchronic oral toxicity – 10/0
diphenylsiloxy phenyl trimethicone chronic oral toxicity – 28/2
diphenylsiloxy phenyl trimethicone dermal toxicity – 37/0
diphenylsiloxy phenyl trimethicone acute dermal toxicity – 15/0
diphenylsiloxy phenyl trimethicone short term dermal toxicity- 26/0
diphenylsiloxy phenyl trimethicone subchronic toxicity- 10/0
diphenylsiloxy phenyl trimethicone chronic dermal toxicity – 27/0
diphenylsiloxy phenyl trimethicone inhalation toxicity – 30/0
diphenylsiloxy phenyl trimethicone acute inhalation toxicity- 13/0
diphenylsiloxy phenyl trimethicone short term inhalation toxicity – 11/0
diphenylsiloxy phenyl trimethicone subchronic inhalation toxicity – 12/0
diphenylsiloxy phenyl trimethicone chronic inhalation toxicity- 14/0
diphenylsiloxy phenyl trimethicone developmental toxicity- 53/0
diphenylsiloxy phenyl trimethicone reproductive toxicity – 24/0
diphenylsiloxy phenyl trimethicone dermal sensitization – 48/0
diphenylsiloxy phenyl trimethicone genotoxicity - 15/0
diphenylsiloxy phenyl trimethicone mutagenicity – 30/0
diphenylsiloxy phenyl trimethicone carcinogenicity- 19/0

Phenyl trimethicone acute oral toxicity-34/0
Phenyl trimethicone shortterm oral toxicity – 72/0
Phenyl trimethicone subchronic oral toxicity – 33/0
Phenyl trimethicone chronic oral toxicity – 54/0
phenyl trimethicone dermal toxicity – 148/0
phenyl trimethicone acute dermal toxicity – 45/0
phenyl trimethicone shortterm dermal toxicity- 109/0
phenyl trimethicone subchronic toxicity- 27/0
phenyl trimethicone chronic dermal toxicity – 51/0
phenyl trimethicone inhalation toxicity – 80/0
phenyl trimethicone acute inhalation toxicity- 37/0

phenyl trimethicone short term inhalation toxicity – 74/0
phenyl trimethicone subchronic inhalation toxicity – 42/0
phenyl trimethicone chronic inhalation toxicity- 78/0
phenyl trimethicone developmental toxicity- 133/0
phenyl trimethicone reproductive toxicity – 100/0
phenyl trimethicone dermal sensitization – 103/0
phenyl trimethicone genotoxicity -112/1
phenyl trimethicone mutagenicity – 105/0
phenyl trimethicone carcinogenicity- 137/0
phenyl trimethcone comedogenic – 159/0
phenyl trimethicone depigmentation – 167/0
phenyl trimethicone phototoxicity – 101/0

Polymethylphenylsiloxane toxicity – 13,200/2
Methyl phenyl polysiloxane toxicity – 622,000/2
Polyphenylmethylsiloxane toxicity – 7,910/0

Search Engines

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

Pertinent Websites

- wINCI - https://incipedia.personalcarecouncil.org/winci/ingredient-custom-search/
- FDA Cosmetics page - https://www.fda.gov/cosmetics
- eCFR (Code of Federal Regulations) - https://www.ecfr.gov/
- FDA search databases: https://www.fda.gov/industry/fda-basics-industry/search-databases
- Substances Added to Food (formerly, EAFUS): https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus
- GRAS listing: https://www.fda.gov/food/food-ingredients-packaging/generally-recognized-safe-gras
- SCOGS database: https://www.fda.gov/food/generally-recognized-safe-gras/gras-substances-scogs-database
- Inventory of Food Contact Substances Listed in 21 CFR: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=IndirectAdditives
- Drug Approvals and Database: https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases
- FDA Orange Book: https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book
- OTC Monographs - https://dps.fda.gov/omuf
- Inactive Ingredients Approved For Drugs: https://www.accessdata.fda.gov/scripts/cder/iig/
- FEMA (Flavor & Extract Manufacturers Association) GRAS: https://www.femaflavor.org/fema-gras
- HPVIS (EPA High-Production Volume Info Systems) - https://iaspub.epa.gov/oppthpv/public_search.html_page
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
  - technical reports search page: https://ntrl.ntis.gov/NTRL/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- EUR-Lex - https://eur-lex.europa.eu/homepage.html
- Scientific Committees (SCCS, etc) opinions: https://health.ec.europa.eu/scientific-committees_en https://health.ec.europa.eu/scientific-committees/scientific-committee-consumer-safety-sccs_en
- ECHA (European Chemicals Agency – REACH dossiers) – https://echa.europa.eu/
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- EFSA (European Food Safety Authority) - https://www.efsa.europa.eu/en
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- AICIS (Australian Industrial Chemicals Introduction Scheme)- https://www.industrialchemicals.gov.au/
- International Programme on Chemical Safety http://www.inchem.org/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) IRIS library - https://apps.who.int/iris/
- a general Google and Google Scholar search should be performed for additional background information, to identify references that are available, and for other general information - www.google.com https://scholar.google.com/

Botanical Websites, if applicable

- Dr. Duke's - https://phytochem.nal.usda.gov/
- Taxonomy database - http://www.ncbi.nlm.nih.gov/taxonomy
- GRIN (U.S. National Plant Germplasm System) - https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
- Sigma Aldrich plant profiler- http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html
- American Herbal Products Association Botanical Safety Handbook (2nd Edition; 2013) - http://abc.herbalgram.org/site/DocServer/AHPABotanicalSafety_FMexcerpt.pdf?docID=4601
- National Agricultural Library NAL Catalog (AGRICOLA) https://agricola.nal.usda.gov/
- The Seasoning and Spice Association List of Culinary Herbs and Spices
- http://www.seasoningandspice.org.uk/ssa/background_culinary-herbs-spices.aspx

Fragrance Websites, if applicable

- IFRA (International Fragrance Association) – https://ifrafragrance.org/
- Research Institute for Fragrance Materials (RIFM) - https://www.rifm.org/#gsc.tab=0 http://fragrancematerialsafetyresource.elsevier.com/

SEPTEMBER 2022 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – September 26, 2022

[The audio recording and transcription of these minutes is currently unavailable]

Cohen Team – September 26, 2022

DR. COHEN - OK, let's move on to Phenyl-substituted methicones. This is the first time we're reviewing this draft report and we're looking at 7 derived ingredients. These are used as antifoaming agents and skin and or hair conditioning agents. We have highest concentration of use of 59.5% and non coloring shampoos and 28.5% in a leave on product. Several of these products are reported to be used near the eye, namely Diphenylsiloxy Phenyl Trimethicone at almost 20% in an eyeliner. And Diphenyl Dimethicone at 24.1% in lipsticks. We recently issued a recent amended report on 30 dimethicone, methicone and Methicone substituted polymers where we concluded that these were safe as used when formulated to be non irritating. Phenyl Trimethicone was adjudicated in 1986. And then reaffirmed in 2006. And are in this report now. There was a fair amount of material cause this came in three sections, right, we there was a lot of material on this. And we have sensitization data 28.67% on phenyl and trimethicone. And need on trimethyl, siloxane phenyl dimethicone. And some other and we have some irritation. And since it is the other data that looks good. I'll stop here and open it for comments. Susan, you want to kick off?

DR. TILTON - So well, I am in terms of including these together as a class, I don't have any concerns about that. In this case. I had noted the lack of chemistry, manufacturing and impurities data. For the ingredients that were part of this group. Outside of what was previously available just for phenyl trimethicone.

DR. COHEN – So we need method and manufacturing and impurities for the group. Largely right?

DR. ROSS - You've got some manufacture info, right, but it's certainly had no impurity.

DR. TILTON - Yes, I.

DR. ROSS - But you haven't got sufficient. You haven't got sufficient method of manufacture.

DR. COHEN - David, how would you word that?

DR. ROSS - I think you're original fine. Just ask them that you know complete method of manufacture and impurities.

DR. COHEN - OK. Yeah, that's what I have here. You know, in some of those in some of the in the S1 supplement, one of the products that 2% trimethyl, siloxane phenyl dimethicone, they look like there may have been some sensitization signals, but the rest of the data and that may have been a product related thing because none of the other data seemed to support that so I just made note of it, but it really wasn't holding me up.

DR. ROSS - So the sensitization data (*inaudible). I'm numbered these you know. Have to match max use I just don't know.

DR. ROSS - Data on the developer you. Maximum use.

DR. COHEN - I'm getting like hammering feedback is. Is anyone hearing that?

DR. ROSS - I'm.

DR. SLAGA - Yeah, I am too.

DR. ROSS - It's not my house.

DR. BERGFELD - Nor mine.

DR. SLAGA - Not fine.

DR. TILTON - Not here.

DR. COHEN - I've never ever said in my house, Eva, can you knock off the hammering? Umm, so I'm pretty sure it's not my house. OK so.

DR. SLAGA - I heard it, but I don't. I don't know if it's here or not. I didn't see anything.

DR. COHEN - Uh, Tom, what was that time?

DR. SLAGA - I'm.

DR. COHEN - I didn't. I didn't get what you said.

DR. SLAGA - Yeah. Anyway, back to the ingredient. The irritation data I think it's relative pretty good. It looks and genotoxicity is OK. We have a similar compound the polymer that is safe.

But it is the first time that we've seen this. There was some concern about sensitization of 1 compound wasn't there?

DR. COHEN - There was a product that had two percent trimethyl siloxane phenyl dimethicone that. In the second week of testing, started to have a number signals. But we didn't see it anywhere else. We have trimethyl siloxane phenyl dimethicone tested neat in an HRIPT.

DR. SLAGA - Yeah.

DR. COHEN - I don't know if we know the number of people. Ohh no 51 subjects and it looked like the overall, data on irritation and sensitization looked OK, the totality of it.

DR. SLAGA - It's OK.

DR. ROSS - Yeah.

DR. SLAGA - It's OK. Yeah.

MS. RAJ - Yeah. And Speaking of Tri--

DR. SLAGA - Yeah, there's a weight of evidence I think is OK too.

MS. RAJ - Sorry, Speaking of Trimethysiloxyphenyl Dimethicone, there is an HRIPT for 205 subjects where it was tested at 38.006%.

DR. COHEN - Yes, yeah. That's why I didn't put a lot of eggs in that one basket of that in the S1 supplement. It was a 2%, which and I don't know what the other 98% was in there, just didn't seem to resonate with the rest of the sensitization and irritation data we have. We'll see what the Belsito team comes out with. But we have an IDA for method of manufacturing and impurities. Anything else in our IDA?

DR. TILTON - I was just going to.

DR. ROSS - I'm not sure whether you ask for any sensitization data. Did it or not. Seems like you're comfortable with that.

DR. COHEN - I'll, I'll take another look.

DR. ROSS - And could I, uh, Table 3? I could maybe quick look at that Preethi had there was a that was my comment here. The dermal contact was listed at max 1.3%. I thought it was 24%.

MS. RAJ - I'm sorry. Where are you looking, Doctor Ross?

DR. ROSS - Table 3.

DR. COHEN - Table 3. Yeah.

MS. RAJ - Are you looking at dermal contact for the diphenyl dimethicone?

DR. ROSS - You go down diphenyl dimethicone. Yeah, and go down to dermal contact. It's listed at, 1.3%.

MS. RAJ - OK. Yep.

DR. ROSS - I thought that would be changed to 24.1 but I don't know.

MS. RAJ - Yeah, you might be right, actually, I'll fix it. Thank you.

DR. TILTON - And I guess that was.

DR. COHEN - That's a nice catch there, huh?

MS. RAJ- Yeah.

DR. TILTON - That was one thing I was going to ask. There are and you know for Phenyl trimethicone compared to previous the studies that were published previously. I'm wondering if the test concentrations if the maximum use concentrations have now exceeded the maximum concentration tested. For some of the studies, the same 24% in lipstick, but I wasn't sure it was tested that high.

DR. COHEN - Define the diphenyl dimethicone is indeed 24%.

DR. TILTON - And it was tested at up to 15%?

MS. RAJ - Yes.

DR. COHEN - A Diphenyl Dimethicone let me we have animal data on that but.

MS. RAJ - You're looking at the subchronic oral. Looks like, right, Doctor Tilton? Yeah.

DR. TILTON - That's right.

MS. FIUME - David, while you're looking, can I just interject, so, **DR. ROSS**, that 24.1 as represented in the table is actually correct. As the use tables are currently formulated, lipstick is represented under incidental ingestion and mucous membrane, but not as skin, not as dermal contact. It's mucous membrane and oral. Or incidental ingestion. So the table as presented right now is correct according to our current format.

MS. RAJ – Thanks, Monice.

DR. ROSS - The maximum concentration for dermal is 1.3 by that read.

MS. FIUME - That would be correct.

DR. COHEN - Can you just reiterate that it just explain that again? Ah, OK.

MS. FIUME – So, as the current format for our use table, if something is used in a lipstick, because it's applied to lips that's considered a mucus membrane exposure and not a dermal skin exposure.

DR. COHEN - OK, I got it. And Susan, your question was are max use concentrations matching the sensitization or is this an or an oral study you're talking about?

DR. TILTON - This was the oral for Diphenyl Dimethicone, so related to the 24% that's in lipstick. It didn't seem like the maximum concentration tested was reflective of the maximum use. That it was.

DR. COHEN - For oral tox.

DR. TILTON - Lower for oral.

DR. ROSS - Yeah, the.

DR. COHEN - I'm not sure. We've always looked at it like that.

DR. ROSS - And NOAEL came in at what, 20 mg/kg/d--

DR. TILTON - Is that what it I'm trying to find it again?

DR. ROSS - It's on page 20.

MS. RAJ - It is, yeah, 20.

DR. ROSS - The PDF.

DR. TILTON - OK.

DR. ROSS - I thought, I mean, there's an awful lot of tox data with these and I, you know, with the acute oral and I thought that was OK and it's subchronic. Yeah, I mean, I you know, there was only two studies I would probably come from the. So that was a bit limited, but (*inaudible).

DR. TILTON - Yeah.

MS. RAJ - Yeah, (*inaudible) the NOAEL is in the DART section.

DR. TILTON - I am OK.

DR. ROSS - Yeah. Yeah, I didn't flag that (*inaudible). I have to say, but I had a question on the respiratory data, whether you thought that was OK.

DR. TILTON - With Phenyl Trimethicone.

DR. ROSS - Umm.

DR. TILTON - Wasn't a lot of description there, but it was tested at an aerosol concentration. Again, that was lower than the max use.

DR. ROSS - 3%.

DR. TILTON - 3% compared to 15%. So if we are, I mean if there is data available at the max, use concentration.

DR. COHEN - So I haven't I need a little help on this because I haven't heard that kind of analogy before on the inhalational or the oral relating to max use. It's something that I generally think of in terminal studies and contact irritation and sensitization. How do we how do we bridge that? Do we need, is inhalational tox going to have to match max use I just don't know?

DR. TILTON - On this case, they don't report. They aren't. They didn't test high enough concentrations like they did with the oral to come out with a

DR. COHEN - OK.

DR. TILTON – NOAEL other than that the 3% would have no effect.

DR. COHEN - What? What PDF a number are you on again?

DR. TILTON - PDF number.

DR. ROSS - That's on now.

MS. RAJ - Is it 19?

DR. ROSS - It's nine right at the bottom of 19. At least the inhalation data.

MS. RAJ - Well, looking at the table again, I think the maximum reported concentration of use for Phenyl Trimethicone in sprays as 7.5 and the 15% you're seeing is for powders I think.

DR. TILTON - OK.

DR. COHEN - If that's the case, that's still a lot lower than what they reported here, right?

DR. SLAGA - You know.

DR. COHEN - So could you articulate the data needs? Susan what's would I ask for?

DR. TILTON - So if there. So I would be interested to know if there are data available at concentrations for the inhalation. Short term toxicity studies that are closer to the max, use concentrations. For

DR. SLAGA - Or at max.

DR. TILTON - Either the Hairspray or the face powders.

DR. COHEN - For Diphenylsiloxy Phenyl Trimethicone?

DR. TILTON - Uh for Phenyl Trimethicone?

DR. COHEN - Of the phenyl. We're Phenyl Trimethicone. OK. Alright, well, here, we'll hear what.

We have a few things. We have method of manufacturing and impurities and inhalation data closer to max use for trying to Phenyl Trimethicone. I'll review the sensitization data again. Was there anything else?

MS. RAJ - I'm sorry, Doctor Cohen, could you reiterate what were you going to look at in that sensitization data?

DR. COHEN - I'm just going to look and make sure that the max use of the specific chemicals aligned, but I think we have I think it's OK because we have neat, we have very high concentration on this, but the team had asked me about it a little early. I think it's fine. I'm just going to, it's a note to myself.

MS. RAJ - Thank you.

DR. COHEN - OK, so let's finish. Phenyl -substituted imethicone do what's the team like to do, we could break or we could make a run for glyceryl diesters. What's the overall feeling?

Full Panel – September 27, 2022

DR. BERGFELD - Alright, well, let me call the question all those opposing? Abstaining? Approved. Safe. OK. We're moving on then to the Phenyl-substituted methicones, Dr. Belsito.

DR. BELSITO - Yes. So this is the first time that we're looking at this cosmetic ingredient group of seven ingredients in this. I won't read them all off. And it took three different PDF's to get us all the data. Reams and reams of data that were quite nice, except that we didn't have manufacturing impurities or molecular weight ranges for any of them. So we are going insufficient for those needs.

DR. BERGFELD - David.

DR. COHEN - Yeah. I would second that. One thing that came up at our discussion for Phenyl Trimethicone. The inhalation tox was at 3% but the max use is much higher than that. And we wanted your thoughts on asking for additional respiratory tox that was more approximating the real life use.

DR. BELSITO - Well, that I guess is going to be an issue with airbrush where we know these are being used. So this will be a very clear statement in the airbrush in the discussion for airbrush, but I mean I think we have our standard boilerplate for respiratory toxicity in terms of inhalation, it didn't come up in my group, but I'll turn that over to Paul, Dan and Allan and Kurt?

DR. BELSITO - Don’t chime in all at once.

DR. SNYDER - Like this was. This ingredient report actually had some of the best data we've ever had from the tox side. I mean it had dermal, oral, all the way from acute all the way up to developmental and repro. So there was no signal anywhere or

no issue. Anything all the findings were at 20 milligrams or greater per kilogram and so we felt it was an extreme (*inaudible) to have a very safe tox profile and we didn't really talk about the inhalation and I didn't pick up on that on the on that inhalation. I know that there was acute and short term inhalation that I was comfortable with, so I would suspect those would be sufficient for any incidental exposure we can address that in discussion regarding the potential for incidental inhalation and address it to the levels that we have data on. So that's my two cents.

DR. KLAASSEN - While the concentration of the compound in the inhalation study was low. It was for a long, much longer time than what humans would be exposed to, so that gives one some security.

DR. BERGFELD - Allan.

DR. COHEN - Susan, Tom. Ohh sorry.

DR. RETTIE - Yeah, I didn't have anything to add to that. I did have a comment, maybe we'll get to later about something's text, but I'm good with it.

DR. BELSITO - I mean. It's insufficient at this point. If you guys want to ask for that data, we can ask for it and come back to the whole respiratory issue later.

DR. BERGFELD - OK. Well, we'll be in the minutes, so we know it's a discussion point that needs to be addressed.

DR. LIEBLER - I agree with it.

DR. COHEN - Susan, any?

DR. BERGFELD - Any other comments? Susan?

DR. TILTON - So I do agree with Kurt's comment that the cumulative exposure over time would exceed what you would expect from normal use so. And I also agree that as long as it's addressed in the discussion, the point with which I guess is a fairly boilerplate statement, then that would then that, you know is could be sufficient.

DR. BERGFELD - OK. David, did you want to comment?

DR. SLAGA - I agree. I agree with that.

DR. BERGFELD - OK. Thanks, Tom. David. No.

DR. COHEN - You meant Dr. David Ross

DR. BERGFELD - Ohh, I don't mean. Alright. That's two David's Sorry, I'm looking at Dr. David Ross. Thank you.

DR. COHEN – Yea.

DR. BERGFELD - Any comment?

DR. ROSS - No, I'm fine with it.

DR. BERGFELD - How about you, David?

DR. COHEN - Yes. So we'll, we'll second uh, Don Belsito's motion.

DR. BERGFELD - OK, so a second.

DR. COHEN - We came to the same conclusions.

DR. BERGFELD - Yeah. And what you're asking for, the writer, I'm not sure I see who the writer is, but do you have the list that's needed?

MS. RAJ - So, Dr. Belsito's team had said all are insufficient for method of manufacture and impurities and also molecular weight range is that it?

DR. BELSITO - Correct, yes.

MS. RAJ - OK. Thank you.

DR. BERGFELD - OK.

DR. COHEN - That's what we have.

DR. BERGFELD - All right. Any other points of discussion? Hearing none, all those opposed? Abstaining? Approved as an IDA. All right, moving on to the last chemical and this particular advancing group, Doctor Cohen, that Trisodium Ethylenediamine Disuccinate.

MARCH 2023 PANEL MEETING – SECOND REVIEW/DRAFT TENTATIVE REPORT

Belsito Team – March 6, 2023

DR. BELSITO: Okay – then we're moving on to phenyl-substituted methicones –

DR. SNYDER: Lots of new data –

DR. BELSITO: Yeah, so – this is a draft Tentative Report – the safety assessment of Phenyl-Substituted Methicones as Used in Cosmetics – this is the second time we are seeing the safety assessment of these 7 ingredients. At the September 2022 meeting, it was a Draft Report – we issued an IDA for the method of manufacturing data and impurities, specific to the cosmetic ingredients, for all 7 of the ingredients, molecular weight range for all of the ingredients, and we, as Paul said, received lots of new data, which I won't run through. The big question I had was – so, we got method of manufacturing and impurities for Diphenyl Dimethicone, Diphenylsiloxy Phenyl Trimethicone, and Phenyl Trimethicone. But, we didn't get them for the Diphenylsiloxy Phenyl/Propyl Trimethicone, Phenyl Dimethicone, Phenyl Methicone, and Trimethylsiloxyphenyl Dimethicone. Does what we have for those 3 ingredients cover the 4 that we don't have manufacturing, impurities – or, are we going to insufficient for those 4-- for those, uh, data points?

MS. RAJ: Dr. Belsito, may I interject? So, in the Wave 2 that you received it wasn't highlighted per se, but, they did seem to provide, um, molecular weight, and possibly, impurity information for the last ingredient you mentioned.

DR. BELSITO: Wave 2—I may, I may have missed that. Let me go open Wave 2. So, that's in the supplement, just on the Phenyl-Substituted Methicones, um—

MS. RAJ: Yes.

DR. BELSITO: There's just a lot of developmental tox – seeing a lot of tox data there – where is the manufacturing and impurities?

MS. RAJ: Right – it's kind of embedded in there, I can give you the PDF number – I'll let you know.

DR. RETTIE: So, we're looking at the Wave 2 Supplement for that?

DR. BELSITO: Yeah, there was a separate Wave 2 Supplement just for the Phenyl Substituted Methicones, because there was so much data.

DR. RETTIE: I'm looking for the information that you just described—

DR. BELSITO: I'm not seeing it, cause I'm just—mmm, hold on. I may have popped into a very different report. This is Wave 2 – and when I scan for impurities in Wave 2, I'm not seeing it.

DR. SNYDER: Yeah, I didn't have it in Wave 3.

MS. FIUME: This is Monice. Molecular weight is described on page 49 of the Wave 2, and then there's a graph that may give an indication of impurities.

DR. SNYDER: Monice! I was wondering where you were.

MS. FIUME: I'm back, I'm here.

DR. SNYDER: It's good to hear your voice.

DR. BELSITO: Well, she's been trying to keep the Cohen team in line – you know, they get a little rambunctious. But I guess they must be done. Once again, they finished before us.

MS. FIUME: They are finished.

DR. BELSITO: Okay, so it looks like it has a relatively large molecular weight there. And then, you said, there's an allusion to impurities someplace, Monice?

MS. FIUME: If you scroll through the next few pages, there's some some graphs, that may, or may not, indicate some of the impurities, but I will leave it to the chemists to make a call on that.

DR. BELSITO: Quite honestly, I didn't get that far, and if I got that far *inaudible*, I would have skipped right over it. This is, like, kitten and caboodles to me.

DR. RETTIE: There's tonnes of info here, if I'm looking at the right, at the right thing. Is this from the Wacker Chemie sponsor?

MS. RAJ: Eh- Yes.

MS. KOCH: The sponsor is the Silicones, Environment, Health, and Safety Center, SEHSC, and the member is – this is Wendy Koch – the member that supplied the data, Wacker, is one of the members.

MS. FIUME: So, Dr. Rettie, on p. 51 and 52, you will see Wacker on there.

DR. RETTIE: 51 and 52 – huh, so those are 2 NMRs?

MS. FIUME: Um, that is what is says on the – like I said, I leave it up to the chemists to decide—um, what it tells you.

DR. RETTIE: So, that's a silicone NMR, and gee, I don't really know what that means, besides it being a silicone NMR. It would take me a little time to figure out.

DR. HELDRETH: So, this is the one on p.52 – is that the one we're looking at?

DR. RETTIE: The diagrammatic presentation and standard procedure? *inaudible—

So, on p.50, I have HPLC and I have 2 NMR traces – is that what we're looking at?

MS. FIUME: Yes, according to Council comments, it was indicated that those may give you information on impurity – but, as I said, I don't know if it gives you information that you need, or not.

DR. BELSITO: According to who, Monice?

MS. FIUME: I believe in the Council comments, um, it said that that may give an indication of purity –

DR. BELSITO: I see.

Dr. RETTIE: So, the silica NMR, would be very specific of course, to silicones containing compounds and impurities. And the HPLC on – I suppose it's an HPLC – on p.50 is clearly a number of components – so, that's probably speaking to molecular range.

DR. HELDRETH: Right.

DR. RETTIE: Heterogeneic, more than anything else. So, I'm not sure that it just jumps out at us, with a clear conclusion.

DR. HELDRETH: Yeah, it looks like molecular weight is almost all above 1000, in both the silicone NMR and the proton NMR, making it clear that it is the Trimethyl – uh, methicone—and not the *inaudible* test articles.

DR. RETTIE: Yup. Yeah, a nice methyl signal and 0 there. But, that doesn't help us a lot.

MS. FIUME: Didn't mean to distract, but – it was pointed out to us that the chemists might be able to get something from this – but it seems like, maybe not.

DR. RETTIE: Something, but not a lot.

DR. BELSITO: Okay.

DR. RETTIE: As Bart said, it's giving you some information about molecular weight distributions, and most of it is above 1000, according to PDF p. 50.

DR. BELSITO: So, getting back to my original question – we have manufacturing and impurities for 3, but not for the other 4. Can we read-across, or we're still going to insufficient for those 4, for manufacturing and impurities?

DR. RETTIE: I think there's a reasonable chance for us to read-across for each of the others we don't have data for, except the silsesquioxane one that was added at the end. That seemed to be kind of different to me.

DR. BELSITO: Which one?

DR. RETTIE: The last one that was added – phenyl silsesquioxanes. The- the caged one, rather than the sheet –

DR. BELSITO: I thought we dropped that –

DR. HELDRETH: So, that was one – that was a chemical that the submitter included in the data package, as a test article, that was supposed to be, uh, equivalent, at least for the purposes of read-across to Phenyl Trimethicone. That's our assumption. We asked the submitter to explain if that is what they meant and they said they'd get back to us—we haven't heard yet. I don't know if—

DR. BELSITO: This is not a cosmetic ingredient, Allen.

DR. RETTIE: You're breaking up, Don. I can't hear ya.

DR. BELSITO: It's not a cosmetic ingredient *inaudible* we're reviewing.

DR. RETTIE: Oh, okay – Well, I think the others, there's a reasonable read-across. What do you think, Curt?

DR. KLAASSEN: Yes, I thought so.

DR. BELSITO: So, we don't need manufacturing and impurities for Diphenylsiloxy Phenyl/Propyl Trimethicone, Phenyl Dimethicone, Phenyl Methicone, and Trimethylsiloxyphenyl Dimethicone?

DR. RETTIE: No, they're just decorated differences.

DR. BELSITO: Okay, if you look at PDF p. 70, you quickly see what data we have for manufacture and impurities, and what materials we don't have. Just to make sure that we're okay with that. Because, otherwise, if you can, I think it's safe as used. They are safe as used.

DR. RETTIE: So, we have Diphenyl Dimethicone, which gives us quite a bit – we're happy with that – so, Phenyl Dimethicone, and Phenyl Methicone, and Phenyl Trimethicone were okay. That only leaves us with the siloxyphenyl dimethicone, and I'm not sure that' so much different that we wouldn't just group it all in together and say that we could read-across.

DR. BELSITO: Well, we have Diphenylsiloxy Phenyl Trimethicone—

DR. RETTIE: We have that one, so even better – I think it's enough.

DR. KLAASSEN: I think we have enough.

DR. BELSITO: Okay. So, then we are going to go safe as used—is that our conclusion?

DR. RETTIE: Yup.

DR. KLAASSEN: Yup.

DR. BELSITO: Paul?

DR. SNYDER: Sorry, I was on mute. I thought we had good data on the 3 – the Diphenyl, the triloxyl, and the Phenyl Trimethicone, so I thought that covered all of them, so— we have quite a bit of data, tox data.

DR. BELSITO: So, we're going safe as used for all of them –

DR. SNYDER: Okay.

DR. KLAASSEN: Yes.

DR. BELSITO: Okay. Any comments on the Draft Discussion?

DR. SNYDER: Well, I think we need to have that in there, about the read-across, right?

DR. BELSITO: Okay. So, Preethi, we need to say that we dropped our method of manufacture and impurities for 4 of them because we felt we could read across from what we have for the 3. So, the methicone covers the dimethicone, the phenylsiloxy covers the other phenylsiloxy—

Anything else we need to add to the Discussion?

MS. RAJ: Just for clarity – so, um, is the Team fine with the substance identified as phenyl silsesquioxanes to be added?

DR. BELSITO: No.

MS. RAJ: Thank you.

DR. BELSITO: Just basically that we thought that the method of manufacture and impurities data we have for the Diphenyl Dimethicone and Phenyl Trimethicone covered the Phenyl Dimethicone and the Phenyl Methicone. Any information on the phenylsiloxy trimethicone covered the other phenylsiloxy methicones that we didn't have data for.

MS. RAJ: Okay – Thank you, Thank you.

DR. BELSITO: Anything else in the Discussion? And then, obviously, add the tremendous amount of Wave 2 data. And this will be a Final that we will have to read very carefully given the amount of data that's being added in. Okay, Wild Yam.

Cohen Team – March 6, 2023

DR. COHEN: Oh, yeah, this is going to be something. Phenyl-substituted methicones. Right. So, this is a draft tentative report for the phenyl-substituted methicones. This is the second time we're seeing this. This is seven ingredients. At the September 2022 meeting, we issued an IDA for the following data needs, method of manufacturing and impurities for all ingredients, molecular ranges for all ingredients. We have method of manufacturing for three and are missing on the others.

We have molecular weight for three, missing on the others. Wave 2 had lots of data on phenyl trimethicone and trimethylsiloxyphenyl dimethicone. We got some irritation and sensitization data at 11 percent for the diphenylsiloxy and 20 percent for phenyl dimethicone which looked good. So, comments from the group?

DR. ROSS: I had lots of comments on this one.

DR. COHEN: Yeah. Please.

DR. ROSS: You want me to start or?

DR. COHEN: Yeah, please start because I'm going to take copious notes.

DR. ROSS: I'm not sure you need to take copious notes yet until we come to a resolution. But, anyway, as you said, the initial submission we got pretty much what we asked for, right? We went out with an IDA. We got the molecular weight ranges, the impurities, the method of manufacture. And so, on the initial document, you know I went through this, tick, tick, tick, yeah, it looks great, off we go. And then the Wave 2 came in and that gave me pause.

But I think there's two basic issues. One is the chemical nomenclature. We got data in that Wave 2 on this silsesquioxanes -- I'm sure I'm going to butcher the name here -- which were identified as phenyl trimethicone in the table. When you actually look at the structure of phenyl trimethicone, it's an open structure where these silsesquioxanes are a caged structure.

So, I had questions regarding the structure and Susan can comment in a minute. Inhalation tox data on that Wave 2 was a little bit eye-popping. And that was with an aerosol. And that was, again, a compound iden- -- sorry, I mean, I --

DR. COHEN: Go ahead, David.

DR. ROSS: Yeah. So, that was with the compound identified as silsesquioxane. So that was with an aerosol. And we essentially had a lot of rat deaths in that study and they're pretty low concentrations. With respect to the incidental inhalation exposure here, we've got 7.5 percent in a spray and 15.6 percent in a powder.

So, I think it's something we need to discuss. They were my two major issues, the nomenclature and inhalation tox. And I can get down into the details here, but I'm going to let others comment at this point.

DR. TILTON: Well, David, just to follow up I also would like to just pose for discussion even the inclusion of the data for the silsesquioxanes identified as phenyl trimethicone. I agree that the structures seem very different and so I'm questioning the rationale for the inclusion of that data.

DR. ROSS: Yeah. I did ask Bart about this, and he said someone would be available for questions on this call. And I don't know if the submitters are on the call.

MS. GUERRERO: Hi. This is Tracy Guerrero from SEHSC. We are on the call. I have Kathy Plotzke from Dow and Wendy Koch (phonetic) representing Evonik and Momentive. So, we do have members on who may be able to help with this.

DR. ROSS: So, the question would be that **DR. TILTON** and I have asked, is what about the different looking structures of phenyl trimethicone and the silsesquioxanes? What are we concluding with that? They're different forms, different structures, or completely different molecules? What's your take on this?

MS. KOCH: This is Wendy Koch. I'm thrown by your pronunciation. I actually have no idea what compound you're saying. I don't know if you'd be kind enough to spell it.

DR. ROSS: Let me get the table. Susan, you want to have a go? I think your pronunciation was much closer than mine.

DR. TILTON: So, this is from Wave 2 where it says that the data that was presented for phenyl trimethicone was presented in two parts. One was where the ingredient was identified as a test substance, and so that was the first part of the table. And then the second set of data was where it's identified as phenyl silsesquioxanes, so S-I-L-S-E-S-Q-U-I-O-X-A-N-E-S.

MS. KOCH: I think it's silsesquioxane.

DR. TILTON: Silsesquioxane.

DR. ROSS: Silsesquioxane. Let's get this right.

DR. COHEN: So, is that phenyl trimethicone?

MS. GUERRERO: Yeah. And for Kathy and Wendy, on the line, it's data that was submitted under phenyl trimethicone. The CAS number is 70131-69-0, where it was listed as the phenyl silsesquioxane.

And maybe it is we need to go back and have some clarification internally. I think that's what I had provided back to Bart. We had global meetings last week and just did not have the opportunity to address the questions that came in from the Panel.

DR. ROSS: Thank you. I mean, if you look at this document on phenyl trimethicone, it actually has six different CAS numbers associated with it, which I found to be quite surprising. But I guess certainly more than one CAS number is not unusual in these documents, but six is quite interesting I think. But, yes, that CAS number you quoted is associated with phenyl trimethicone also, so.

DR. COHEN: So, I guess the question is, if they are indeed different as a lot of this tox data, does it belong here? And if it doesn't belong here, are we back to clearing the group? And if it is similar, we have a quandary with inhalation, right?

DR. ROSS: Yeah. I think there were three inhalation studies in the original document and one was done with diphenyl dimethicone. That's where the pretty low LC50 at 18 mg/l. But that was a vapor, it wasn't an aerosol. So that, I think, was a crucial difference in that study.

The second study was a phenyl trimethicone at 3 percent, that was an aerosol. And that was on PDF Page 24. That was a rat whole body, twice daily, five days a week for four weeks. But it actually had, I think, a more realistic exposure scenario where it was a 30 second burst followed by a 15-minute exposure in a large volume chamber. So that's probably more relevant. And there were few effects there at 3 percent. I think it was only effect on weight.

And then we had a third study on phenyl methicone, a different compound. Again, seven hours a day for ten days in a variety of animals. But there were no controls and, again, that was aspirated into a mist.

So that second study with phenyl trimethicone, you know, the more intermittent exposure, I think, takes on importance. But, again, it's not at the maximum concentration of use. You know, we have -- in the spray, we had up to 7.5 percent here, powder up to 15 percent. That study is at 3 percent.

Now I'm not an inhalation toxicologist. I do believe we have one on our panel and I'm sure she can comment. **DR. TILTON**, putting you on the spot again.

DR. TILTON: Your summary was very good regarding the past studies. I do think that from the original report, the study with 3 percent phenyl trimethicone is the most relevant. And really no toxicity was observed there. But if the information from the Wave 2 is regarded as being phenyl trimethicone, it would lead -- because it is also an aerosol study, with pretty acute inhalation toxicity, it could lead to some concern.

I mean, I will note that it looked like a number of years ago the panel reviewed other silsesquioxanes as a group. And they have a pretty distinct cage-like structure. And I would just question whether or not the data that are presented as that should be interpreted as phenyl trimethicone.

DR. COHEN: So, for tomorrow and just to structure what we're looking for. For our IDA, for method of manufacturing and molecular weights, we have some but not all. Is that sufficient data to clear those IDAs?

DR. ROSS: The initial IDA we issued, I think -- yeah, we got what we requested for the most part.

DR. COHEN: Well, we asked for all of them.

DR. ROSS: Yeah., I think we got three of four.

DR. COHEN: We got three.

DR. ROSS: Yeah.

MS. RAJ: We also, **DR. COHEN**, if I may add in the submission it wasn't highlighted as such, but there appears to be molecular weight and perhaps impurity information for trimethylsiloxyphenyl dimethicone, I think.

DR. COHEN: So, a fourth one?

MS. RAJ: Yes.

DR. COHEN: Yeah, let me just --

DR. ROSS: Yeah.

DR. COHEN: Yeah. Okay.

DR. ROSS: So, I think that's clear that -- I think what we're looking for is clear. It's just this additional data, how we interpret that. Again, the two questions, the chemistry question, the nomenclature question and, secondly, the inhalation -- you know, the derivative of that question is what about this inhalation tox?

DR. COHEN: So, I think we can go out with an insufficient conclusion right now. Wait, it's not an IDA because it's not a draft report. Right. So Monice, what's the proper term?

MS. FIUME: So, the next stage would be a tentative report. If there is something specific that you now have a need for, we could issue a second IDA, but that would be whether or not you have a need. You can opt not to include the data on the silsesquioxanes and then, if you find out at the next meeting that it is appropriate, we can bring it back. Or there is always the option of holding until we found out exactly what those data are, to see if the concern about inhalation needs to be raised in the discussion or conclusion.

DR. COHEN: I think the latter is more judicious.

DR. ROSS: Yeah.

MS. BERGFELD: Hold it.

DR. COHEN: So we can clear the initial two IDAs, but issue a new IDA -- simply because this is new data that came between the draft report and now. So, I think it's a legitimate IDA. We need clarification on whether this silsesquioxanes are phenyl trimethicone. What's the nomenclature? There are seven CAS numbers for it. And as David said, derivative from that is this inhalation toxicology data relevant to this assessment?

DR. ROSS: I mean, if you did want to do an IDA, I mean, I think this is down the line after the discussion. But, you could go with what I thought was a more realistic exposure scenario, the 30 second bursts, but asks for maximum concentration of exposure if you really want to do an IDA. But I think it's more judicious to wait and see what the conclusions would be with respect to the silsesquioxanes.

DR. BERGFELD: I think it's pertinent to hold it because you have representatives here saying they didn't get to these details to get back to us. But we would hold it and reflect that we expected to get it between now and the next meeting.

MS. FIUME: And Tracy, do you have a time frame on when we would expect a clarification on that ingredient?

MS. GUERRERO: Yeah. I think that realistically we could give this to you well before your meeting in June.

DR. SLAGA: We're waiting on that clarification, can we table it until relatively soon.

DR. BERGFELD: Yep, we can.

DR. COHEN: That's an interesting strategy. So, you're suggesting, Tom -- well, if we table it, we don't issue the IDA for the request for information, though, right?

DR. BERGFELD: No.

DR. ROSS: That's coming anyway.

DR. COHEN: Yes, that's true. But it's --

DR. BERGFELD: We can put a hold on it with the expectation of receiving it due to the pledge of the companies.

DR. COHEN: Tell me the upside of that rather than just issuing the IDA with specific requests.

DR. BERGFELD: At least you can say that -- I think it's either one or the other.

DR. SLAGA: Either way. Issuing a new IDA is fine too. That would be a longer period, wouldn't it?

MS. FIUME: No. Not necessarily. I guess my question would be -- the question for the IDA would be first to identify, is the silsesquioxanes actually the same ingredient or would you need inhalation -- if you find out it is a totally separate ingredient, do you still need inhalation data at maximum concentration of use, based on the existing information in the report?

DR. SLAGA: Okay.

DR. COHEN: That's a very good question.

DR. ROSS: Yeah, that's --

DR. BERGFELD: Are you supposing that you would just disregard that particular ingredient's information and also inclusion of it in the document? Or just get rid of it? Put it for another review?

MS. FIUME: I guess that was my question when you were asking the table versus the IDA. If the new data are not relevant, do you still have questions about safety of inhalation, regardless? Or are the information currently in the report sufficient?

DR. COHEN: Right. So, if the pulmonary data wasn't even in Wave 2, would we clear -- Susan, would we clear this? Because our other IDAs were met --

DR. TILTON: So, we've had discussion before about when testing wasn't done at the highest -- or at the max use concentration. And in that case, for inhalation, we've relied on the boilerplate statement and the fact that there is likely little inhalation --

DR. BERGFELD: Risk. Risk.

DR. TILTON: -- but we're also not observing, there's no evidence for toxicity. But if the Wave 2 data were included, we would certainly have more evidence of toxicity.

DR. ROSS: Also, Susan, I think there's a point here with respect to the boilerplate. I think that data has some implications for the boilerplate language. Because here, I mean, this stuff was applied as an aerosol and in our boilerplate, we say that aerosols droplet particles deposited in the nasopharyngeal tracheal bronchial regions present no tox concerns based on the chemical and biological properties. The available information indicates an incidental inhalation would not be a significant route of exposure that might lead to local respiratory effects.

And, you know, that's what we're stating in this document if we have this in here. Even if we don't have it in here, we now have the example where we are seeing respiratory effects with an aerosol. This is not a mist or a vapor. I mean, this is with an aerosol.

So I think we have to discuss what it means for that boilerplate language also. And that's a downstream effect we have to think about. I mean, the initial two comments if they're summarized and the nomenclature issue and an inhalation tox issue. And then the downstream issue is what this means for that boilerplate.

DR. TILTON: Yeah. My statement was if the information from the silsesquioxanes in Wave 2 was found to not be relevant and was not going to be included.

DR. COHEN: We have the inhalation at 3 percent, and it looks like sprays and powders go up to 5.7 percent or --

DR. ROSS: Fifteen.

DR. COHEN: -- fifteen.

DR. ROSS: That's what I have in my notes if someone could help me with that.

MS. RAJ: 15.6 percent in face powders and 7.5 percent in aerosol hairsprays.

DR. ROSS: That's what I've got, yeah.

DR. TILTON: I thought it was at 7.

DR. COHEN: I'm just trying to find that.

MS. FIUME: PDF Page 33 is the Use Table that shows the actual concentrations. So, you can see the face powder there and then the aerosol hairspray is also listed there.

DR. COHEN: You said PDF 33?

MS. FIUME: Yes.

DR. COHEN: Okay. Face powders, 15.6. I see. And then, okay. Yeah, so, Susan, is that too far apart?

DR. TILTON: I had seen the 7 percent in the sprays and the face powders going up to 15 percent is quite higher. In the absence of the Wave 2 data, we don't have a lot of indication for toxicity. But if we are going to request new data then it could be helpful to request inhalation data at the max concentration.

DR. ROSS: That was my sense of it when I looked at it. And I had that 15 percent in there. And even if we don't include the silsesquioxanes, I think it's something to consider.

DR. COHEN: So, we want respiratory tox data at max use?

DR. ROSS: If we go for another IDA, that would be the request, yeah. And I would say probably with that more realistic exposure scenario, yeah, which was the previous study with the phenyl trimethicone. But I mean that's open for discussion, I don't know. Others may have opinions on that.

DR. COHEN: Oh, I'm sure it'll be a lot of discussion tomorrow. You know, we have had conclusions where it's safe as used, but insufficient for incidental inhalation if we don't get anything like that. But I think that'll be a valuable discussion with Belsito's team on what they feel. But my gut is to go with an IDA.

MS. FIUME: I think, administratively, part of the difference would be if the report is tabled and then it comes back and you find that the inhalation data in Wave 2 are relevant but doesn't answer your question. It would put the report on hold again while you issue an IDA since those data were not asked for before.

If you issue the IDA now, that would take one of those on hold steps out because you could always -- based on what you get or don't get, or find out about wave two, the next meeting you could still go forward with a conclusion because you've already asked the question. So, then that would be the difference, administratively, between tabling it now versus issuing an IDA.

DR. COHEN: It sounds like the IDA gets all our data requests out and takes one step away.

DR. SLAGA: Yeah.

DR. COHEN: Right? I think, Monice, you were favoring an IDA with that argument?

MS. FIUME: I'm just laying out the options.

DR. COHEN: Okay. I've interpreted it that way.

MS. FIUME: It would take one of the steps. But it's going to go on hold one way or the other and you are concerned that the respiratory will then also be an issue based on what comes back. By issuing an IDA that takes a second hold. It reduces the whole process by one step.

DR. BERGFELD: Sixty days.

MS. FIUME: Yeah.

DR. COHEN: Okay.

DR. ROSS: And IDA would be what? Clarification of chemical nomenclature as used around the two groups of molecules? And then, secondly, inhalation toxicity data under a realistic exposure scenario at maximum concentration of use.

DR. COHEN: Well, yeah. I added a two, which is the Wave 2 respiratory data applicable based on the answer to one.

DR. BERGFELD: Yeah.

DR. COHEN: Right. I'd rather be clear on what we're asking for.

MS. FIUME: So was it clarification of the names or is clarification of the CAS numbers also something that needs to be known?

DR. ROSS: I think Bart's had a little discussion that CAS numbers are basically unregulated so you can get multiple CAS numbers which cover different crystal structures, for example. Which is what I think we've got here. But I think that issue, Monice, to answer your question, specifically, the clarification of structure, I think the CAS number discussion would come up in that.

MS. FIUME: Thank you.

DR. BERGFELD: We can put that in parentheses to make sure they understood that.

MS. RAJ: DR. ROSS, would you mind maybe giving a little more detail on what you mean by a realistic study scenario for the inhalation tox data?

DR. ROSS: It was one -- and again David's making the motion, he may change this. But there was one study in there, which is my interpretation -- my own interpretation. But that was a fairly realistic exposure scenario. That was with phenyl trimethicone. And it did that with, I think, with 30 second --

DR. BERGFELD: At 3 percent.

DR. ROSS: -- yeah, 30 second bursts. That was the 3 percent study, and it followed it with a 15-minute exposure in a 350 liter chamber. So that's as opposed to a whole-body exposure, you know, for one hour, four hours or longer. And that seemed to me and, again, inhalation toxicology experts can chime in with respect to whether that's more realistic scenario or not, but it seems to me that it was. And there was, I think, some effects on body weight there were major changes.

MS. RAJ: Thank you.

MS. TILTON: Yes, and that was in the original report.

DR. ROSS: Correct. Yeah.

DR. COHEN: And, David, you said they had seven CAS numbers?

DR. ROSS: I think six, I think. Yeah.

DR. BERGFELD: Six I thought. Six.

DR. ROSS: Six. Yeah, if you look, it's in there.

DR. COHEN: Okay. Well, I knew I had to take copious notes.

DR. BERGFELD: I think you could turn some of that over to David to speak on.

DR. COHEN: Yeah, no, I fully intend to. But I want to be clear when we issue the IDA, exactly what we're going to ask for. And then we can have discussion and further detail on those IDAs.

DR. BERGFELD: I wonder if the industry people that are on could clarify that by tomorrow.

MS. RAJ: So, **DR. COHEN**, the CAS numbers for phenyl trimethicone can be seen on PDF page 32. And I believe the one associated with this phenyl silsesquioxanes is the 701316901.

DR. COHEN: 70131?

MS. GUERRERO: Yeah.

DR. COHEN: Okay.

DR. ROSS: And it's interesting because the one above that, phenyl methicone, has two different CAS numbers as well. So, I mean, it's not totally unusual.

DR. COHEN: Okay.

MS. FIUME: Tracy, were you going to respond to **DR. BERGFELD**?

MS. GUERRERO: Yeah. So, just waiting for the appropriate time. Yes, I think we will need additional time. We've got multiple member companies and I will need to go back to the group before I can provide a response.

DR. COHEN: Okay. So, we'll have the IDA anyway, and that'll give everyone time to get the information we need.

DR. ROSS: David, do you have the IDA formulated yet or not?

DR. COHEN: Yeah. Well, I'll create prose tonight, but the prior IDAs have been satisfied. There are new IDAs based on the Wave 2 data, which is clarification of the nomenclature of phenyl trimethicone, in particular the phenyl silsesquioxanes.

If these are, indeed, similar chemicals or the same, just in different crystal forms, is in fact that Wave 2 pulmonary toxicity data applicable to this report? If it is, it could influence our final decision. And if it is not, we're adding the additional IDA, of respiratory tox data at max use, in a test scenario similar to the phenyl trimethicone that has the 30-second burst and 15-minute chamber exposure.

DR. BERGFELD: We want it at max. That one was at 3 percent.

DR. COHEN: We have it at 3 percent and the max is over 15 percent, right?

DR. ROSS: Right. Beautifully phrased.

DR. COHEN: I'll try to be even more eloquent tomorrow. I think it'll be a very interesting and informative discussion.

DR. BERGFELD: I think so.

DR. ROSS: And as part of the discussion, could you bring up implications for the boilerplate? I think that's quite important.

DR. COHEN: Could you be a little more specific.

DR. ROSS: Yeah. You know, in that draft discussion in this document we have the boilerplate there. It's highlighted in yellow. And it's just that aerosol use generally is not giving you these pulmonary effects. Now, we have an example here where whether we use it or not, you know, whether it's included or not, where it is. And I just need some clarification and discussion around that. And it may be that this is the exception that proves the rule but --

DR. TILTON: So, you're saying --

DR. COHEN: A respiratory boilerplate?

DR. TILTON: -- if the Wave 2 data is included, that we don't have any additional data and we use the boilerplate, in that case we would have some data and -- we would have data indicating toxicity, which is not addressed in the boilerplate?

DR. ROSS: Correct. Yeah, I'm not sure you can use the boilerplate.

DR. BERGFELD: You can't use it. It doesn't address it.

DR. TILTON: I would keep the -- yeah, we couldn't use it.

DR. ROSS: That's my point, yeah.

DR. BERGFELD: Just call it an inhalation tox -- a void.

DR. COHEN: Right. Well, we would have a conclusion that it's -- the data does not support safety when incidentally inhaled, right?

DR. BERGFELD: Right. Exactly.

DR. COHEN: If that's what happens. I mean, we're far from coming to a conclusion on this.

DR. ROSS: Yeah.

DR. COHEN: Okay. Anything else? Well, we all knew what we were getting into with this one, so I would suggest that we move on to one or two before lunch just to get them behind us. If I have the team's permission, I would like to move on to wild yam.

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DR. BERGFELD: Okay, the last group is phenyl-substituted methicones. **DR. COHEN**.

DR. COHEN: Okay. So this is a draft tentative report on the safety of phenyl-substituted methicones. This is the second time we're seeing this assessment of 7 ingredients. At the September meeting, we issued an insufficient data announcement with the following needs; method of manufacturing and impurities and molecular weight ranges for all ingredients. We received information on some items for both of these data requirements.

Wave 2 provided a lot of data on phenyl trimethicone and trimethylsiloxyphenyl dimethicone. We also got some additional irritation and sensitization data. In this Wave 2 data, phenyl trimethicone, the ingredient was either identified as a test substance or as phenyl silsesquioxane. The latter caged or cuboidal structure is not similar to the open phenyl trimethicone.

Additionally, phenyl silsesquioxane (trimethicone?) had six CAS numbers and the one we apparently had data on was 70131-69-0. Commensurate with that data load from Wave 2, was some notable acute inhalation toxicity including five dead mice.

Given our uncertainty of the fungibility of the Wave 2 dataset to the original safety assessment of the 7 derived ingredients, we're making a motion with insufficient data.

Our needs are clarity of the nomenclature used in Wave 2. Two, applicable to the prior need, whether Wave 2 toxicities are applicable and salient to our review of the original seven derived ingredients. And three, we'd like additional respiratory toxicology at max use near the face, which I think is 5.7 percent. We have a realistic exposure scenario similar to that reported for phenyl trimethicone, namely 30-second bursts followed by 15-minute chamber exposure.

So that is our motion.

DR. ROSS: The incidental exposure was 7.5 percent spray --

DR. COHEN: Okay, thanks for clarifying that.

DR. ROSS: -- 15.6 on the powder.

DR. COHEN: Okay. Yeah. Okay. As I was writing this out yesterday, I saw one of them and I recalled it being higher. So, I'll just amend that additional respiratory tox at max use near the face, 15.6 percent with realistic exposure scenarios as previously described.

DR. BERGRELD: Don?

DR. BELSITO: We thought it was safe as used. The comments came from the Wave 2 read-across. I'll let Allan address that because we felt that the reported manufacturing and impurities for diphenyl methicone and phenyl trimethicone covered phenyl dimethicone and phenyl methicone, as did the data on diphenylsiloxy phenyl trimethicone covered that for diphenylsiloxy phenyl/propyl trimethicone.

So, Allan, I'll let you comment on the applicability of that and the read-across for Wave 2.

DR. RETTIE: So I had a lot of concerns about this because of the silsesquioxane piece and David and I talked a little bit about that, and several of us actually talked about it. But at the start of our discussion yesterday, I heard that we were dropping the silsesquioxane and it wasn't part of our list for approval. Perhaps that's not what everybody thinks?

DR. COHEN: Didn't it get added to the chart after the Wave 2 came in? In the Wave 2 there's a new chart with it listed.

DR. RETTIE: In some of those charts where it appears, that's where the confusion arises because it's also referred to as phenyl dimethicone and that's not right. If silsesquioxane is in there, the read across to silsesquioxane I don't think is good because it's quite a different material in terms of it's 3D. It's been mentioned as a caged structure as opposed to the others which are flat and provide slip, I guess, was the term that read quite a bit about.

So, if silsesquioxane is not in there, I feel we have decent read across. We have NMR data as well in that Wave 2 and spent a bit of time going through that last night. And it all looks pretty good for the test article which -- help me here, Bart -- which one is that? The test article for the NMR is one of our six.

DR. HELDRETH: That's right. It's the siloxy one.

DR. RETTIE: It's the siloxy one, yeah. And so, it looked like that NMR was actually pretty good picking out the different cone activities of the methyl groups, whether there's two or there's three. So, I thought that was actually quite convincing after having read through it.

Again, so I was kind of happy with that on a number of levels, but again it's predicated on us not dealing with the silsesquioxane.

DR. BELSITO: Which was my understanding, we're not dealing with. It's that correct, Bart?

DR. HELDRETH: Right, so --

DR. COHEN: But -- okay.

DR. RETTIE: Yeah. I was confused because it was still in our table --

DR. COHEN: It's in the table on PDF 5 of the Wave 2 supplement.

DR. ROSS: We didn't get that from our discussions yesterday and also discussions -- we asked for some clarifications from industry representatives on the structures and we didn't get that either. So, we were going with it was still in there and the inhalation data, as David just said, was of concern.

And going back to the other three inhalation studies we have with different materials. One was a vapor, one was a mist and the only other one that was an aerosol was the phenyl trimethicone done under these more, sort of, what we considered realistic conditions.

So, this particular inhalation tox was done with an aerosol and so we discussed in our panel that was of concern. I don't know if anyone else wants to comment.

DR. COHEN: Susan?

DR. TILTON: Well, the concern was only if the silsesquioxane data was going to be included. So, the concern came from that dataset where phenyl trimethicone was identified as the phenyl silsesquioxanes.

DR. BERGFELD: Bart?

DR. HELDRETH: I just wanted to interject. So, it's correct. The phenyl silsesquioxane is actually not even a cosmetic ingredient. And so, it's not been proposed to be part of the report and isn't now. Instead, when our friends at the Silicones Environmental Health and Safety Center made the submission, it included therein some study results based on a chemical, this phenyl silsesquioxanes, and it wasn't clear from the submission whether this was an error and they really meant to say something like phenyl trimethicone, or if they were proposing read-across from the silsesquioxanes to the trimethicone.

So we posed that question back to them and they promised that they're working on it with their members, and that we should have an answer from them by June.

DR. COHEN: Right. They were on our call and we got the same information. And we felt we wanted to hold this until we knew a little bit more about that. And PDF 5 had it listed there in the table. So, we thought that that table was updated for us to discuss this and draw information from it.

DR. BELSITO: First of all, we didn't consider the phenyl silsesquioxane as a new ingredient. As Bart said, it's not even in the dictionary. But even if it were, it sounds like, chemically, it's a very different molecule. It's a caged structure, which should not be included in this grouping anyway, so we kick it out, right?

So, if we get rid of that ingredient, are these phenyl-substituted methicones, are they safe as used as far as your team is concerned?

DR. COHEN: I think so, but this -- we got wrapped around the axel on this Wave 2, I got to say. I'll throw it back to the group. So, are we going to move forward and specifically exclude this before we have any further information from industry, or are we going to wait?

DR. BELSITO: But it's not a cosmetic ingredient.

DR. ROSS: I mean, I think our (audio skip) industry. Yes, we discussed two options. One, waiting for two months, basically, to get that information. Or going back to the -- you know, this was an aerosol study. So, go back to the aerosol study under realistic conditions of exposure and ask for maximum concentration of exposure.

So whatever came back with the silsesquioxanes, it wouldn't matter because you would have aerosol maximum concentration of exposure with phenyl trimethicone at realistic concentrations of exposure, i.e., max.

So, there were our two options that we considered. We didn't consider the option of just removing it and moving forward as if it wasn't in there. Because we didn't think we had that option.

DR. COHEN: And we also got information that further data would be forthcoming from industry in the next few months. If we knew it was going to be removed, why would've we even considered that further data from industry?

DR. BELSITO: Well, I mean, the point is, is that it's not a cosmetic ingredient, so.

DR. BERGFELD: Bart, can you give us some guidance on this?

DR. HELDRETH: Yeah. I think, at this point we're curious about the utility of the data that we received. I will also say, there was some additional data that the silicone folks provided to us; however, it was marked confidential so we couldn't share that with the panel. So that will also be forthcoming once they return it to us with the confidential markings redacted.

So I would propose, since there is a quandary here, that the best bet moving forward is to issue an insufficient data announcement with these data needs, and in all likelihood we won't see this report again until September anyway and you'll get plenty of time for everybody to submit the missing information. And this report can proceed forward in that way.

DR. BELSITO: I'm confused. So you're now considering adding phenyl silsesquioxane? (Inaudible) data.

DR. ANSELL: Why would we wait for data that's not going to be relevant to the assessment?

DR. BERGFELD: Bart, do you want to explain what the conversation was with the industry regarding what data submissions they had done?

DR. HELDRETH: So, there's two parts. So the one part was this issue with the silsesquioxane. We asked a question back to the silicone folks, is this an error, did you really mean to say phenyl trimethicone? Or were you suggesting some sort of read-across from the silsesquioxane?

So at this point, we don't know if the data's relatable or not and we're waiting to hear back from them. Additionally, they also had provided us with some genotox data that was on some of these tested ingredients, but we couldn't provide that because it was marked confidential.

MS. RAJ: I'm sorry, I just wanted to add, we are also waiting for details for two short-term oral tox studies. One for the silsesquioxanes and one for trimethylsiloxy phenyl dimethicone.

DR. ANSELL: We've already concluded that the data's not going to be relevant for the assessment of the other materials. It's not in the report. I'm a little confused as to what we would do with this data since we've already concluded it's not going to be relevant for the assessment of the ingredients of interest.

DR. COHEN: So, Jay, we got a 119 page Wave 2 supplement to consider in this assessment. We didn't ask for it. It got downloaded to us and it was labeled as phenyl trimethicone. And the question was, is there fungible data in that report that we have to consider in this assessment, although the obvious part of it is, it's different. It's just, it's extraneous information that we can't -- has no fungibility into this report. But that was not clear to us.

In addition, industry suggested that they're going to interrogate this Wave 2 a little bit better and say, hey, you know, this wasn't supposed to be here or there is value to this.

Of course on the surface, on its face, yes, if we never got that Wave 2 we probably wouldn't be in this predicament. Maybe we would ask for higher max use respiratory data, maybe we'd be able to talk through it. But we have it and there's consequential respiratory toxin there, so we just want to make sure can we jettison it because it was sent to us.

DR. BELSITO: So you don't think a respiratory boilerplate covers the respiratory toxins?

DR. SNYDER: I would urge a little backing off on the respiratory inhalation tox. I mean, all of them -- these are acute inhalation studies and one of them has it -- it's at 18 milligrams per kilogram, is the LC_{50}. The other one is similarly high, probably 5,000. Or, no, not that, that's the dermal.

But they're pretty high. The only one that's an outlier is this phenyl silsesquioxane one and even it at 0.5 -- it was only tested at 0.5 and at 5 and all those deaths were very acute and so they were in a chamber, and they were exposed for an hour. And so, that's not replicating aerosol intermittent use by personal care products.

I was concerned about that, but then when we had the discussion saying that this was an outlier, we had data sufficient enough to clear all of them using the three that we had the complete datasets on. We did not have read across data for this outlier, so I thought we were going to say they were safe as used for those, all of them, except for the phenyl sisesel- -- however you say it.

DR. BELSITO: Silsesquioxane.

DR. SNYDER: Yeah, and we were going to recommend not to include it because it's different. It probably inappropriately got grouped with this one. It's not used in cosmetics, we have no data. So my recommendation is we say all the rest of them are safe as used with the read across. This one is insufficient, it's not used, and we don't have any data.

DR. BELSITO: It's not part of our report.

DR. SNYDER: Right. So either way, it's out.

DR. COHEN: It appeared in the table in Wave 2. It appeared in an updated table in Wave 2.

DR. BELSITO: I understand. But we're now told that it's not a cosmetic ingredient and it's not part of this report, right?

DR. COHEN: I think having a clarification before making the determination is not unreasonable.

DR. ROSS: I'm with David on this one. I think it came in with the same CAS number. And Bart and I had a discussion about CAS numbers and how they vary, et cetera. Phenyl trimethicone was six different CAS numbers, I think. But this stuff came in with the same CAS number.

So I think -- and okay, it might be a different crystalline form, which I think is where we ended up, and would be a basis for exclusion, I think, because the caged versus open is going to be very different. But we don't have that information yet. So, I'm not sure we can move forward with that safe as used conclusion with the information we have.

DR. BELSITO: What information do we not have? Could we not put that into the discussion that the Panel was given information on phenyl silsesquioxane. It noted that it had the same CAS number as one of the ingredients used in this. However, the panel also noted that this was a caged structure. That it was not listed as a cosmetic ingredient and could not be read across and is not considered part of this report. Couldn't that be part of a discussion.

DR. ROSS: It could be. But given the inhalation tox, we felt we needed more information on that. And I hear Paul's comments as well. I think they're relevant, but that was an aerosol exposure. But anyway, I mean, the major issue was, is it or is it not part of the grouping that we're going to measure and going to assess. And I think industry said that they were going to get back to us and we don't have that data yet.

DR. TILTON: So, I also agree that if that data is identified as being from phenyl silsesquioxane, then it doesn't belong in the dataset. I guess we had some confusion as to whether or not industry was going to come back with identification as to whether -- because it was identified both as phenyl trimethicone and as phenyl silsesquioxane, and it has the same CAS number.

So, I was under the impression that we were waiting to hear back as to actually whether or not that dataset was for phenyl trimethicone and should be included, or whether it was for this other chemical structurally unrelated and would not be included.

DR. COHEN: And that's a perfect articulation of what we discussed.

DR. BERGFELD: Allan, do you want to respond and then Thomas. Allan Rettie? How are you feeling about this? You're not on. Your audio is off.

DR. RETTIE: No, I'm here. I'm sorry, I was muted. It seems more a procedural thing to me. Because at the end of the day, as long as the silsesquioxanes are eliminated from everything, purged from the report, purged from the tables that we've been looking at -- which are very confusing -- I just don't really know what to say about that in terms of procedurally moving forward. I'd definitely be guided by others.

But I'd just reiterate that the read across is fine for the other compounds, in my opinion. And if we can all agree that silsesquioxane is not in the report, and we have updated tables and updated report to just purge that, we're probably going to be moving forward. At least, I think our team here would be suggesting that that's what we do.

DR. COHEN: I think we'd just like clarification on that. That's all.

DR. BELSITO: So if you'd like clarification, then we should just table it, right?

DR. COHEN: Well, we have data needs.

DR. BELSITO: Your data needs are clarification of the current data we have, right?

DR. COHEN: I would suggest that that may be new information. I don't know what the clarification is going to have. I don't know what it's going to say. You have two structures with the same CAS number and a 119-page report added in Wave 2.

So is the obvious going to execute, which means this is extraneous information, jettison it, it has nothing to do with it. Or is there something that we haven't -- because yesterday the industry was not clear and did not say to us, just get rid of that information, we don't know why you have it.

DR. BELSITO: I'm not a chemist, but I've been confronted with my experience on the RIFM panel where two different materials had the same CAS number, too. So CAS numbers don't necessarily -- just because they have the same CAS number doesn't mean that they're the same materials. That classification system seems to need someone to get it in order.

So, even if it comes back with the same CAS number, we have molecular structure that shows that it's a different molecule, it's not a cosmetic ingredient. Even if it were, we wouldn't include it in this report because we don't feel you can read across from it.

And so why are you concerned about the respiratory toxicity of that molecule, which is not going to be part of this report? Number one. And number two, why wouldn't the respiratory boilerplate cover you for these materials?

DR. COHEN: You want to, let's see what Thomas has?

DR. BERGFELD: Thomas, do you want to talk? Sorry about that.

MR. GREMILLION: No. I had a comment and a question. And the comment is that the CIR always seems to favor gathering more data and it seems like there's forthcoming data. The question is just whether there's precedent for adding the report in stating an ingredient -- I guess here an ingredient with the same CAS number as another one is excluded from the report. Is that something that CIR does a lot, or has done a lot in the past?

DR. BELSITO: Thomas, we have used read-across for materials that aren't cosmetic ingredients when we felt that they were in the same grouping as the material we were looking at. So, we've done that. But here, we got information that we felt we can't use to read-across because the chemicals are not structurally the same.

DR. BERGFELD: Bart, can you respond to that as well?

DR. HELDRETH: Yeah. So I think the question I'm hearing that may -- if everybody can agree on the answer -- may solve the issue here is if we just assumed that that data is from the silsesquioxanes. And at this point, we just set it aside and throw it out, can we rule on the safety of the ingredients in front of us from the trimethicones? If we can do that --

DR. BERGFELD: That's what Don is proposing.

DR. BELSITO: We could.

DR. HELDRETH: And if we can do that and come to a conclusion of safety -- and again, this is only tentative, so we're not final here -- next time we see this report, we'll get that additional information and if somehow miraculously it changes your mind, then we can move from there.

DR. COHEN: What changed between issuing the IDA, that you mentioned before, to this solution?

DR. HELDRETH: Because I'm hearing that if we didn't have this data in here, you may be making a ruling on safety. If they had submitted it --

DR. BERGFELD: I heard that from everyone, yes.

DR. HELDRETH: Go ahead, I'm sorry.

DR. TILTON: So, David, I just want to mention -- so we had talked about inhalation toxicity. I do feel comfortable with the data that was in the original report, about not having concerns with regard to safety. The concern primarily was from that new dataset in Wave 2 where there was acute toxicity. And I understand the exposure may not really be that relevant, but it was at low concentrations.

So, outside of that dataset, I wouldn't have a concern about moving forward with safe as used, including the boilerplate language.

DR. BERGFELD: David, you want to survey your team?

DR. COHEN: Well, I guess the other question is if we table this, would it come back in June with the answer from industry?

DR. BELSITO: Bart already said September.

DR. BERGFELD: Yeah. Not necessarily.

DR. COHEN: Well, if it was an IDA it would come back in September, right?

DR. HELDRETH: Chances are it'll come back in September regardless of how the Panel chooses to move forward with it. If someone is planning to submit some information in June -- you know, our meeting is in June -- that may fall after the meeting. It certainly won't fall far enough ahead of time to give the panel the information in advance of the meeting if that's the case. So, yeah, September would be the most likely time that you would see this report again, whether it's IDA or you issuing a tentative report.

DR. COHEN: Tom?

DR. SLAGA: Well, after hearing both sides -- I initially agreed that the one compound we were talking about is an outlier and the simplest thing to do is to eliminate it if it's really not related to the other compounds, and go for safe with the others.

DR. BERGFELD: Okay.

DR. COHEN: Susan, you already made your comment about it, right?

DR. SLAGA: Right.

DR. TILTON: Yes, that's correct. And to be clear, I don't think that silsesquioxanes should be included. The question was whether or not the data in that table, which chemical was actually being used in those studies. So, outside of considering that I would certainly agree that they are structurally dissimilar, so you wouldn't include read-across.

DR. COHEN: So, when you look at Wave 2, you have comfort that the concerning pulmonary toxicology was from the silsesquioxane and not from phenyl trimethicone?

DR. RETTIE: I don't think we know that, do we?

DR. TILTON: I mean, that's the question.

DR. COHEN: Well, that's the whole argument that we've been making before. Is that we'd like clarity on that. If you could tell me that that Wave 2 is not phenyl trimethicone then --

DR. SNYDER: I can almost assure you that's not phenyl trimethicone, because that is an outlier study. There's other data in the original report that has much much higher LC_{50}s. And so, when I pinged it as an outlier and said, why is this, then when I found out it was the outlier chemical, all the rest of the data matches up. There's very low toxicity with this stuff.

All that data's negative. Everything is negative, negative, negative except for that one inhalation study, which we had the caveat of potentially being a different player. Even if the other data in the report are all related to that molecule, then we have to see a concentration of use because if it's only used at 0.0002 percent, okay, we discuss it, it's not an issue at the concentration of use.

But we don't have any uses. So, I think we're kind of beating at the bush here inappropriately. Yes, we had this signal, but it's not an ingredient that's a cosmetic. We don't have any data on it. It's inconsistent with structure with all the rest of them.

So at this stage, I say we just all agree to eliminate it from the report. If it comes back that it's used, then we'll do it on its standalone report. And just clear these three based on read-across. That's my two cents.

DR. SLAGA: I agree with Paul.

DR. BERGFELD: Okay. How about David Ross.

DR. ROSS: Yeah, I had a question for Paul. Which data -- I mean, the rest of the data looked very, very good. I think basically Susan's point, I think, was what we discussed yesterday. If we had just seen this dossier without the Wave 2, we would've approved the safe as used. The only concern was that inhalation tox data with the phenyl silsesquioxanes.

DR. SNYDER: Yeah, David, I think even with Wave 2 we would've cleared it if it hadn't been for that one acute inhalation study. Because it's all very consistent with what's already in the report.

Very low toxicity across the board. Then we've got tons -- we've got acute dermal, we've got developmental tox -- multiple developmental tox studies. We have multiple inhalation studies. We've got genotox.

This is a pretty complete dossier here in my opinion. It all matched up until I got that Wave 2 and that one outlier. And then I said well this is a bad actor so we've got to figure out what's going on.

Even that, in the context, 0.5 milligrams per kilogram is not great but I wanted to know what it was in relation to the concentration of use in the consumer product.

DR. ROSS: Yeah. I mean, that's fair enough. I mean, which data were you referring to in the inhalation data that was a much safer profile?

DR. SNYDER: It's in the original report where there were acute inhalation studies where there was -- I got 18 milligrams per kilogram for an LC50 and the other one was equally as high, I thought. Table 4.

DR. ROSS: I thought it was 18 milligrams per liter but -- yeah, 18 milligrams per liter. And that was a vapor. And the third study that I quoted was a mist. The only one we had with an aerosol that came up, that was the phenyl trimethicone.

DR. SNYDER: But we don't even know if it's used in an aerosol, right? It could be in a powder.

DR. ROSS: Well, it's spray and powder in the document. Yeah. So --

DR. SNYDER: Yeah, but not for the outlier. That's what I'm saying. If it's trimethicone -- if it's phenyl trimethicone that's a different issue. But I was basing my interpretation of the data, saying it was not phenyl trimethicone, that it was this outlier molecule ingredient.

DR. ROSS: We're just reading off the data we had. It said it was an aerosol with the new data. Yeah. Triphenyl silsesquioxane. I have trouble saying that was well. And so, that was our concern with the aerosol. So, I mean, I guess we all --

DR. SNYDER: I think we're all talking the same. We're all in agreement, it's just how are we going to proceed?

DR. ROSS: Exactly right. What --

DR. COHEN: I agree, Paul.

DR. BERGFELD: So, is there a new proposal or are we going to just stand with David's recommendation of going insufficient? Are we going to go safe or insufficient?

DR. BELSITO: It sounds like that Tom Slaga and my group, and possibly Susan think we can go as sufficient, which would be a majority.

DR. COHEN: Don, don't count your chickens yet.

DR. BELSITO: Well, I'm just telling you what I'm hearing, right. I mean --

DR. COHEN: Well, when faced with the question, are we resolutely sure? And it's important that Wave 2 was not phenyl trimethicone. And when that question was given to industry, we did not get an answer, no this is not phenyl trimethicone. It was, we're going to need a little time to look at that to make sure.

Okay. And so the only reason we issued the IDA was to be sure we can dispose of Wave 2. Because I didn't ask for Wave 2, I got Wave 2. I got Wave 2 with complexity and ambiguity, right.

Listen, we held up Basic Blue for a concentration of use. It might be interesting to know that that Wave 2 is not phenyl trimethicone. Because if it is, it does change a lot of what we do. We're all agreeing, Don. We're not disagreeing on really anything, here, other than how we -- do we wait until September or do we do it now?

DR. BELSITO: We have repeated inhalation on phenyl trimethicone from the old reports.

DR. COHEN: At what percent? Isn't that at 3 percent?

DR. ROSS: Three percent.

DR. COHEN: Three percent. And it's used at 15 percent around the face in powders.

DR. BELSITO: And again, the respiratory boilerplate doesn't help you there? I mean, there are so many ingredients that we have had no inhalation toxicity that are used in sprays and powders, and we go ahead with the boilerplate.

DR. COHEN: I think the ways these are used is probably a bit more important to have some respiratory tox. And I know we're going to have the airbrush in here. But I'm not quite sure what the need for expediency is on this, when we were provided this data that's not clear.

DR. BELSITO: I'm not saying that there's any need for expediency. I'm just saying that we have the data that we need. I mean, that's what we act on, right. We don't necessarily act on expediency.

DR. COHEN: Well, we have data that's ambiguous, we can agree to that, right. And I have a high suspicion you will be correct in September. But I'll also have the assurance that industry has clarified their data dump to us as being non-fungible and unnecessary here.

DR. BELSITO: So, it's a non-fungible token, is that what you're saying?

DR. COHEN: It's a non-fungible -- yeah, I mean. I think --

DR. BELSITO: Get some bitcoin in there.

DR. BERGFELD: Okay, I think that our discussion is only going to circle now.

DR. COHEN: I was going to hold the IDA.

DR. BERGFELD: You were going to hold it?

DR. COHEN: That was my plan.

DR. BERGFELD: That's your motion?

DR. COHEN: I was going to hold the IDA.

DR. BERGFELD: Do we have a second somewhere so we can vote this up or down?

DR. ROSS: What's the motion?

DR. BERGFELD: The IDA.

DR. COHEN: It's the IDA.

DR. ROSS: Okay.

DR. BERGFELD: Do we have a second anywhere?

DR. ROSS: And the IDA was -- can you repeat the IDA?

DR. COHEN: Clarity on the nomenclature used in Wave 2. Applicability of the Wave 2 toxicities to the report on the seven derived ingredients. And we did add additional respiratory tox at max use near the face in an exposure scenario similar to phenyl trimethicone, understanding that the answer to one may not require the other, but we're asking for everything.

DR. ROSS: Okay. I'll second that and see how this vote goes.

DR. BERGFELD: Okay. All right. That's a positive for IDA and I'm going to call the vote. I'm going to say all those in favor please indicate by raising your hand. If we can make a count -- Bart, can you help me? So we have two, Tom is not voting for it. Susan, not. Oh, you are. So it's three. Opposing?

DR. SNYDER: I oppose.

DR. BELSITO: I oppose.

DR. BERGFELD: Paul -- okay, to two.

DR. RETTIE: I oppose.

DR. BERGFELD: Allan is three.

DR. BELSITO: Curt, is four.

DR. BERGFELD: Four.

DR. COHEN: Wait, Tom, which way did you vote.

DR. BERGFELD: You're opposing the IDA or for it?

DR. SLAGA: On the IDA.

DR. BERGFELD: You're opposing it or for it?

DR. SLAGA: For it.

DR. BERGFELD: Okay.

DR. COHEN: It's a tie.

DR. BERGFELD: It's a tie. I'm going -- Bart, did you count that as a tie?

DR. HELDRETH: Yes.

DR. BERGFELD: Okay, then I cast the vote.

DR. HELDRETH: Okay.

DR. BERGFELD: I'm voting for the IDA. So, it goes out as an IDA. Thank you. Sorry, Don. Okay.

DR. COHEN: Don's going to be victorious, ultimately, anyway. But I'd rather have the info.

DR. BERGFELD: Well, I think the discussion is well discussed. And I think all the issues were put out on the table so our minutes will reflect that. It was a good discussion.

JUNE 2023 PANEL MEETING – THIRD REVIEW/DRAFT TENTATIVE REPORT

Belsito Team – June 12, 2023

DR. BELSITO: Phenyl-substituted methicones. So, we'll do this and then I think we need a break. So, on this we got a Wave 2 and a Wave 3. We got several waves on this. I guess people liked it. Okay, so let's see what we've got in Wave 2. What page is it on, Monice?

MS. FIUME: PDF page 17.

DR. SNYDER: CIR 17 and 19, and WVE, 19 to 24.

DR. BELSITO: Ah. This was the whole respiratory thing that we were going to ask Bart about.

MS. FIUME: Or Jinqiu.

DR. BELSITO: Or Jinqiu. I mean, this is just concerning. I mean, this paper by Berrada-Gomez, did you read it? I mean, it looks pretty efficient to me. Did you get a chance to pull it up? And the diagrams are all here. I mean, just look at the graphs, they're very --

DR. SNYDER: I just peer reviewed a study by the first author.

DR. BELSITO: I mean, the dry shampoos are --

DR. SNYDER: Very high. Very high.

DR. BELSITO: Yeah. I mean, a small number of products but it raises a whole --

MS. RAJ: Yeah. But it's an unreported category in VCRP. Dry shampoos are not reported in the VCRP.

DR. BELSITO: Yeah. I understand that, Preethi, but even their propellant-based sprays were higher, you know, in some cases up to 32 percent. And their pump sprays in some cases up to 2 percent.

I mean, again, it's a small number of products, it's not large, but I think it raises the issue as to whether our numbers are too low. Are we not being conservative enough?

Again, respiratory toxicology is not my expertise. I just look at data and it causes red flags that I don't necessarily understand because I'm somewhat making an allergy colorblind in that area.

DR. SNYDER: Well, we're very reliant on this data in our resource document says it's particle size --

DR. BELSITO: Right.

DR. SNYDER: -- is not respirable. But if they're 30 percent higher than are, than that's a different dataset.

DR. BELSITO: I know. So, I mean, what do we do with this? I mean, I don't think we can ignore it.

DR. SNYDER: We have lots of data. We have no inhalation data?

DR. BELSITO: No.

DR. EISENMANN: There should be another reference added to be your respiratory research document.

DR. SNYDER: Yes.

DR. BELSITO: But then does it change our boilerplate?

DR. EISENMANN: I thought you'd taken out the numbers in the boilerplate for the most part.

DR. BELSITO: But we say that -- the boilerplate does talk about --

DR. EISENMANN: Well, the boilerplate was focused on the hairsprays, so maybe you focus on the product category rather than -- and I don't have a good answer. Because, frankly, it's going to be variable. I mean, there's no way --

DR. BELSITO: Right.

DR. EISENMANN: I mean, in some ways I had thought that maybe you should say, or it should be less than a certain percent. But it's hard what that percent is supposed to be, but I don't know -- have an answer. I mean, in other words, provide industry with guidance on what you think is appropriate rather than -- because it's going to be a quick range.

DR. BELSITO: But, inside of -- so this is a new paper, right, this just came out --

DR. KLAASSEN: Right.

DR. BELSITO: -- 2023. And as I was reading it and seeing this and thinking about it, are manufacturers moving to give finer and finer sprays for cosmetic elegance? You know what I mean? What has changed that -- so instead of getting a clunky hair spray or a clunky dry shampoo, you get a nice fine mist that you can comb through your hair. I mean, this is -- again, this is all hypothetical. But why are we seeing this as new data and has the technology in pump and propellant sprays changed, and we're not keeping up with that?

And I don't know the answer to that. You know, we have air brush technology now. There seems to be a movement to finer sprays to give a more elegant cosmetic effect. I mean, that's the whole point of air brush. It's a really nice spray and you can essentially paint on your makeup, and it looks absolutely gorgeous.

And every bride in New York City now is getting air brushed. It's an exaggeration, but you know what I mean? That's where you're at when you're going to professional makeup artists. They are all, or virtually all, are using air brush technologies when available.

I don't know. I mean, I'm interested in other people's viewpoint. Did you look at the paper, Curt?

DR. KLAASSEN: Yeah, I sure did. It was very concerning. And as I looked at it on PubMed it gave another half a dozen papers that are similar, you know how they always do. And I didn't look any of those up, but the titles of some of those looked that it might be appropriate to look at, too. I mean, I think this whole thing -- we may begin to completely redo this inhalation thing.

DR. SNYDER: So, my question is how come we didn't find this paper? Do we have a periodic review for looking for new publications on some of our important --

MS. FIUME: So, we had just done it.

DR. SNYDER: Okay.

MS. FIUME: Was it March?

DR. ZHU: Yes.

MS. FIUME: We had done in March, we just had --

DR. SNYDER: Well, you don't have -- I get a ping on certain things. Say something's published, I get a ping if it's an area of interest.

DR. BELSITO: Right.

DR. SNYDER: So, we don't have that set up? Do you have that set up?

DR. SNYDER: Did you get pinged on this? Because this came from Women's Voices of the Earth. I think that bothers me more than anything that it didn't come from us.

DR. ZHU: Yes. But this is instead particle size, it's not related to the ingredient. It's just a rarely discussed item.

DR. SNYDER: Cosmetic spray preparation. That should hit us. That should've been an alert.

MS. FIUME: So, you're asking for our resource document, did we get a ping on the inhalation tox?

DR. ZHU: We can definitely collate -- bring the new data into our --

DR. SNYDER: No, you can incorporate it, but what I'm asking is we -- I wish we would've known about it before they knew about it, because I think we should.

DR. BELSITO: Right.

DR. ZHU: I mean, we find this paper is not related to the ingredient. It's not --

DR. SNYDER: It's highly related.

DR. BELSITO: It's related to every ingredient we review, based upon our not having inhalation toxicity. We use that boilerplate for every ingredient. So, you should get, whenever there's a new publication, particularly entitled cosmetic --

DR. SNYDER: Cosmetic spray products.

DR. BELSITO: -- spray products, you should have, as Paul said, pings that will alert you to publications. You can go into PubMed and set those.

DR. SNYDER: Well, I mean, we have to relook at it.

DR. BELSITO: Yeah. I mean, I think we need to reopen the respiratory boilerplate.

DR. SNYDER: This is not insignificant.

DR. KLAASSEN: Not at all.

DR. SNYDER: We've been making the presumption it's all less than 5 percent.

DR. BELSITO: Always. And clearly there are exceptions here. So, that's why I raised this point first thing in the morning, where does that put us for everything that we don't have any inhalation tox?

DR. SNYDER: Well, I mean, it's kind of a game stopper right now for all the reports that are in progress, right?

MS. FIUME: So, this does have inhalation tox, is that at all helpful?

DR. SNYDER: Okay. Yeah, that's what I was looking for before we started --

MS. FIUME: So, there's acute tox --

DR. SNYDER: Because I have that we have plenty of data, I just didn't specify, I said plenty of tox data.

DR. BELSITO: Right. Let's look at Wave 3 before we move on. So that was Wave 2. And then Wave 3, I think, were just PCPC comments. Is that correct?

DR. EISENMANN: Yeah. And the biggest issue is that we've taken out three CAS numbers. And SEHSC submitted data based on CAS numbers. And the one material that we've taken out the CAS numbers, they've came back and they say it's still relevant for phenyl trimethicone, and we don't think it is.

We agree with you guys that the siloxane material, that is not relevant and that data should be out of the report. Because we did have an INCI committee member look at the CAS numbers again. He's an expert in this area and it was not just the one CAS number that was wrong, there were three CAS numbers that were wrong. Unfortunately.

DR. BELSITO: Okay. You're okay with the report and removing those CAS numbers and then everything else is just editorial comments?

DR. EISENMANN: The data on the one CAS number needs to be removed from the report. It's under the name phenyl trimethicone.

DR. BELSITO: Right. But it was not phenyl trimethicone, it was the siloxane and that has been removed.

DR. EISENMANN: No. It was added to the report.

DR. BELSITO: It was added. So, it nee- --

DR. EISENMANN: Because, unfortunately, SEHSC came -- before I said that we removed those numbers, before we had done it, before they had gotten the review, they came back and said, yes, it's appropriate for the report.

MS. FIUME: Well, they said it was phenyl.

DR. EISENMANN: I know that's what they said but they also put it under the CAS number, and I think you should go with the CAS number. I've been trying to get them to contact you again and do another correction, but apparently they have not, even though I put urgent.

DR. BELSITO: So, they told us it was phenyl trimethicone but the CAS number they gave us was a siloxane and we can't read across from it. So, when in doubt, drop it. So, get rid of the data --

DR. SNYDER: We're not just dropping it, it's been cleared. It's not phenyl trimethicone.

DR. BELSITO: No, it's not been cleared is what I'm hearing from Carol. They have to clarify.

DR. EISENMANN: SEHSC says it's not been cleared -- said that it's for phenyl trimethicone.

DR. BELSITO: The SCCS?

DR. EISENMANN: No, the Silicones Environmental, Health, and Safety Center.

DR. SNYDER: The SEHSC.

DR. BELSITO: Okay, so the Silicone group said -- okay. That it's not?

DR. SNYDER: No, they said it is.

DR. EISENMANN: They said it is.

DR. SNYDER: The sesquioxane and it is the phenyl, they said it's equal. But then I have one outlier is now cleared. In the comments.

DR. BELSITO: How much do we need that --

DR. RETTIE: I thought this was settled.

DR. BELSITO: How much do we need that read across data?

DR. EISENMANN: It caused the problem rather than being a help, because that where the inhalation study results in deaths.

DR. BELSITO: Oh.

MS. FIUME: Because it's not read across. It's an ingredient in the report.

DR. BELSITO: Right, okay.

DR. EISENMANN: It's not really an ingredient in the report because it's on that wrong CAS number. And that material is actually in the dictionary under a different name as a -- what's it called?

DR. BELSITO: Okay. So now --

DR. EISENMANN: Yes, it's very confusing.

DR. SNYDER: You've got to look at the report --

DR. BELSITO: Yeah. Let's go to the report.

DR. SNYDER: -- and take out all that data because it's not relevant.

DR. RETTIE: So, where do we stand on this lung toxicity and linking it as an ingredient? Because after reading all of this iteration in this report, I form the impression that we were talking about phenyl trimethicone all along and that the lung toxicity, inhalation toxicity, all resided with phenyl trimethicone after all. And I could sort of see how that would happen because we had lung tox signal for another silicone, I think it was the diphenyl dimethyl. So that all seemed to kind of gel together for me.

That's not the case then? The concerning lung toxicity data, what is it for?

MS. FIUME: Phenyl trimethicone.

DR. EISENMANN: It's for -- the INCI name is now is polyphenylsilsesquioxane.

MS. KOWCZ: You're right, Allan, it's not for phenyl trimethicone.

DR. EISENMANN: But in the report currently, it's being called phenyl trimethicone because SEHSC said it is appropriate. But I think they said that because we had the wrong CAS number associated also with phenyl trimethicone. So, yes, it's very confusing, unfortunately.

DR. RETTIE: So, we're still waiting for clarity then, in terms of the nomenclature to some degree.

MS. FIUME: Well, the issue is that the submitter said even though it said silsesquioxane, that is the phenyl trimethicone.

DR. EISENMANN: But they still associate it with the CAS number.

MS. FIUME: Right.

MS. KOWCZ: The CAS number's wrong.

MS. FIUME: But the problem is the only information we have is them saying, yes, this is your cosmetic ingredient. And we don't -- based on the synonyms used, they didn't -- I can't find my -- can you find the email that they say, based on the CAS number? Or did they say it was a material tested?

MS. RAJ: They said there was no error in naming. Because when we asked them pointedly, is this indeed phenyl trimethicone, they were, no. There was no error in naming, this is phenyl trimethicone.

MS. KOWCZ: But that was based on the CAS number. The CAS number was not correct.

DR. EISENMANN: In the original submission, didn't they line up the data with CAS number?

MS. RAJ: They did. They did. Yeah.

DR. RETTIE: But didn't we have a long discussion about multiple CAS numbers?

DR. BELSITO: Where is the inhalation data here? Because all I see is inhalation data from the old report.

DR. EISENMANN: Right. So, that's why I went back to the INCI committee and said, can you please check these.

MS. RAJ: And there's one short-term study for phenyl methicone. It says trimethicone but it's phenyl methicone.

DR. BELSITO: Preethi, you have a bunch of oral studies under the inhalation subheading.

MS. RAJ: Say that again?

DR. BELSITO: PDF Page 41, you have inhalation subheading. And then, you say details of subchronic toxicity studies summarized below and are provided in Table 5 and then you talk about oral. So, you need a new subheading there of Oral.

MS. RAJ: Are you looking at PDF Page 40, Dr. Belsito?

MS. FIUME: We need to probably flip it because typically in the report we --

DR. BELSITO: Do oral first.

MS. FIUME: Well, we report the data from the original studies or the original CIR report first.

DR. BELSITO: Right.

MS. FIUME: And then, when we're referring to the table, it has multiple routes. We don't give a heading for the routes. So, we probably just, in that case, need to flip it so it's clear that it's not --

DR. BELSITO: Because the oral studies are appearing under inhalation subheading. It's PDF Page 41.

MS. RAJ: Okay. Sure.

DR. EISENMANN: If you do decide to leave the data in, which I hope you don't, it would be helpful to put the CAS numbers associated with the data. So this is on this CAS -- so there are -- I don't think you should leave it in, but make it clear for historical purposes later, that they submitted this data under this CAS number. And now that CAS number is not right. Rather than just calling it phenyl trimethicone. That'll be the compromise.

DR. RETTIE: So in terms of this respiratory toxicity question, there was a suggestion of what we needed in terms of additional respiratory toxicity data ambiguously done on something. And that suggestion was -- I think it came from Dave Ross -- that phenyl trimethicone be used in a short-term inhalation study rats, exposed to an aerosol at 3 percent phenyl trimethicone. I think maybe 7.5 would be more appropriate as described in the original report, a 30-second bursts, 15 minute exposure in a chamber. We didn't get that, right?

So, is that what we need, something everyone can agree is phenyl trimethicone?

DR. SNYDER: Well, the 7.5 percent counts because that's the maximum concentration of use.

DR. RETTIE: Yes.

DR. BELSITO: Well, I mean it sounds like we still don't know the applicability of the data to the assessment.

DR. EISENMANN: The data on the CAS number that was taken out is not applicable, that's what I think.

DR. BELSITO: But are they just giving us the wrong CAS number and the right material or vice a versa?

DR. EISENMANN: I think they've given you material on that CAS number, which is no longer appropriate for this report.

DR. BELSITO: But they said it was triphenyl --

DR. EISENMANN: They said it was phenyl trimethicone.

DR. BELSITO: Phenyl trimethicone.

DR. EISENMANN: It wasn't the naming. But when they said that, that was before I had gotten the results of the CAS number review for the ingredient. And I have not -- I mean, I've tried -- I've sent that memo to them, too.

DR. BELSITO: They've sent you a report.

DR. EISENMANN: They didn't send me anything. They went directly to CIR.

DR. BELSITO: Okay, so they sent CIR a report, and they said this is phenyl trimethicone and this is the CAS number. Is that right? Or did they say, here is a report on a CAS number?

DR. EISENMANN: They sent data on several materials under different CAS numbers, which are all being used for phenyl trimethicone in the dictionary.

MS. RAJ: Did you want to tell them --

MS. FIUME: I'm trying to see, because there's different color -- I don't know.

MS. RAJ: It says, "The data set provided" -- this is their response -- "is associated with CAS number 70131-69, which was removed. But, you know, I guess, they had not seen that by then. "Can be described as silsesquioxane or resin, as well as phenyl trimethicone." So, they said as well as phenyl trimethicone. They're kind of saying they're the same.

DR. BELSITO: Read what they say again, because I'm reading that as saying the CAS number they're giving could be used to describe two different materials. And we know that happens all the time where the same material has multiple CAS numbers.

MS. RAJ: Would you like me to read their whole response?

DR. BELSITO: Yeah.

MS. FIUME: I think their whole response needs to be read.

MS. RAJ: Sure, so I'll start again. "The dataset provided that is associated with CAS number can be described as silsesquioxane or resin as well as phenyl trimethicone. The end key monograph associated with this CAS number, and referred to as phenyl trimethicone, exactly describes the product that was tested and reported in our data submission to the CIR. Therefore, the dataset can be considered representative data on phenyl trimethicone. There was no error in the naming of the test article."

DR. EISENMANN: But that test article has a different INCI name now. It is polyphenylsilsesquioxane. So, in other words, the CAS number 70131-69-0 is associated with an ingredient in the dictionary, it's associated with something else.

DR. BELSITO: I understand, but what they're saying could be interpreted as the CAS number can be used for either/or of these materials, but be aware that the information we sent you was on phenyl trimethicone. Is the way that their response could be interpreted. Right?

The first sentence says basically, this CAS number can be this or that. It can be this as well as that. To me that suggests they're saying, that CAS number's been used to describe two different materials, but the information we sent you was on phenyl trimethicone. Is the way that that could be interpreted as well.

DR. SNYDER: Well, let's trust and verify. Have them confirm that the data received is on phenyl trimethicone.

DR. BELSITO: In which case? Then we have this acute lung toxicity, and we have this paper that makes us want to relook at our respiratory boilerplate.

DR. SNYDER: We have to look at respiratory boilerplate because of this separate.

DR. BELSITO: But you had five animals in high dose group die.

DR. SNYDER: Yeah, that was at 5 percent, right?

DR. BELSITO: Point --

DR. SNYDER: That short-term 28-day study, they had it five days a week for 28 days, right?

DR. BELSITO: Yeah.

DR. SNYDER: Five percent, I believe is what it was. There was an LD50 study done, but that doesn't really matter.

MS. FIUME: I think it was the LD50, the acute tox, that gave concern, that if this material -- it was actually found trimethicone tested, which it may not have been, that's where the concern was raised. But I believe either way, because you have issued an IDA, asking for inhalation data and did not receive inhalation data, if you'd like, you can go forward with a tentative report that you didn't receive the data you asked for. So, it is possible to go forward with a tentative.

DR. BELSITO: I would at this point and, again, query them.

DR. SNYDER: Three percent, that's too (inaudible).

DR. BELSITO: So, I would just -- we didn't basically get any of the data we asked for, right, because there was more than just that. We asked for --

MS. RAJ: You did get verification in part.

MS. FIUME: So, for any of the other data that were received, that may not actually phenyl trimethicone, something that the panel bases a conclusion on -- or based safety on.

MS. RAJ: Well, we did receive some timethylsiloxyphenyl dimethicone --

MS. FIUME: I meant on the phenyl trimethicone.

MS. RAJ: Oh, let me see.

DR. BELSITO: So, we asked for classification of the identity and chemical nomenclature for test substances referred to in the SEHSC data submission and we still haven't gotten that.

DR. EISENMANN: No, you did get it.

DR. BELSITO: Oh, we did get that.

DR. EISENMANN: Yes.

DR. BELSITO: But then there's a question that hasn't been answered.

DR. EISENMANN: I also had them do the review of the CAS numbers, which said we had some mistakes in our dictionary. And that has since been corrected so the three CAS numbers --

DR. BELSITO: So, meaning the CAS number issues with the dictionary have been corrected. Now, the question is whether the acute respiratory study they sent us is on phenyl trimethicone or on the CAS number that they associated it with.

DR. SNYDER: Well, it says the --

DR. EISENMANN: Correct.

DR. SNYDER: -- study was done with a combination of the two ingredients that are under that CAS number. It says it right here.

DR. BELSITO: Where? Where does it say that, Paul? What PDF are you on?

DR. SNYDER: Just a second, I just had it here. On Page 41. Oh, wait a minute, it was before that.

DR. BELSITO: It says the study that we're talking about is right at the top of 41 and another acute inhalation --

DR. SNYDER: Page 40, towards the bottom, there's three highlighted sections. It says, "in two separate acute dermal tox --" wait, that's dermal tox? I thought that was the inhalation study.

DR. BELSITO: No, it's 41. It says, in another acute inhalation toxicity study, 5 male, 5 female, aerosol, phenyl trimethicone, 0.5 and 5 milligrams per liter for 4 hours. Half of the animals in 0.5 and all in the 5 died within 24 hours.

DR. SNYDER: So, what David wanted was he wanted that same 28-day study that they did at 3 percent. He wanted that repeated at the max concentration of use at 7.5 percent. We did not get that.

DR. BELSITO: 28-day, we --

DR. SNYDER: Inhalation. Short-term inhalation study, same as the 3 percent. The wording that we used. It was a 3 percent study.

DR. BELSITO: Right.

DR. SNYDER: They were treated five days a week for four weeks. He wanted that at 7.5 percent. That's what we agreed to ask for, we didn't get it. I mean, that's the bottom line. We're still insufficient.

DR. BELSITO: So, insufficient then?

MS. FIUME: That's insufficient completely, or insufficient for --

DR. BELSITO: Inhalation.

DR. SNYDER: But I think with that dermal study, with that combination of those two ingredients, that's why they -- that must be a category that you can buy or something, huh? Because that dermal study has those two -- it's weird that they had those two ingredients that they say could be listed under that CAS number.

DR. BELSITO: So, who's reporting on this tomorrow?

MS. FIUME: You are.

DR. RETTIE: You are.

DR. SNYDER: You are.

DR. BELSITO: Sweet. Thank you.

DR. SNYDER: It's easy. Still insufficient for the inhalation data.

DR. BELSITO: No. So how do we do this with the split conclusion? Safe as used, except in products that may be inhaled, I don't know, aerosolized? How have we done this?

DR. SNYDER: Well, we can't even go there because we've got to do the respiratory boiler because the whole Discussion --

DR. BELSITO: No, but we're excluding -- we're saying it's insufficient for respiratory. We haven't gotten what we want. Monice, this is like a tentative final, right?

MS. FIUME: It'll go out as a tentative.

DR. BELSITO: It'll go out as a tentative final. So, we're asking for more data on the inhalation. What I'm asking is what is the boilerplate when we -- because we've done this before where we've said it's safe as used except under conditions where it could be an incidental inhalation. Is that what we've said?

MS. FIUME: Yes. I mean, we'll have to find the exact wording to keep it --

DR. BELSITO: Except under conditions where incidental inhala- --

MS. FIUME: Use products that may be incidentally inhaled. But I guess at some point then -- because the data that are in yellow in the report, are the data that are in question with citation 20. So, I guess the other part of it is making sure that anything that's in yellow, with citation 20, talking to phenyl trimethicone, isn't something that you're using to say safe as used in everything else. Because those are being questioned.

DR. SNYDER: Go to Page 52, Don, please.

DR. BELSITO: Hold on. Let me just type this. And the data needs are the original data needs for respiration?

DR. SNYDER: Well, maybe.

DR. BELSITO: Well, let me type that and then we can maybe you.

DR. SNYDER: Page 52.

DR. BELSITO: Fifty-two.

DR. SNYDER: Table 3.

DR. BELSITO: Table 3.

DR. SNYDER: Exposure type, incidental inhalation spray is only up to 3.5 per- -- oh, it's up to 5 percent, 0.3 to 5. And then an incidental inhalation powder is up to only whatever it is, but it's not 7.5.

MS. FIUME: Table 2 has the 7.5.

DR. SNYDER: Table 2?

MS. FIUME: For the phenyl trimethicones.

DR. SNYDER: Well how come it isn't represented in this Table?

MS. FIUME: Because phenyl trimethicone was reviewed before so it includes the historical data.

DR. SNYDER: Oh, okay. I thought maybe we had a way out there.

DR. BELSITO: No.

DR. SNYDER: All right. Sorry.

DR. BELSITO: Okay. Well, that's what I'll report. We'll see what the other group says. And we'll continue to try and determine what they meant in this statement back to us. Is it phenyl trimethicone?

DR. SNYDER: Well, that whole Discussion needs to be deleted then.

DR. BELSITO: Okay, let's look at that.

DR. SNYDER: We don't want that report going out with that Discussion because that's not right now. Particle size, distribution things. It's all wrong in there.

DR. BELSITO: I mean, yeah, we need to readdress the respiratory.

DR. SNYDER: Yeah. So, don't send that back out wrong.

MS. FIUME: Well, if we have the insufficiency for inhalation, we would make sure to remove the Discussion saying that is not --

DR. BELSITO: Respirable.

MS. FIUME: Or that's not a concern.

DR. BELSITO: So, in terms of the Discussion, Paul, your point is we need to just remove all of the inhalation part.

DR. SNYDER: Yeah, that one big paragraph on page 48.

MS. RAJ: And am I hearing that you would want data removed for what was called phenyl trimethicone?

DR. BELSITO: I think it needs to be bracketed right now and make one more good faith attempt to determine what they actually meant by that statement. Because I could easily interpret it to mean that they said CAS number can apply to this material or that material. And, by the way, the material we provided you data on is phenyl trimethicone.

MS. KOWCZ: That's it in a nutshell. Yeah.

DR. BELSITO: And if that's the case, then we use the data. If it's --

DR. EISENMANN: I still say put the CAS number with the data so it's clear down the road.

DR. BELSITO: Oh, yeah. No, no, no, no. I mean, I think that we have to do that. Do that and say, this CAS number has now been assigned to this material. And the caveat, you know, that the supplier of this data said that it was phenyl trimethicone and not this material. But this is the CAS number they used. I mean, you can wordsmith it to death. But I think we need -- regardless of what they say -- we need to --

MS. KOWCZ: It confirmed.

DR. EISENMANN: Right. Identify it --

DR. BELSITO: Identify it. And these people charge you for this service, right? For CAS numbers?

DR. EISENMANN: Oh, yes.

DR. BELSITO: Yeah. And it's like it's such a ridiculous -- I mean, where do they get off?

DR. EISENMANN: Yeah.

DR. BELSITO: You know, I mean, they're useless numbers because they don't help you. A number of times -- I mean, we get this within the fragrance industry all the time, where one material has five different CAS numbers.

DR. RETTIE: So, it'll be in here no doubt. You were able to trip off the CAS number of the phenyl trimethicone.

MS. FIUME: Right.

DR. RETTIE: What are we using?

DR. EISENMANN: Whatever three were left. I can't remember. I don't know if I have it in my notes or not.

DR. RETTIE: I can find it. That's okay.

DR. EISENMANN: I can give you the ones that were taken out. So, PDF Page 50 you can see the remaining CAS numbers, Dr. Rettie.

DR. RETTIE: Yeah. So, we have three there.

DR. BELSITO: Okay. So, I think we have a way forward with this and the respiratory document we're reopening.

MS. RAJ: I guess you'll wait until tomorrow to determine all the data insufficiencies, Dr. Belsito?

DR. BELSITO: No, the data insufficiency is simply what was stated before.

MS. RAJ: Not insufficiency, the data needs.

DR. BELSITO: The data need is only the inhalation data need that was needed before.

DR. SNYDER: 28-day short term --

DR. BELSITO: Short-term inhalation at 7.5 percent.

Cohen Team – June 12, 2023

DR. COHEN: So, moving on to phenyl-substituted methicones. We have in front of us a draft-tentative report. This is the third time we're seeing this for these seven cosmetic ingredients. At the March meeting, a draft tentative report was presented with new data that we had gotten in Wave 2. However, upon reviewing the data the Panel issued a second IDA for the following needs: clarification of the identity and chemical nomenclature for the test substances referred to in the data submission, the applicability of these data for use in this assessment, additional respiratory tox near the face, preferably in a protocol outlined here.

Subsequently, the SEHSC confirmed that the test article referred to as phenylsilsesquioxane were in fact phenyl trimethicone. So we are now back to reviewing this with all of this new information. I guess I'll open it up -- one second. David, how do we reconcile the IDA and the respiratory toxs since that Wave 2 data was phenyl trimethicone? Right. My recollection was that we were going to dismiss that data as not being phenyl trimethicone.

DR. ROSS: That was one proposal. And so, you know, I'll just basically summarize my critic notes on this after going through it. You're right that the clarification we requested, we got.

The phenylsilsesquioxane -- I've always had trouble saying that -- actually is phenyl trimethicone. So, my read of that, as you said, is the inhalation data is in play and we have to consider it. We asked for the new aerosol study, we didn't get that. So, that's where I was. I won't give you my conclusion yet because Susan wants to add something.

DR. TILTON: Well, I guess I just want clarification on how that determination is made, that this was phenyl trimethicone. I mean, my understanding is that phenyl trimethicone is listed with three CAS numbers in the report. I don't know if confirmation of it was just by name. It seems like phenyl trimethicone might be a synonym for a number of different things. So, is the confirmation that the compound in that study has the same structure? Do we know --

DR. COHEN: Can have the same structure?

DR. ROSS: Well, there's slightly different crystal structure. It was a cage structure as opposed to a linear structure, but you can get different polymorphic forms of the same compound. And we asked for clarification and we got the clarification that that's what the compound is.

DR. ANSELL: We believe their clarification was wrong.

DR. COHEN: Oh gosh. I was worried you were going to say that.

DR. TILTON: That's my question. Because if you look at, even the CAS numbers, I mean, if you go to the substance information for one of them, it's clearly listed as fatal if inhaled. And silsesquioxanes, I mean, that's consistent for that structure and the cage structure. I mean, that's not surprising data. So, the question remains, is that study related to the structure of the compound that's in the report?

DR. ANSELL: So, we went back to the INCI committee and asked them to review this. And they came in and said that three of the numbers which were included are incorrectly associated with the phenyl trimethicones, specifically, 70131690. That is not a trimethicone. Although you're right, that's what the silicone folks wrote back. But we believe it's associated with the polyphenylsilsesquioxane, which is not a phenyl trimethicone. So we believe that those three should be removed from this report. And any data associated with it, you know, migrate with wherever those three end up.

DR. COHEN: Well, I guess the problem from the last meeting is, there was that -- whether it was an official motion or not -- it's just disregard that Wave 2 because it's not what we're looking at. And then remember, it got down to Wilma making the split decision to keep it in. And then we see it come back and it's like, wait guys, it is data we're supposed to keep from the manufacturer. But I was worried you might come back and say that it's still not right.

I don't think we're in any position to jettison the data based on the manufacturer response. Now we might decide to table it. You know, I don't know what administratively is the right thing to do. We could either go back with another insufficient announcement and say, are you sure? Like, the insufficient responses, are you sure? Or table it and say, you guys can have a little more time to straighten this out. But I don't think with what we have here, we can say we can't use that tox data now.

DR. ROSS: Right. I'm not questioning what Jay is saying but, Jay, in the report we have in front of us is that, you know, this phenyl trimethicone. Susan has asked a good question. And I'm sure that'll be the discussion we get tomorrow from Don's group as well. But in terms of process, how do we deal with what's in the report? Do we say, well, no, it's not -- but that's not what's in the report. So then we have to somehow develop the process to deal with that.

DR. BERGFELD: Adjudicate it.

DR. ROSS: Yeah.

DR. ANSELL: So, I think from a process standpoint, we can turn to staff on how to do this. But we believe that the INCI committee is the touchstone. And so, we have to rely on INCI. They're the ones that do the naming. And we should rely on their position over anyone else.

DR. ROSS: And that would be fine, but it's not in the report.

DR. ANSELL: Right.

DR. ROSS: And so, I think that needs to be in there. Because right now, at least what's in the report is insufficient for incidental inhalation exposure from sprays and powders. Because it says that's what it is. Now if it's not that, then that's a different story, right? But if it is, then that's one issue.

And then the second issue is we can't use the respiratory boilerplate. And I want that in this discussion, and I brought this up last time. Clearly, if it is that compound and it is inducing significant respiratory toxicity and death in an aerosol, and so it'd be crazy to -- but it wouldn't be correct, wouldn't be appropriate, to use the aerosol oil plant, which says aerosols don't use them. I'm not questioning --

DR. COHEN: Would you clear the product?

DR. ROSS: Would I? No.

DR. COHEN: So, you wouldn't even qualify it?

DR. ROSS: Well, all I'm saying is, you know, that respiratory boilerplate, if this compound was going forward like this, it should be nowhere near this discussion. because you've used an aerosol, it's inducing deaths, it's inducing respiratory effects, and that is obviated in our aerosol boilerplate, so get rid of that, can't use it. But the major problem is where we were last time, is it or is it not?

DR. COHEN: We're back to where we were.

DR. ROSS: Yeah, exactly. And I'm fine with, you know, getting other opinions. But right now, what's in front of me, I couldn't clear it.

DR. COHEN: And the discussion has to narrate what we've gone through with this to a degree. Right. Because the likelihood is it's going to be -- it's not the same thing. But we have no evidence of that right now.

DR. ANSELL: Right. Just so long as we're clear that the process is correcting the report. I think that the INCI group has to be identified as the gold standard for identities,

DR. ROSS: But then re-reviewing the report somehow.

DR. ANSELL: Right.

DR. ROSS: Because this group would have to re-review it. I mean, if INCI came in and said, no, it's not.

DR. ANSELL: Yeah.

DR. ROSS: I mean, it would still have to come back in some shape or form to this committee, correct?

DR. HELDRETH: Right. Yeah. I mean, if we look at the history of these different chemicals, the sesquioxanes and the phenyl methicones, the confusion occurred even before INCI named it. The CAS file, If you look in them, make the same confusion. One CAS number talks about the sesquioxanes, talks about the phenyl methicones, so that confusion has been there for ages.

But I think when we're looking at this data that came in and the panel, it sounds like, is unsure of the identity of the test article, I think that's absolutely the Panel's prerogative to say, just like they would if they felt that the quality of the data was equivocal, they would say, it's insufficient, we don't have enough information here.

So, if it's equivocal what the test article even was, then I think you're in the same position where you could say we don't have the appropriate data to make a conclusion on safety. And you already had that out there as an IDA before. We didn't know what these were.

And so, I mean, one possibility is that this Panel could proceed with insufficient data conclusion because we don't know if we can trust this data. We want you to feel comfortable with what's in front of you to make a decision. If you don't, then we don't want you to say it's safe or unsafe or safe with a qualification.

DR. COHEN: Wouldn't you think, though, that the SEHSC would have understood this issue?

DR. ROSS: You would've thought. If you remember when we first got this, I think it was seven CAS numbers associated with these molecules. And I commented that initially. And I think -- then it was some clearing up and I think we got fewer now, there are three or four, maybe?

DR. TILTON: There's three.

DR. ROSS: And the crystal structures were different, so that gives you pause. But you can get different polymorphic forms, so it still needs clarification.

DR. HELDRETH: Yeah. It's very possible that the folks we're talking to from the Silicon Association maybe are not the experts per se. I mean, like Jay was saying, there are some fantastic silicones experts on the INCI committee, like Starks, for one, could run circles around anybody that I can think of for talking about silicones.

But we don't know the expertise of this Association, or the representative from the Association. If you remember back when we did formaldehyde years ago, they sent a representative from the hair straightening folks. And frankly he clearly did not know what he was talking about.

He presented a lot of test data that proved that there was no formaldehyde there. But the test wasn't a test that could detect formaldehyde. So, even if there was a hundred percent in that formulation, it would've said there's no formaldehyde.

DR. COHEN: It's like a chest x-ray for a broken ankle.

DR. HELDRETH: So we don't know. We don't have information in front of us to say, yep, they knew what they were talking about.

DR. ANSELL: Yeah. I just have to emphasize that if there's ever a disagreement about nomenclature, INCI is the gold standard. And so, anyone who disagrees with INCI is wrong.

DR. TILTON: I mean, I do think it's a nomenclature issue.

DR. HELDRETH: Mm-hmm.

DR. ANSELL: But of course that doesn't respond to the fact that now we need to resort this.

DR. COHEN: So the manufacturing of the non-caged product, is it possible you could get contaminants of that caged product in the manufacturing?

DR. ROSS: I don't know the answer to that.

DR. COHEN: Because if it is, that also raises a safety issue, no?

DR. TILTON: But I mean, we're not seeing a lot of toxicity in any of the other data and we do have inhalation data. It is not at max use.

DR. ROSS: It's 3 percent.

DR. TILTON: But, yeah, that's right, it's not a max use.

DR. COHEN: We often don't do this max use thing on inhalation. But I think in this case, we got stuck in it.

DR. ROSS: I think because the LD50s -- I mean, these LD50s were so low.

DR. COHEN: Yeah.

DR. ROSS: That gave us pause. And that's where we kicked this whole discussion off and asked for clarification. And what we have is, yeah, that's what it is. Now, what Jay has said, well, that's actually not the case. So again, we're still in this sort of circle asking for more clarification.

DR. BERGFELD: So that comes back to what do you say tomorrow.

DR. COHEN: That's exactly -- we were completely aligned. I just wanted to get Tom's final comments on it and then reiterate this group's statement. Tom, what are your thoughts?

DR. BERGFELD: Unmute.

DR. COHEN: Are you on mute, Tom? We can't hear you.

DR. SLAGA: Yeah. Okay. You talked about tabling it possibly for verification of some information?

DR. COHEN: Well, yeah. But just any other comments on the discussion, other than the process? Anything else that you wanted to add?

DR. SLAGA: No, I don't have anything else. I had the same questions related to the respiratory. The rest of you know, in Wave 2, they had clarification. So it's only the respiratory aspect that was a concern.

DR. COHEN: So should we maintain the last IDA? Just issue an IDA? I mean, I don't know if it's changed at all. So our last IDA was clarification of the identity and chemical nomenclature for test substances referred to in the SEHSC. Like, basically, we have one more time, applicability.

DR. BERGFELD: How do we say that?

DR. ROSS: And I think the second thing we asked for last time was to bypass the whole thing and say, well, you know, if there is inhalation data out there at max use, then with that intermittent exposure realistic scenario, let's have that. But we didn't get that.

DR. COHEN: We could keep it in. I mean, the next bullet was applicability of this data for use of this assessment.

DR. ROSS: I mean, if it's not, you know, if this is not phenyl trimethicone, if it's a different structure, then you don't need point two, because you don't need the study.

DR. COHEN: Well, right. I guess that's a good point. So if it is --

DR. ROSS: Because these studies are expensive. But in this case, I think, it was that inhalation tox that caused us to ask for it.

DR. BERGFELD: I think you have to table this. I don't think you can send out two data insufficient announcements, the same request.

DR. HELDRETH: Historically, when we table something it's because we are given a timeline that this certain thing that we're talking about is coming along.

DR. BERGFELD: Or we ask for the timeline.

DR. HELDRETH: However, I would suggest in this situation where we've issued an IDA, and we still have the same data needs, or at least we don't have any new data needs, the next step typically is to issue a tentative report with an insufficient data conclusion.

DR. COHEN: Right. I think if we do the IDA, it puts time, right?

DR. BERGFELD: No, it's an insufficient tentative report.

DR. HELDRETH: Data conclusion.

DR. ANSELL: We don't think there is additional information necessary. I mean, we have the opinion from INCI. The report needs to be segregated to identify the relevant information. It's not that the information isn't there. We think that there's a lot of information if it's sorted --

DR. BERGFELD: We're talking about clarification.

DR. ROSS: We don't have it in the report though.

DR. ANSELL: No, no, no. I absolutely agree. I absolutely agree.

DR. ROSS: So, I think that's the issue.

DR. ANSELL: Right. So it's not an IDA, specifically, it's -- well I guess --

DR. COHEN: It's, we need more data. I guess we would need data in the report.

DR. BERGFELD: We need clean data.

DR. TILTON: We just need a report with that information in the report, and then that dataset removed.

DR. ANSELL: Right. Right.

DR. COHEN: I don't know why we wouldn't do this as an IDA, because if we don't get the data we need, the report is going down. It's going to close as insufficient. No?

DR. ROSS: for incidental inhalation.

DR. COHEN: Huh?

DR. ROSS: For in- -- for --

DR. COHEN: Well it's not going to get a safe as used.

DR. ROSS: Well, it's a strong dossier for everything else. It's just the inhalation is the problem.

DR. COHEN: So you'll split the conclusion?

DR. ROSS: Yeah.

DR. TILTON: But it sounds like we are going to get a report with that dataset that is not (inaudible). That's correct right? I mean, that is the next step?

DR. BERGFELD: Jay, you're going to send a report for the INCI stuff? Are they going to clarify?

DR. ANSELL: You know, I think if we go for an insufficient as opposed to a tabling, that the next step is to get that formal opinion from INCI.

DR. ROSS: That's what you do.

DR. COHEN: Yeah. So it is an IDA -- an insufficient data.

DR. HELDRETH: The conclusion.

DR. ANSELL: Right. It's the what's insufficient that I was trying to clarify.

DR. ROSS: It'd be the clarification of the chemical nature of the phenylsilsesquioxanes.

DR. ANSELL: Yes.

DR. ROSS: They're not clearance of the quioxanes.

DR. COHEN: It's still the first -- it's the original IDA, first pulled.

DR. ROSS: It basically is.

DR. COHEN: It is. It's the same.

DR. BERGFELD: I think you have to lay that out differently, not just the same. If it's truly clarification, that should be in the request. Because you've got some information.

DR. COHEN: They clarified it for us. They said it was.

DR. ROSS: It was, so that's what we got.

DR. ANSELL: Well, you got two opinions.

DR. BERGFELD: Question, reclarification.

DR. ANSELL: So my understanding is --

DR. COHEN: What's the coutervening opinion, in the report?

DR. ROSS: We haven't got it.

DR. COHEN: In the report?

DR. ANSELL: Right, but that was a staff decision, right? I mean you, you had the opinion from INCI.

MS. RAJ: I'd like a little bit of clarity. I'm not sure what the Panel would like included in the report. If you could explain a little bit.

DR. ROSS: Well, we need -- you know, the issue is the inhalation toxicity with the phenylsilsesquioxane, and you changed that in the report, you know, which was correct based on what you had to identify that as phenyl-substituted methicones. So, you went through the report and changed that.

And that was fine because, you know, what we were told is this stuff is phenyl trimethicone.

MS. RAJ: Right.

DR. ROSS: But our question is -- which Susan raised -- is this truly phenyl trimethicone? And so, that's what we're trying to get at.

MS. RAJ: So, is this something that you would want to kind of outline in the discussion as far as how we talked about it, or?

DR. ROSS: No, what we need is another insufficiency asking for more clarification on what this phenylsilsesquioxane actually is. And whether it really is phenyl trimethicone. Jay is saying there's an opinion out there that says it's not, but we don't have that in front of us.

DR. COHEN: So, it shouldn't be in the report if it's not.

DR. ROSS: It shouldn't be there. And so, we need that clarification. And the best way to get that is an insufficient.

DR. COHEN: And I think when the report is redone, when we highlight new data in this report, we should highlight it in yellow. But I think we should have a strikethrough on the stuff that gets removed.

DR. ROSS: Yeah.

DR. COHEN: Because if it comes out, I'm going to go back and forth with the two reports to see what was taken out. I'd like to see strikethrough on what was removed.

DR. BERGFELD: Good idea. Jay, can I just ask you a question? The INCI report is available?

DR. ANSELL: I said that, but I'm not sure, I'll check my notes again.

DR. BERGFELD: Okay.

MS. RAJ: Thank you for that, **DR. ROSS**.

DR. HELDRETH: And what would the INCI report provide?

DR. ANSELL: I think it would provide the nomenclature. What exactly should be included in this report. That certain CAS numbers should not have been included and just the nomenclature part. And then it would be up to staff to re-sort the data as to what studies are associated with what.

DR. ROSS: I would be fine with that, but I think there has to be also some description of the reasons why it shouldn't be in the report. And really the reasons why we got a response saying that it was phenyl trimethicone. I mean, I think it's important to get at the reasons why whoever provided that information did that.

DR. ANSELL: Yeah.

DR. ROSS: And it might be that, as Bart said, maybe they're not the experts.

DR. ANSELL: Right. It would be beyond INCI's expertise to start talking about safety data.

DR. HELDRETH: Right.

DR. COHEN: No, but I think if INCI had the report and SEHSC had the INCI report, they need to come back and retract their statement. I don't want to be the one adjudicating. I got the Silicone experts saying it is, and I got the INCI people saying it isn't and now we have to decide which one is correct?

DR. HELDRETH: Right.

DR. COHEN: No, they have to review the INCI report and withdraw their last comment.

DR. ANSELL: We'll take this to SCCS.

DR. COHEN: Yeah, take it to the streets.

DR. ANSELL: But, that's a good point. It's not up to you.

DR. COHEN: And then it's easier.

DR. HELDRETH: Yeah. All the INCI folks will be able to tell is that certain CAS numbers are not appropriate.

DR. COHEN: Right.

DR. HELDRETH: But whether or not test article was properly assigned to a name and the number, we can only get that from the Silicon folks.

DR. BERGFELD: Well, it seemed to me that the INCI report has to be sent to the Silicon people and have them re-review what they've sent us.

DR. HELDRETH: True.

DR. BERGFELD: And I'm not sure that that is another insufficient, or that's a table? Or that's just a whole --

DR. COHEN: I think it's insufficient, because a table is passive. And this, we're going back and we're -- it's specifically insisting on certain data.

DR. BERGFELD: Yeah, but you're really asking them to review what's in the INCI and what they're presenting and adjudicate it.

DR. COHEN: Yeah.

DR. BERGFELD: Right. So it doesn't exactly say that in that request.

DR. ROSS: But we don't know that there is an INCI report.

DR. BERGFELD: Well, we heard that there was.

DR. HELDRETH: Yeah. I mean, and the INCI report is just a matter of saying, these two CAS numbers don't belong here in the monograph.

DR. ANSELL: Yeah. Right. I mean, we went to INCI, they said these belong and these don't belong. And I don't know that -- my report doesn't say how far that was communicated.

DR. HELDRETH: Okay. Yeah. I agree with Jay that INCI are the experts for nomenclature. But honestly, I don't understand their involvement in what we're doing here at the moment.

I think instead, I will write a letter to the Silicone folks, say INCI has changed their minds on what belongs in the monograph. They don't think these two numbers are actually for phenyl-substitute methicones. We think that those are silsesquioxane or something else. Please provide confirmation to our Panel because they are not going use your data until we have clarification.

DR. ROSS: I don't think you should say that. I think you should just ask them for clarification.

DR. COHEN: Yeah, that's too prescriptive. I'd like to -- like, what was the stuff in that pulmonary tox report? What was it? And you're going to tell them it wasn't --

DR. ROSS: You shouldn't.

DR. HELDRETH: Well, I'm just going to tell them we're getting contradicting information. Can you please confirm the actual chemical that was the test article?

DR. COHEN: Right. I don't think we should tell them what they should say or do.

DR. HELDRETH: Right.

DR. ROSS: Bottom line is we only reviewed what's in front of us.

DR. BERGFELD: So, how are you presenting this tomorrow? I'm coming back to that. It's insufficient?

DR. COHEN: Yes.

DR. BERGFELD: And the letter goes out under that to the Silicon people?

DR. COHEN: Well, I mean, I think it goes out to everyone, that insufficient.

DR. BERGFELD: No, no, no. I meant in addition to the insufficient report. An additional letter will go out from Bart requesting the specifics.

DR. COHEN: Okay.

DR. BERGFELD: I mean, we've talked about it and talked about it in a circle here, and let's share it with them, have them resolve this.

DR. HELDRETH: Absolutely.

DR. COHEN: I have the last IDA bullets looking the same. Right. with an additional comment that we need an INCI report if it exists. And SEHSC needs to review that INCI report and determine what product was used in those pulmonary tox studies.

DR. ROSS: Perfect. I second that.

DR. COHEN: Good.

DR. TILTON: Do we need to discuss Wave 2 then? Or is that --

DR. COHEN: Well, please comment on it.

DR. TILTON: Well, I guess my question is these uses that are described in aerosol sprays, are they already included in the use categories that are in the table?

DR. COHEN: Are we talking about the propellant sprays, the dry shampoos?

DR. HELDRETH: Right?

DR. TILTON: Is that already captured?

DR. BERGFELD: That's the Women's Voices?

DR. COHEN: Yeah.

DR. BERGFELD: Particle size and distribution.

MS. RAJ: That's an unreported category in VCRP.

DR. COHEN: Dry shampoo.

MS. RAJ: Mm-hmm. So, Women's Voices for the Earth, many times they bring up things that was not captured by VCRP or reported.

DR. COHEN: So, how would we handle that? So, it's not in the VCRP, we're aware. The problem is, is this is going to happen all the time. Right? And the VCRP is very imperfect and it's very old. Right. It just doesn't capture the information that's salient anymore.

DR. BERGFELD: Well, it never did.

DR. COHEN: But it hasn't morphed.

DR. BERGFELD: It's the best we have.

DR. HELDRETH: A few things me and CIR staff were thinking about. For one, the VCRP actually doesn't even exist anymore.

DR. COHEN: Oh, it won't exist anymore, right?

DR. HELDRETH: No, it's no longer being updated as of March. Because of the new legislation, FDA is working out a mandatory process. Now I don't know if you can comment yet if there's going to be new use categories in there, but the way we were looking at this with the dry shampoos, is it kind of falls into something similar with airbrush.

We don't know about particle size, specifically, with dry shampoos. We know that things like underarm deodorant and hairsprays have different particle. We also don't know habits and practices information and data with dry shampoos. There's a lot of risk type exposure scenarios that we don't really have all of the information on when it comes to dry shampoos.

And of course, as Preethi said, it's not a category that we have reporting on so we really don't know how many people are exposed to this. We certainly don't have formalized survey data to give us concentration of use in this category.

DR. BERGFELD: What are we going to do about that?

DR. HELDRETH: That's what I'm asking you.

DR. COHEN: Well, we can put it in the discussion.

DR. ROSS: Yeah.

DR. COHEN: Because it's a leave-on powdered product, right. I mean, it's not terribly different than putting a powder on your face. It's put on your head. And it's suspended in the hair. I don't know how well it sticks. But we should put it in the discussion.

I think it's a good point that was brought up in this letter. And just because the collecting data that we have is not so great doesn't mean we can't discuss it. We can't comment very much further about it.

DR. BERGFELD: Well we're going to have to do that for everything in the future then, on specifics, if we don't have the data on concentrations and use.

DR. COHEN: Use with the mandatory collection, is there a change in the form? Because about six months ago I pulled the form and the form is very restrictive on what you could put in there. There are codes that you have to use. Has that been updated, do you know?

DR. MANGA: We're working on it.

DR. COHEN: So, I think this is one situation that maybe we should be involved in because you guys are collecting the data, and I'm not sure you're doing much with it. I don't know if you are, I shouldn't say that. But we're certainly reliant on analyzing that data. So, if we have certain needs it may be a good opportunity to address what those collection reports look like because we're principally the ones reviewing them.

DR. BERGFELD: I'm not sure the FDA will allow that.

DR. COHEN: Well, they take public commentary.

DR. MANGA: Yeah. Right now we're just in the process of figuring the system out. As we kind of do that, we'll take that into advisement for sure.

DR. BERGFELD: So the mandatory will go forward when? When is the approximate date?

DR. MANGA: We don't have a date yet.

DR. BERGFELD: Like a year or two from now? We're going to be void for a couple years?

DR. MANGA: The system is supposed to be up by the end of the year according to MoCRA. That's the timeline that we're working on.

DR. BERGFELD: Okay.

DR. COHEN: So, just a technical question. Why retire the VCRP if the mandatory reporting isn't live?

DR. MANGA: Because we did not get funding from MoCRA. And so we have to support two systems. And VCRP wasn't considered sufficient for what we needed. That was the reason for taking it down.

DR. COHEN: I want to avoid busy work, right. But does it make sense for the CIR to create a wish list of what the collection form ought to look like and submit it to you guys? Would that be looked at, would that be reviewed and considered? Is there some open period are we in that we could do that?

DR. MANGA: I mean, a letter structured to FDA for consideration from CIR, is always something we could take a look at.

DR. COHEN: Or probably just a small subcommittee just to, like, what would we wish was in there?

DR. TILTON: Yeah. So, in this case, I think the unreported uses we can bring up in the discussion. It should be noted they're presented elsewhere in the report. But I also think it's covered really by the respiratory resource document.

DR. COHEN: I'll mention it tomorrow.

DR. ROSS: If you use the boilerplate.

DR. TILTON: Yeah.

DR. COHEN: Well why wouldn't you use the boilerplate? I mean, you could use the boilerplate, assuming that the caged structures come out.

DR. ROSS: Exactly. Then you could use it. And I'm saying that to say that my suggestion is we do not use it. Because It would be contradictory to the actual data.

DR. COHEN: You're saying if that respiratory tox data from the cage structure is in, it changes the whole report?

DR. ROSS: Absolutely. Yeah.

DR. TILTON: Yeah.

DR. COHEN: That was my first thing, how do we reconcile this? Okay. It's not going to be reconciled at this meeting.

DR. ROSS: No.

DR. COHEN: Okay, let's move on.

DR. ROSS: I should've had coffee before that one.

DR. COHEN: Well, everyone peeled out right before.

DR. ROSS: So, back in 30 seconds.

DR. COHEN: Oh, it's on this side.

DR. ROSS: Okay.

DR. COHEN: We could give you a 30-second hold.

DR. BERGFELD: Bart, there's some action items here that don't belong to this particular agreement, we just need to act on.

DR. HELDRETH: You're talking the letter to --

DR. BERGFELD: And the format. I think that we should involve the SCCS from the PCPC as well as your staff and then let us take a look at it.

DR. HELDRETH: Yeah, yeah. I can craft both of those letters and circulate those to the Panel before I send either one of them out.

DR. BERGFELD: Yeah. We could send it now and then have public review to make sure they get it. I wouldn't just send it once.

Full Panel – June 13, 2023

DR. BELSITO: This is another report that we got comments from Women's Voices for the Earth. And in this report they also submitted new data on propellant in dry shampoo, which we thought is a reason for us, even though we just recently looked at the respiratory boilerplate to reopen that boilerplate.

DR. BERGFELD: To reopener or include it?

DR. BELSITO: To add that report, to look at other reports that may have come out on propellant size and to further tweak --

DR. BERGFELD: Distribution?

DR. BELSITO: Yeah. To further tweak our respiratory boilerplate. Having said that, looking at this particular material, and looking at all of the data on it, including the fact that we still haven't gotten clarification on the silsesquioxane and the CAS numbers, et cetera. We thought that this was safe as used except in products that could be incidentally inhaled. And the data for that would be inhalation toxicity and clarification that we still haven't gotten on what was the material that caused the acute lung toxicity.

DR. BERGFELD: That's a motion?

DR. BELSITO: That's a motion.

DR. COHEN: It's an interesting take on it. Not bad. We were throwing the prior IDA back again. We thought the SCHSC should connect with INCI, because their clarification was that that material was Phenyl Trimethicone. And that gave us this quandary with the pulmonary tox. And, we wanted greater clarity before even moving on with it. I certainly understand your motion because it silos that out, right. But, we'd like either a withdrawal of that clarification that said it is --

DR. BELSITO: But this was an insufficient data announcement, right. So the next step is to go --

DR. COHEN: It's insufficiency.

DR. BELSITO: Right, but the next step is to go to a tentative final. And if we don't have the data at this point, we go to a tentative final, and what is our final conclusion on this. Do you have any concern about its use other than in a product that could be inhaled?

And so, when we reach this point, typically as occurred at our last Panel meeting, it's safe as used except in products that could be incidentally inhaled, and the information that we need is the information that you're asking for and that's a tentative final. And if someone is using it in products that could be incidentally inhaled, once it change that they'll provide the data.

DR. COHEN: Yeah, so you're clearing for non-incidentally inhaled products.

DR. BELSITO: Right.

DR. COHEN: Okay, I like that. And, then, it's insufficient at -- what's the specific request you're asking for?

DR. BELSITO: We need clarification, as you said, on that acute tox study, what was the material that was studied. And we need the respiratory study that **DR. ROSS** had proposed at the last meeting that it -- under Use conditions. I forget exactly the details, 4 hour exposures.

DR. ROSS: It was intermittent exposure.

DR. BELSITO: Yeah, intermittent exposure.

DR. ROSS: Yeah.

DR. BELSITO: Which we asked for and we didn't get. So that's the clarification of what that material was that caused acute toxicity, and the intermittent exposure respiratory study that was asked for the last time.

DR. ROSS: Yeah, I think that aligns with our other discussion.

DR. COHEN: It does.

DR. ROSS: I mean we had safe as used, but insufficient to conclude safety for incidental inhalation, which is exactly your motion.

DR. COHEN: It was very, very well done motion.

DR. RETTIE: And for my own clarification, we're asking for the additional respiratory tox at 7.5 percent?

DR. BELSITO: Yes.

DR. COHEN: Yes, that was what our original IDA had suggested.

DR. BELSITO: We're still asking for that.

DR. RETTIE: Yeah.

DR. COHEN: Susan, you're okay with accepting that motion?

DR. TILTON: I'm okay accepting that motion. And we had a lot of discussion yesterday just about the CAS numbers and the nomenclature issue, and the fact that we need clarification on that. And so, you know, in lieu of having that, which it does seem like additional information should come forward, then that inhalation exposure study data wouldn't be necessary.

DR. BERGFELD: So you're accepting Dr. Belsito's --

DR. COHEN: I just want to make sure. Tom, were you able to hear the motion from Don that we're likely going to sign onto?

DR. SLAGA: Yes, I do.

DR. COHEN: Okay, second.

DR. ROSS: Just one quick point of discussion. We talked about not including the respiratory boilerplate in this document because we --

DR. BELSITO: Yes. It gets struck in the discussion.

DR. ROSS: Yeah. Good, okay.

DR. BERGFELD: Okay? Everyone has agreed now? You're moving the boilerplate on inhalation?

DR. COHEN: Right.

DR. ROSS: Because we have clear toxic effects with an aerosols, yeah.

DR. COHEN: Right, because we're not clearing it.

DR. BELSITO: In the discussion.

DR. BERGFELD: Yeah, in the discussion. I'm going to call for a vote on this then. All those in favor please indicate by raising your hand. Unanimous. We're moving on to the next ingredient which is 6-Amino-o-Cresol, **DR. COHEN**.

JUNE 1985 PANEL MEETING

The Schroeter team noted that it had taken some time to clean up the physical chemistry of this ingredient and that "n" was not defined. The UV spectrum had been provided showing minor absorption in the UVB range, negating the need for photosensitization data. An increase in the number of resorptions noted in the reproductive/teratogenicity studies was not considered significant.

Dr. Hoffmann reemphasized the need for a paragraph on impurity data, and if no such data exist, a statement to that effect.

Subject to minor revisions, the following Discussion and Conclusion were unanimously accepted and approved:

Discussion

No photosensitization data are available on Phenyl Trimethicone; however, as the UV spectrum indicates only weak absorbance at 327 nm, the Panel did not feel it was necessary to request clinical photosensitization data. An increase in the number of resorption sites was noted in two of three teratogenicity/reproductive studies although these results were statistically significant in only one study. However, as the doses tested in these studies are higher than those used in cosmetics, the Panel did not feel further data were required.

Conclusion

Based on the animal and human data included in this report, the CIR Expert Panel concludes that Phenyl Trimethicone is safe as a cosmetic ingredient in the present practices of use and concentration.

The document will shortly be issued as a Tentative Report for a 90-day public comment period.

[Minutes of the meeting at which a Final Report was issued were not found]

JUNE 2004 MEETING – RE-REVIEW

Dr. Belsito said that, in 1986, CIR published a Final Report with a conclusion stating that Phenyl Trimethicone is safe as a cosmetic ingredient in the present practices of use and concentration. He noted that no new studies have been identified in the published literature since the Final Report was published; however, the uses of Phenyl Trimethicone in cosmetics have increased from 169 in 1986 to 279, currently. Additionally, the current use concentration range (0.0075% to 36%) is broader than it was in 1986.

Dr. Belsito noted that the data presented in the published Final Report cover the new use concentration range and product uses.

The Panel unanimously concluded that the Final Report on Phenyl Trimethicone should not be reopened.

Concerning current use concentration data, Dr. Andersen said that Phenyl Trimethicone is used in lipsticks at a reasonably high concentration (36%) and noted that a calculation was done at yesterday's Team meeting to evaluate this use concentration in light of the data included in the published report. The Final Report indicates that a dose of 200 mg/kg/day was a fetotoxic dose, and, thus, the Panel wanted to know whether it is remotely possible that the use of Phenyl Trimethicone in cosmetics could result in this level of exposure.

Dr. Andersen said that lipsticks at an average of 10 mg/day, for a 70 kg individual, produce a dose that is lower than the fetotoxic dose. He added that this calculation and the Panel's decision not to reopen the Final Report will be captured in the Annual Review that CIR produces. The Annual Review is published in the *International Journal of Toxicology*.

The Panel agreed that the calculation referred to above should be included in the Annual Review.

Safety Assessment of Phenyl-Substituted Methicones as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: August 18, 2023
Panel Meeting Date: September 11-12, 2023

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.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel member involved in this assessment: Daniel C. Liebler, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume. This safety assessment was prepared by Preethi Raj, M.Sc., Senior Scientific Analyst/Writer, CIR.

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ABBREVIATIONS

AICIS	Australian Industrial Chemicals Introduction Scheme
CAS	Chemical Abstracts Service
CII	cumulative irritation index
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
CPSC	Consumer Product Safety Commission
cSt	centistokes
DNCB	2,4-dinitrochlorobenzene
DPM	disintegrations per minute
ECHA	European Chemicals Agency
FCA	Freund's complete adjuvant
FDA	Food and Drug Administration
GHS	Globally Harmonized System
HRIPT	human repeat insult patch test
LC	lethal concentration
LD	lethal dose
LLNA	local lymph node assay
MED	minimal erythema dose
MII	mean irritation index
MMTS	maximum mean total score
MW	molecular weight
NOAEL	no-observed-adverse-effect-level
N/A	not applicable
NR	not reported/none reported
NS	not specified
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
PDII	primary dermal irritation index
PII	primary irritation index
SEHSC	Silicones, Environmental, Health, and Safety Center
SI	stimulation index
SIOPT	single insult occlusive patch test
SLS	sodium lauryl sulfate
SPF	sun protection factor
TG	test guideline
US	United States
UV	ultraviolet
UVA/UVB	ultraviolet radiation A (long-wavelength)/ ultraviolet radiation B (mid-wavelength)
VCRP	Voluntary Cosmetic Registration Program
wINCI; *Dictionary*	web-based *International Cosmetic Ingredient Dictionary and Handbook*

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 7 phenyl-substituted methicones as used in cosmetic formulations; Phenyl Trimethicone has been previously reviewed by the Panel. These ingredients are reported to function in cosmetics mostly as anti-foaming agents and skin and/or hair conditioning agents. The Panel reviewed the relevant data to determine the safety of these ingredients and concluded that these ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment, with the exception that the available data are insufficient to make a determination of safety for these ingredients in products that may be incidentally inhaled.

INTRODUCTION

This assessment reviews the safety of the following 7 phenyl-substituted methicones as used in cosmetic formulations:

Diphenyl Dimethicone
Diphenylsiloxy Phenyl Trimethicone
Diphenylsiloxy Phenyl/Propyl Trimethicone
Phenyl Dimethicone
Phenyl Methicone
Phenyl Trimethicone
Trimethylsiloxyphenyl Dimethicone

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), the majority of the ingredients included in this assessment are reported to function in cosmetics as anti-foaming agents and skin and/or hair conditioning agents (Table 1).[1]

The rationale for this grouping of ingredients stems from the fact that these ingredients are structurally-related as phenyl-substituted methicones (i.e. polymers of methicone and dimethicone). In 2022, the Expert Panel for Cosmetic Ingredient Safety (Panel) issued a final amended report on 30 dimethicone, methicone, and methicone-substituted polymers, with the conclusion that these ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating, with the exception that the available data are insufficient to make a determination of safety for use of these ingredients in products that may be incidentally inhaled when applied using airbrush devices.[2]

In 1986, the Panel published a final report on the safety of Phenyl Trimethicone, with the conclusion that Phenyl Trimethicone is safe as a cosmetic ingredient in the practices of use and concentration described in the safety assessment.[3] The Panel reaffirmed this conclusion, as published in 2006.[4] Excerpts of data from the original 1986 safety assessment of Phenyl Trimethicone are included throughout the text of this document, as appropriate, and are identified by *italicized text*. (This information is not included in the tables or Summary section.) For complete and detailed information, the original report can be accessed on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/ingredients).

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; the search was last conducted July 2023. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Much of the data included in this safety assessment was found on the European Chemicals Agency (ECHA)[5,6] and Australian Industrial Chemicals Introduction Scheme (AICIS)[7] websites. Please note that these sources provide summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when these sources are cited.

CHEMISTRY

Definition and Structure

The definitions and structures of the phenyl-substituted methicones included in this review are provided in Table 1. The ingredients in this group are all phenyl-substituted methicones (siloxane polymers). Generically, ingredients are organic derivatives of silica, SiO_2, with organic groups replacing some of the oxygens in the polymeric silica molecule.[3] These polymers comprise an alternating framework of silicon with other molecules. The interspersed molecules are covalently bonded to the silicon through a carbon-silicon linkage.

For example, Diphenylsiloxy Phenyl Trimethicone (CAS No. 352230-22-9) is a siloxane polymer that conforms to the idealized structure depicted in Figure 1.

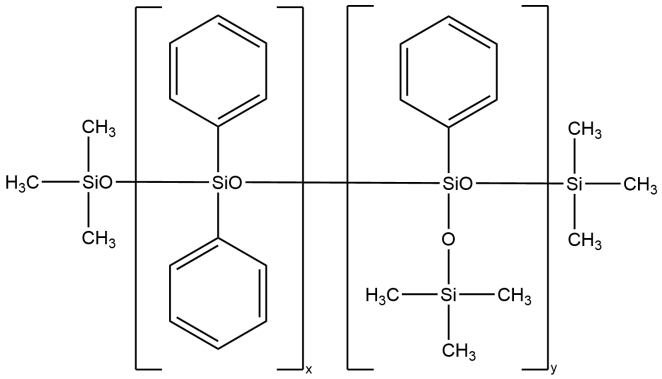


Figure 1. Diphenylsiloxy Phenyl Trimethicone (x and y are undefined)

Chemical Properties

Phenyl Trimethicone is a water white, almost odorless, fluid silicone polymer.[3] Physicochemical properties of Phenyl Trimethicone include a boiling point of 265 °C (at 760 mm Hg), specific gravity of 0.970 (at 25 °C), kinematic viscosity between 5 and 30 centistokes [cSt], a refractive index of 1.459, and a total acid number of 0.25 (maximum). The ultraviolet spectrum for Phenyl Trimethicone indicates weak absorbance centered at approximately 327 nm.

According to one supplier, a sample of Diphenyl Dimethicone had a number average molecular weight (MW) of 1711 g/mol, a weight average MW of 3105 g/mol, and a polydisperity index of 1.816.[8] Another supplier described the number average MW of Diphenyl Dimethicone to be > 1000 g/mol and the number average MW of Diphenylsiloxy Phenyl Trimethicone to be 500 - 1000 g/mol.[9] A sample of Phenyl Trimethicone was described by a supplier as having a number average MW of 725 g/mol, a weight average MW of 920 g/mol, and a polydisperity index of 1.27.[10] Another sample of Phenyl Trimethicone was deemed to contain greater than 70% material < 1000 g/mol when measured by conventional gel permeation chromatography against polystyrene standards.[11] A sample of Trimethylsiloxyphenyl Dimethicone was described as having a number average MW of 3279 g/mol and a weight average MW of 20,569 g/mol.[12] Additionally, 97.5% of this sample was deemed to comprise a MW > 1000 g/mol, while 0.05% was deemed to comprise a MW ≤ 500 g/mol.

Method of Manufacture

In one industrial process, silica is first converted to tetraethoxysilane, and the ethoxy groups are replaced with the desired chemical group by the Grignard reaction. The resulting organosilanes are hydrolyzable to organo-substituted silicic acids, called "silanols," which rapidly condense with each other to produce the silicon-oxygen-silicon framework of the silicone polymers. In these silicone structures, the organic radicals are firmly bonded to the silicon through a carbon-silicon linkage. Each silicon atom is linked to neighboring silicon atoms through an oxygen atom.

Diphenyl Dimethicone

A supplier described the manufacture of Diphenyl Dimethicone as a five-step process, involving hydrolysis, polymerization, neutralization, distillation, and filtration.[8] The hydrolysis reaction produces diphenyl dimethyl silicone hydrolysate, which along with dimethylcyclosiloxane and methyl-ended siloxane, is added to the reactor and mixed with a base catalyst for synthesis. Upon neutralization, the reaction is terminated, and the unreacted polymer is removed via distillation, prior to filtration and packaging. The general manufacturing process of Diphenyl Dimethicone is described by another supplier as the hydrolysis of a mixture of dichlorodiphenylsilane, dichlorodimethylsilane, and chlorotrimethylsilane, followed by catalyst polymerization.[13]

Diphenylsiloxy Phenyl Trimethicone

The general manufacturing process of Diphenylsiloxy Phenyl Trimethicone is described by a supplier as the hydrolysis of a mixture of trichlorophenylsilane, dichlorodiphenylsilane, and chloromethylsilane followed by catalyst polymerization.[14]

Phenyl Trimethicone

A supplier described the manufacture of Phenyl Trimethicone as a three-step process, involving hydrolysis, distillation, and filtration.[10] The hydrolysis reaction produces phenyl trimethicone hydrolysate, which is then distilled to remove low molecular weight impurities and filtered prior to packaging. In another method of manufacture provided by a supplier, silanes first undergo hydrolysis to produce Phenyl Trimethicone.[11] The resulting hydrolysis product is then stripped, filtered, and tested for quality prior to packaging.

Impurities

Diphenyl Dimethicone; Diphenylsiloxy Phenyl Trimethicone

According to a supplier, a sample of Diphenyl Dimethicone and a sample of Diphenylsiloxy Phenyl Trimethicone each contained < 0.1% of cyclotetrasiloxane, < 0.1% cyclopentasiloxane, and < 0.1% cyclohexasiloxane.[9]

Phenyl Trimethicone

A sample of Phenyl Trimethicone was described by a supplier as comprising ≤ 50 ppm methanol and ≤ 1 ppm benzene.[11]

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics and does not cover their use in airbrush delivery systems. Data are submitted by the cosmetic industry via the FDA's Voluntary Cosmetic Registration Program (VCRP) database (frequency of use) and in response to a survey conducted by the Personal Care Products Council (Council) (maximum use concentrations). The data are provided by cosmetic product categories, based on 21CFR Part 720. For most cosmetic product categories, 21CFR Part 720 does not indicate type of application and, therefore, airbrush application is not considered. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, 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.

According to 2023 VCRP survey data, Phenyl Trimethicone has the greatest reported frequency of use; it is reported to be used in 705 formulations, 659 of which are leave-on products (Table 2).[15] Diphenylsiloxy Phenyl Trimethicone is reported to be used in 275 formulations, and Diphenyl Dimethicone is reported to be used in 150 formulations (Table 3). All other ingredients are used in less than 37 formulations. The results from concentration of use surveys conducted by the Council in 2021 and 2022 indicate that Phenyl Trimethicone has the highest reported maximum concentration of use, at 59.5% in non-coloring shampoos; it also has the highest reported maximum concentration of use in leave-on formulations, at up to 24.8% (in other makeup preparations).[16,17] Use concentration data were reported for Diphenylsiloxy Phenyl/Propyl Trimethicone in makeup bases at 5.3%, but no uses were received in the VCRP; however, it should be presumed there is at least one use in this category.

Since its last review in 2006, the reported frequency and concentrations of use have increased for Phenyl Trimethicone. Notably, reported uses in non-coloring hair products have increased from 69 to 174 and the maximum reported concentrations of use for this category have also increased from 18% to 59.5%.[4,15,16] Recent and historical frequency and concentration of use data for Phenyl Trimethicone are provided in Table 2.

Several of the ingredients are reported to be used in products applied near the eye (e.g., Diphenylsiloxy Phenyl Trimethicone is used at up to 19.9% in eyeliners), and in products that can result in incidental ingestion (e.g., Diphenyl Dimethicone is used at up to 24.1% in lipsticks). Phenyl Trimethicone is reported to be used in baby products at up to 6.5%. Additionally, some of these ingredients are used in formulations that could possibly be inhaled; for example, according to the Council survey, Phenyl Trimethicone is reported to be used at up to 7.5% in aerosol hair sprays, at up to 15.6% in face powders, and at up to 2.2% in aerosol deodorants.

Although products containing some of these ingredients may be marketed for use with airbrush delivery systems, this information is not available from the VCRP or the Council survey. Without information regarding the frequency and concentrations of use of these ingredients, and without consumer habits and practices data or particle size data related to this use technology, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

The phenyl-substituted methicone ingredients named in the report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[18]

Non-Cosmetic

Phenyl Methicone and Phenyl Trimethicone are both approved as indirect food additives and are used as adhesives in the components of articles intended for use in the packaging, transporting, or holding of food [21CFR § 175.105]. Additionally, Phenyl Trimethicone is an approved indirect food additive used as a polymeric coating for food-contact surfaces of articles intended for use in food processing, manufacture, and packaging [21CFR § 175.300]; furthermore, Phenyl Trimethicone is required to contain no more than 2%, by weight, of cyclosiloxanes, having up to and including 4 siloxy units, for this use.

TOXICOKINETIC STUDIES

Dermal Absorption

The dermal absorption of Phenyl Trimethicone was evaluated in 5 male subjects.[3] During a 25-d pretest period, baseline analysis of 24-h silicon urine levels was conducted. Phenyl Trimethicone (50 mg/kg) was applied once daily over the entire back surface of the 5 subjects for 10 d; the test material remained on the skin for 20 h, before the excess was removed by washing. Blood and urine silicon concentrations obtained on day 1, 3, 6, 8, and 10 of treatment did not show any significant increases in blood or urinary silicon concentrations.

Diphenylsiloxy Phenyl Trimethicone

Based on its physicochemical properties, Diphenylsiloxy Phenyl Trimethicone has an estimated dermal absorption value of 10%.[7] % (However, this is possibly for the monomer (< 1000 g/mol).)

Absorption, Distribution, Metabolism, and Excretion (ADME)

Phenyl Trimethicone

Seven rats were fed Phenyl Trimethicone (4% in the diet; between 944 - 1071 mg), with olive oil and rat cake powder (16% and 80% of the diet, respectively) for 8 d.[19] Tissues, feces, and urine were examined for silicon presence. No silicon was found in the lipids of the gastrointestinal tract, feces, liver, kidney, or fat depots of control animals which were only fed rat cake powder and olive oil. For animals treated with Phenyl Trimethicone, almost all of the siloxane was recovered as silicon in the feces or gastrointestinal tract, indicating no siloxane absorption (mean % siloxane fluid recovery of 96.0 ± 1.0).

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

An acute, 24-h, dermal application of Phenyl Trimethicone was considered non-toxic to 10 albino rats when administered at 2000 mg/kg via an occlusive sleeve.[3] In 3 separate experiments, no deaths occurred in groups of 10 male albino mice which received a single oral dose of 10 ml/kg of a cosmetic product, containing 10% Phenyl Trimethicone. Single doses of Phenyl Trimethicone, ranging from 10,200 - 34,600 mg/kg were orally administered to groups of 8 male and 8 female Sprague-Dawley rats, and the animals were observed for 14 d before necropsy. One rat in the 34,600 mg/kg group died; others at the highest dose exhibited hypoactivity, muscular weakness, diarrhea, diuresis, ruffled fur, and weight loss. No significant gross lesions were found in the tissues and organs; the test material was deemed non-toxic. No mortality, body weight changes, behavioral changes, or gross pathological changes occurred in 540 male rats administered an oral dose of 3.3 mg/kg Phenyl Trimethicone for 7 d. An acute, oral, 5 ml/kg dose of a product containing 5% Phenyl Trimethicone resulted in leg weakness, transient vasodilation of the ears, and hypoactivity in 5 male and 5 female Sprague-Dawley rats; these effects resolved within 6 h post-treatment and no deaths occurred.

The acute dermal, oral, and inhalation toxicity studies summarized below are described in Table 4.

The acute dermal LD_{50} of Diphenylsiloxy Phenyl Trimethicone, when applied under semi-occlusion to male and female Wistar rats, was determined to be > 2000 mg/kg.[6,7] In an acute dermal toxicity study, the LD_{50} value was determined to be > 2000 mg/kg bw when Trimethylsiloxyphenyl Dimethicone was applied for 24 h under occlusive conditions to male and female Sprague Dawley rats.[20]

The acute oral LD_{50} of Diphenyl Dimethicone, administered via a stomach tube at doses of 8190; 16,380; 32,770; or 65,540 mg/kg in rats, was determined to be > 65,540 mg/kg bw.[21] One rat from each of the 3 highest dose groups died 3 or more days after dosing, each exhibiting diffuse pulmonary and hepatic hemorrhage; no other gross abnormalities were found upon necropsy. A single dose of 5000 mg/kg bw Diphenyl Dimethicone was administered to male and female albino rats in an acute oral toxicity study; the LD_{50} was determined to be > 5000 mg/kg.[22] In other acute oral toxicity studies, the LD_{50} value for Diphenylsiloxy Phenyl Trimethicone was > 2000 mg/kg in female Wistar Han rats,[6,7] and the LD_{50} values for Phenyl Trimethicone were ≥ 2000 mg/kg in female Wistar rats and > 5000 mg/kg in male and female rats.[5] The acute oral LD_{50} value for a test material comprising 78 - 82% Phenyl Trimethicone and 18 - 22% Polysilicone-11 was determined to be > 5000 mg/kg in male and female Wistar-derived albino rats.[23] An LD_{50} of > 2000 mg/kg bw was determined in an acute oral toxicity evaluating Trimethylsiloxyphenyl Dimethicone, administered via gavage, in corn oil, to CD rats.[12]

In an acute inhalation toxicity study of Diphenyl Dimethicone, groups of 5 male and 5 female albino rats were exposed to the test article (whole body) at concentrations of 5, 10, 23, 24, 42, 90, 101, 168, or 214 mg/l for 1 h.[21] One animal from the 42 mg/l and one from the 101 mg/l group died during the exposure period. All dosage groups, except the 5 mg/l group, had animals that died within 24 h of dosing. Severe and diffuse pulmonary hemorrhages accounted for most of the deaths and pulmonary consolidation was found in surviving animals. The LC_{50} was determined to be 18 mg/l.

Short-Term and Subchronic Toxicity Studies

Dermal

No adverse effects were observed in 4 rabbits which received daily dermal applications of 50 ml/kg Phenyl Trimethicone for 20 d.[3] Groups of 10 New Zealand albino rabbits were dermally treated with 2, 6, or 20 mg/kg Phenyl Trimethicone, in polypropylene glycol (control), for 20 d. Local skin reactions were characterized by slight desquamation at the application site of both test and control animals. No toxic effects were noted in body weight, hematological values, blood chemistry, urine analysis, and gross or microscopic pathological findings of the test or control groups. Ten male New Zealand rabbits were dosed for 28 d with 200 mg/kg Phenyl Trimethicone to evaluate dermal toxicity. No significant adverse effects were noted with reference to body weight, mortality, behavioral reactions, testicular histology, and spermatogenic activity. The dermal toxicity of a skin moisturizer containing 2.5% Phenyl Trimethicone was evaluated for 90 d in groups of 10 New Zealand white rabbits.[3] Two treatment groups were administered 5.5 or 8.4 mg/cm^2 per 8.4% body surface area of the test article, and compared to a control group. Erythema, slight edema, and slight desquamation were observed in both groups throughout the experiment. These effects appeared slightly more severe at the 8.4 mg/cm^2 dose during the first month of exposure; no differences between dose groups were observed by the second month. Signs of dermal irritation were nearly maximal in the first week and increased gradually in severity during the last month of exposure. No treatment-related effects in hematology, clinical chemistry, organ weights, or histopathology were observed.

Oral

Details of the short-term and subchronic toxicity studies summarized below are provided in Table 5.

Groups of 10 male and 10 female Sprague-Dawley rats were dosed with 0, 5, 20, or 80 mg/kg/d of a mixture containing 15% Diphenyl Dimethicone (in a vehicle solution of 10% polyethylene glycol 660 hydroxystearate, in purified water), via gavage, for 90 d.[24] No deaths related to treatment with the test article occurred and no changes were observed in body weight and food consumption. Higher absolute and relative liver weights in animals given 80 mg/kg were considered to be treatment-related and were correlated with slight hepatocellular hypertrophy seen in 8 males and 10 females in the 80 mg/kg group; both effects were considered toxicologically significant. Liver enlargement was noted in 3 males from the 80 mg/kg group, which was attributed to treatment with the test article. The no-observed-adverse-effect-level (NOAEL) for the test item containing 15% Diphenyl Dimethicone was determined to be 20 mg/kg/d. In a short-term oral toxicity study, performed in accordance to the Organisation for Economic Development (OECD) test guideline (TG) 407, groups of Wistar Han rats (5/sex) were given 0, 200, 600, or 1000 mg/kg bw Diphenylsiloxy Phenyl Trimethicone, in corn oil, via gavage, for 28 d.[6,7] A statistically significant reduction in body weight gain was observed in male rats (18 - 19%) in the 1000 mg/kg group and in female rats (48%) from the 600 and 1000 mg/kg groups. Compared to controls, relative liver weights increased in the low-, mid-, and high-dose groups for both males and females. Treatment-related microscopic liver changes were observed in all test animals, and minimal hypertrophic changes in the follicular epithelium of the thyroid gland were observed in 2 males from the low-dose group, 1 male from the mid-dose group, and 4 males from the high-dose group. The NOAEL was determined to be > 1000 mg/kg. In a short-term oral toxicity study, CD rats (5/sex) were administered 0, 20, 150, or 1000 mg/kg/d Trimethylsiloxyphenyl Dimethicone in corn oil, via gavage, for 4 wk.[25] No deaths or significant changes related to the test material were observed; the NOAEL was determined to be 1000 mg/kg/d.

Inhalation

Five male and 5 female rats were exposed (whole body) to an aerosol containing 3% Phenyl Trimethicone, twice daily, 5 d/wk, for 4 wk.[3] A single exposure consisted of a 30-s burst, followed by a 15-min exposure to the test material within a 350 l inhalation chamber. The animals exposed to the Phenyl Trimethicone aerosol gained slightly less weight than the controls; no other toxic effects were observed.

One cat, 2 guinea pigs, 2 rabbits, and 4 rats were exposed, whole-body, to a mist of Phenyl Methicone at the rate of 67.4 mg/min over 10 d, for 7 h/d.[26] No deaths occurred and moderate degenerative changes in the livers of cats and guinea pigs were considered only circumstantially associated with siloxane exposure.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Dermal

Phenyl Trimethicone was tested in several dermal developmental and reproductive toxicity studies.[3] In one study using 3 groups of 26 rats and 3 groups of 15 rabbits, 50 or 500 mg/kg Phenyl Trimethicone was applied topically to 2 groups of each species on days 6 - 16 or 6 - 18 of gestation, respectively. Untreated animals served as controls. Rats were killed on day 20 and rabbits were killed on day 30. Fetuses were removed by cesarean section, and one half were examined microscopically, while the other half were examined for skeletal abnormalities. In the rats, the mean number of implantation sites and mean number of live fetuses derived from control and test group dams were comparable; however, 10 fetuses from the low-dose group and 3 fetuses from the high-dose group had incompletely developed sternebrae. A greater number of rat fetuses derived from the test groups had bipartite sternebrae and lack of closure of the coronal suture, compared to controls. Of the rabbits tested, one dam died in the control group and two animals died from the low-dose group. The control rabbit group had a greater mean number of implantation sites than the test groups, although the mean number of live fetuses from all 3 groups

was comparable. None of the fetuses delivered from dead dams in the control (8), low-dose (9), or high-dose (2) groups were abnormal, besides showing signs of immaturity. All live pups had fully developed sternebrae and normal ribs with no abnormalities in the soft tissues; the delayed ossification found in both test groups of rats was therefore considered a species variation. Two separate studies evaluated the teratogenicity of Phenyl Trimethicone, in groups of 10 or 15 rabbits; 200 mg/kg of the test material was applied on days 6 - 18 of gestation in both studies. Rabbits in the first study received either 200 mg/kg corn oil, Phenyl Trimethicone in corn oil, or were untreated. A slight but significant increase in the number of resorption sites and decreased viability of the Phenyl Trimethicone-treated fetuses was observed. Rabbits in the second study received either 200 mg/kg Phenyl Trimethicone (undiluted), sesame oil, or were untreated. No deaths, unusual reactions, or adverse effects on maternal body weight, or the viability and external/internal development of the fetuses was observed. Consequently, Phenyl Trimethicone was not considered teratogenic in either study.

Oral

Phenyl Trimethicone was assayed for effects upon uterine weights in groups of 6 immature female Wistar rats which were bilaterally ovariectomized 3 d prior to treatment.[3] On the fourth day, groups of 6 rats received 0.01, 0.1, 1, or 10 mg/kg Phenyl Trimethicone in sesame oil, via gavage; animals received a daily dose for 3 d and were necropsied after the final dose. Controls received the oil vehicle. No toxic effects or changes in uterine weights were observed in treated animals.

Details of the oral developmental and reproductive toxicity studies summarized below are provided in Table 6.

The effect of maternal (and paternal) consumption of Diphenylsiloxy Phenyl Trimethicone upon reproductive and developmental toxicity was evaluated in accordance with OECD TG 422.[6] Groups of Sprague-Dawley rats (10/sex/group) were administered 0, 100, 500, or 1000 mg/kg bw/d Diphenylsiloxy Phenyl Trimethicone, in corn oil, via gavage; both males and females were treated with the test substance 2 wk prior to, and during, mating. No statistically significant changes in body weight, food consumption, or organ weights were observed or treatment-related effects were apparent for reproductive endpoints in the parents (including testis weight, epididymis weight, mean gestation length, mean number of corpora lutea, mean number of implantation sites, mean mating and fertility indices) nor were there effects observed in the offspring for gross pathology, mean litter size, mean litter weight, or mean ration live births/litter size. Thus, under the conditions of this study, the NOAEL for reproductive (male and female) and developmental toxicity was determined to be ≥ 1000 mg/kg bw/d. Groups of 20 male Wistar rats were given Phenyl Trimethicone, in oil (oil identity not specified), via gavage, at doses of 100, 300, or 1000 mg/kg bw, 5 d/wk, for 4 wk.[5] The main purpose of this study was to observe if testicle weight reduction occurred with repeated doses of the test article. No visible changes, body weight fluctuations, or deaths occurred during the course of the study, and no effects on testicle weight or histology were observed. The NOAEL for effects on body weight, testicle weight, and histology was determined to be > 1000 mg/kg.

GENOTOXICITY STUDIES

Phenyl Trimethicone was not mutagenic in an Ames test using Salmonella strains, both with and without metabolic activation.[3] (Test concentrations were not stated.)

Details of the genotoxicity studies summarized below are provided in Table 7.

Diphenylsiloxy Phenyl Trimethicone, dissolved in ethanol, was not genotoxic when tested at concentrations up to 5000 µg/plate in an Ames test performed, in accordance with OECD TG 471, using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2, with or without metabolic activation.[6,7] In a mammalian chromosomal aberration study performed in accordance with OECD TG 473, the genotoxic potential of Diphenylsiloxy Phenyl Trimethicone (in ethanol) was tested in the Chinese hamster lung (V79) cell line, with and without metabolic activation.[6,7] Cell lines were treated with 0.025 - 0.3 µl/ml of the test article for 4 h, 0.006 - 0.2 µl/ml for 18 h, or 0.013 - 0.1 µl/ml for 28 h, without metabolic activation; cells treated with metabolic activation were treated with either 0.003 - 0.2 µl/ml or 0.040 - 5 µl/ml of the test substance for 4 h. Cell numbers below 50% of the controls or poor metaphase quality were observed in cells treated with ≥ 0.15 µl/ml of the test substance in the absence of metabolic activation for 18 h. No statistically significant increase in the frequency of cells with chromosome aberrations was induced in either the absence or presence of metabolic activation. The test article was considered non-clastogenic to Chinese hamster lung cell lines. Trimethylsiloxyphenyl Dimethicone, dissolved in 10% Tween 80 solution, was not genotoxic in an Ames test when tested in *S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538 strains at up to 100 µl/plate, with and without metabolic activation.[27]

CARCINOGENICITY STUDIES

No carcinogenicity studies were found in the published literature, and unpublished data were not submitted.

DERMAL IRRITATION AND SENSITIZATION STUDIES

An undiluted, 24-h dose of 0.5 ml Phenyl Trimethicone was non-irritating to the skin of 6 albino rabbits.[3] A foundation cream containing 5% Phenyl Trimethicone was applied at 0.5 ml to 6 rabbits, for 14 d; slight erythema, slight edema, and desquamation were observed. The cream had a primary irritation index of 1.9 (max = 8) and was considered mildly irritating.

Three separate products, each containing 10% Phenyl Trimethicone, were found to be slightly irritating to groups of 6 male New Zealand white rabbits when tested at 0.5 ml in single insult occlusive patch tests. Phenyl Trimethicone (tested at 5% in propylene glycol during induction, and at 10 and 20% in petrolatum during challenge) was not irritating or sensitizing to 10 female guinea pigs in a maximization test.[3]

In clinical testing, the cumulative irritation score of a moisturizer containing 2.5% Phenyl Trimethicone was found to be 13 (max = 630) in 9 subjects.[3] The product was classified as a mild material (essentially no experimental irritation). Undiluted Phenyl Trimethicone was not found to be irritating or sensitizing in a human repeated insult patch test (HRIPT) of 50 subjects.[3] In an HRIPT using groups of 8 subjects, the highest total irritancy score of 17 cosmetic products, each containing 10% Phenyl Trimethicone, was 5 (max = 256) and the highest individual score was 1 (max = 8); overall, the products were considered minimally irritating. No irritation or sensitization was observed in 2 separate modified Draize-Shelanski HRIPTs of a cosmetic foundation containing 5% Phenyl Trimethicone (189 subjects) and a moisturizer containing 2.5% Phenyl Trimethicone (239 subjects).

Details of the dermal irritation and sensitization studies summarized below are provided in Table 8.

Diphenyl Dimethicone and Diphenylsiloxy Phenyl Trimethicone (100% pure and applied neat) were not irritating when applied to New Zealand white rabbit skin (0.5 ml) in 2 separate primary dermal irritation tests.[28,29] In a primary skin irritation test, performed in accordance OECD TG 404, a semi-occlusive application of 0.5 ml 100 % pure Diphenylsiloxy Phenyl Trimethicone was not irritating when applied neat to the skin of 3 New Zealand white rabbits.[29] In a similar study, Diphenylsiloxy Phenyl Trimethicone was deemed slightly irritating (or non-irritating, in another description) to 1 male and 2 female New Zealand white rabbits; very slight to well-defined erythema was noted in all animals 1 h after patch removal and mean erythema/eschar scores were 0.33 for animal 1 and 2, and 0.67 for animal 3.[6,7] Very slight erythema persisted in all animals until the 24-h reading and in 1 animal at the 48-h reading; all effects were reversible within 72 h. The one-time application of a mixture comprising 72 - 82% Phenyl Trimethicone and 18 - 22% Polysilicone-11 (0.5 ml) was not irritating to 6 New Zealand white rabbit skin in an acute skin irritation test.[30] Trimethylsiloxyphenyl Dimethicone was not irritating when applied to New Zealand white rabbit skin (0.5 ml) in a primary skin irritation test, performed in accordance with OECD TG 404.[31] Several 24-h single insult occlusive patch tests (SIOPTs) were performed using: a lip color formulation containing 9.06% Diphenyl Dimethicone (20 subjects), an ampoule formulation containing 0.5 % Diphenylsiloxy Phenyl Trimethicone (20 subjects), an eye primer formulation containing 10% Phenyl Trimethicone (21 subjects), and a shine gloss formulation containing 5% Trimethylsiloxyphenyl Dimethicone (18 subjects); the test substances were deemed non-irritating.[32-35] A SPF cream containing 3.2363% Phenyl Trimethicone and a serum formulation containing 2% Trimethylsiloxyphenyl Dimethicone did not cause irritation in a 14-d cumulative irritation test of 25 subjects and in a 15-d cumulative irritation test of 28 subjects, respectively.[36,37]

The sensitization potential of a product containing 15% Diphenyl Dimethicone (tested at concentrations of 2.5, 5, 10, 25, or 50%, in acetone: olive oil (4:1 v/v)) was evaluated using groups of 4 female CBA mice in a local lymph node assay (LLNA).[38] Two of 4 of the animals in the 10% group died on day 3 and 1 of the animals in the 50% group died on day 6; these deaths were not attributed to the test article. No positive lymphoproliferative responses were noted at any of the concentrations and the test article was deemed non-sensitizing. Diphenyl Dimethicone (100%) was not sensitizing in a Buehler test using 6 male and 6 female Hartley albino guinea pigs.[28] Groups of 4 female mice were tested with Diphenylsiloxy Phenyl Trimethicone (tested at concentrations 25, 50, or 100% w/w in acetone: olive oil (4:1 v/v)) in two separate LLNAs.[6,7,29] All mice in the 100% group exhibited slight ear swelling on both ear lobes on day 2 and 3, and similar results were seen for all mice in the 50% group on day 3; these results persisted throughout the observation period; the test materials were not considered sensitizing. The sensitizing potential of Trimethylsiloxyphenyl Dimethicone was evaluated in a guinea pig maximization test, in accordance with OECD TG 406.[39] Groups of 10 Dunkin Hartley guinea pigs received intradermal injections of the test article as supplied, at 50% in isotonic solution, at 50% in Freund's complete adjuvant (FCA) combined with isotonic solution. Since a subsequent 48-h, occlusive application of the undiluted test article did not cause irritation, 0.5 ml of 10% sodium lauryl sulfate (SLS), in paraffin oil, was applied to the skin on day 8, followed by a 48-h, occlusive application of the test article, applied neat, on day 9. On day 22, a 24-h occlusive challenge application was made, and challenge sites were scored 24 and 48 h after patch removal; the test article was deemed to be non-sensitizing.

A modified Marzulli-Maibach human repeated insult patch test (HRIPT) of a formulation containing 2% Diphenyl Dimethicone was completed in 111 subjects; the test material was neither irritating nor sensitizing.[40] An ampoule containing 0.5% Diphenylsiloxy Phenyl Trimethicone and a lip balm containing 11% Diphenylsiloxy Phenyl Trimethicone were not irritating or sensitizing in 2 separate occlusive HRIPTs performed in 112 and 109 subjects, respectively.[41,42] A formulation containing 0.2% Phenyl Methicone was neither irritating or sensitizing in a Marzulli-Maibach HRIPT performed in 107 subjects.[43] A product containing 20% Phenyl Trimethicone was neither irritating or sensitizing in an occlusive HRIPT performed in 53 subjects.[44] A concealer formulation containing 26.18% Phenyl Trimethicone was not sensitizing to 26 subjects in a maximization assay.[45] Similarly, a semi-occlusive HRIPT of a product containing 28.67% Phenyl Trimethicone was performed in 203 subjects; the test material was not sensitizing.[46] HRIPTs performed using a cream formulation containing 3% Trimethylsiloxyphenyl Dimethicone (103 subjects), a product containing 38% Trimethylsiloxyphenyl Dimethicone (205 subjects), and 100% pure Trimethylsiloxyphenyl Dimethicone (51 subjects) yielded negative results.[47-49]

Photosensitization/Photoallergy

Phenyl Trimethicone

The photosensitization potential of a lotion containing 7.5% Phenyl Trimethicone, and 2 other products, was assessed in a photocontact allergenicity assay of 27 subjects.[50] During the pre-testing phase, the minimal erythema dose (MED) of each subject was determined by exposing one side of the midback to a series of radiation exposures from a xenon arc solar simulator (290 - 400 nm; long-wave ultraviolet light (UVA) = 75 mW/cm^2). During the induction phase the following procedure was performed twice a wk, over 3 wk (total of 6 exposures): 24-h occlusive patch applications of 40 mg of the test materials were wiped dry, exposed to 2 MED doses, left open for 48 h, and exposed to a subsequent 24-h occlusive application, made to the same test site. After a 10 - 14 d rest period, during the challenge phase, the test materials were applied as done during the induction phase, in duplicate, to previously untreated sites; one set of patches were wiped dry and irradiated with 0.5 MED of solar simulated radiation plus 4 J/cm^2 of UVA. The second set of patches were not radiated and served as control treated sites. All test sites were examined for reactions at 48 and 72 h following UV exposure. No reactions were observed at either timepoint. The test material was not considered to be a potential photosensitizer.

Trimethylsiloxyphenyl Dimethicone

The photo-allergic potential of a serum containing 2% Trimethylsiloxyphenyl Dimethicone was assessed in a similar manner to the study described above in 26 subjects (minor differences: 40 µl patch applications, UVA/mid-wavelength ultraviolet light (UVB) during induction, one additional blank control was irradiated during challenge).[51] No reactions were observed, and the repeated dermal application of the test material was not contraindicated with sunlight exposure.

OCULAR IRRITATION STUDIES

Phenyl Trimethicone, tested undiluted (in 6 rabbits) and at 10% in 3 cosmetic products (in groups of 6 rabbits), was not considered irritating to rabbit eyes in several Draize tests.[3] Slight conjunctivitis occurred from instilling 0.10 ml of a foundation cream, containing 5% Phenyl Trimethicone in 6 albino rabbit eyes; no evidence of corneal dullness or iritis was observed.

Details of the ocular irritation studies summarized below are provided in Table 9.

Groups of 3 albino rabbits had Diphenyl Dimethicone instilled, undiluted (0.1 ml) into one eye.[21] In the first group, eyes remained unwashed, while eyes were washed after 2 s or 4 s after exposure in a second and third group; eyes were observed for irritation for up to 7 d. A maximum score of 8 (out of 110), which indicated slight irritation was observed within 4 h for 1 animal in the second group. By day 3 all eyes appeared normal, regardless of rinsing status; the test article was considered slightly and transiently irritating to the eyes of rabbits. According to the Globally Harmonized System (GHS) classification, Diphenylsiloxy Phenyl Trimethicone was not irritating to 1 male and 2 female New Zealand white rabbit eyes in an acute, 72-h ocular irritation study, performed in accordance with OECD TG 405.[6,7] When evaluated using Kay and Calandra criteria (same test), the test article was deemed slightly irritating; mild ocular changes, including reddening of the conjunctivae and sclerae, discharge, and chemosis were observed 1 h after instillation, but resolved within 24 h. Directly instilled Phenyl Methicone (unspecified amount) was determined to be non-irritating to rabbit eyes (number and strain not specified) in a 48-h ocular irritation test; slight irritation observed 4 and 8 h after exposure subsequently subsided.[26] A mixture of 78 - 82% Phenyl Trimethicone and 18 - 22% Polysilicone-11 produced a maximum mean total score (MMTS) of 0 when tested for ocular irritancy potential in 6 New Zealand white rabbits; the test article was deemed non-irritating.[52] In another acute ocular irritation study, Trimethylsiloxyphenyl Dimethicone was slightly irritating to male New Zealand white rabbit eyes, when instilled as supplied without rinsing.[53] Eyes were examined for up to 72 h after instillation. The mean values for opacity to the cornea, congestion to the iris, and chemosis and enanthema to the conjunctiva were 0, 0.5, 0.5, and 1.39, respectively.

EXPOSURE ASSESSMENT

In an Australian exposure assessment, total daily systemic exposure to Diphenylsiloxy Phenyl Trimethicone, from concurrent use of cosmetic products applied via various routes, was calculated using concentration of 30% in all cosmetic products, except in aerosol products (in which a maximum concentration of 3% was used).[7] Dermal exposure use patterns were assumed to be similar to those in Europe, and were calculated using 10% dermal absorption; exposure from aerosol products was calculated assuming an adult inhalation rate of 20 m^3/d, in a two-zone approach. Based on these daily systemic exposure calculations, assuming maximum aggregate exposures from simultaneous use of all possible cosmetic products, the combined internal dose of Diphenylsiloxy Phenyl Trimethicone was estimated to be 7.68 mg/kg bw/d.

SUMMARY

According to the *Dictionary*, the phenyl-substituted methicone ingredients included in this safety assessment are reported to function in cosmetics as antifoaming agents and skin and/or hair conditioning agents. This group of phenyl-substituted methicones are either siloxane polymers or compounds of silicone molecules attached to phenyl or propyl groups. Data from the 2023 VCRP and Council survey indicate that Phenyl Trimethicone has the highest reported use in 659 leave-on products, as

well as the highest reported concentration of use, at up to 59.5% in non-coloring shampoos. Phenyl Trimethicone is also reported to be used in leave-on formulations at up to 24.8%.

Based on its physicochemical properties, Diphenylsiloxy Phenyl Trimethicone is estimated to have a dermal absorption value of 10%. Phenyl Trimethicone fed to rats at 4% in the diet for 8 d was mostly recovered as silicon (mean % recovery: 96 ± 1.0) in the feces or gastrointestinal tract, indicating no siloxane absorption.

In an acute dermal toxicity study, the LD_{50} of Diphenylsiloxy Phenyl Trimethicone, when applied under semi-occlusion to Wistar rats, was determined to be > 2000 mg/kg. The acute dermal LD_{50} value for Trimethylsiloxyphenyl Dimethicone was determined to be > 2000 mg/kg bw when applied to Sprague Dawley rat skin under occlusive conditions. The acute oral toxicity of Diphenyl Dimethicone was evaluated in rats administered a single oral dose of 8190; 16,380; 32,770; or 65,540 mg/kg Diphenyl Dimethicone, via gavage. One rat from each of the 3 highest dose groups died 3 or more days after dosing, each exhibited diffuse pulmonary and hepatic hemorrhage; the acute oral LD_{50} was determined to be > 65,500 mg/kg. In another acute oral toxicity study, male and female albino rats received a single dose of 5000 mg/kg bw Diphenyl Dimethicone; the LD_{50} value was determined to be > 5000 mg/kg. The oral LD_{50} value for Diphenylsiloxy Phenyl Trimethicone in Wistar Han rats was determined to be > 2000 mg/kg. The acute oral LD_{50} values for Phenyl Trimethicone were determined to be > 2000 mg/kg in female Wistar rats and > 5000 mg/kg in male and female rats. The acute oral LD_{50} value for a test material comprising 78 - 82% Phenyl Trimethicone and 18 - 22% Polysilicone-11 was determined to > 5000 mg/kg in male and female Wistar-derived albino rats. An LD_{50} of > 2000 mg/kg bw was determined in an acute oral toxicity study evaluating Trimethylsiloxyphenyl Dimethicone in CD rats.

In an acute inhalation study, albino rats were exposed (whole-body) to undiluted, vaporized Diphenyl Dimethicone at concentrations of 5, 10, 23, 24, 42, 90, 101, 168, or 214 mg/l for over an hour. Animals from every dosage group, except the 5 mg/l group, died within 24 h of exposure. Severe and diffuse pulmonary hemorrhages accounted for most of the deaths and pulmonary consolidation was found in surviving animals; the LC_{50} was determined to be 18 mg/l.

Groups of 10 male and 10 female Sprague Dawley rats were orally dosed with 0, 5, 20, or 80 mg/kg/d of a mixture containing 15% Diphenyl Dimethicone, via gavage, for 90 d. Higher absolute and relative liver weights, liver enlargement, and slight hepatocellular hypertrophy in animals from the 80 mg/kg group were considered to be treatment-related and toxicologically significant. The NOAEL for the test article was determined to be 20 mg/kg/d. No treatment related changes or deaths occurred during a short-term oral toxicity study in which Wistar Han rats were dosed with 0, 200, 600, or 1000 mg/kg Diphenylsiloxy Phenyl Trimethicone in corn oil, via gavage, for 28 d. Statistically significant reductions in the body weight gain of male rats (18 - 19%) in the 1000 mg/kg group and females (48%) in the 600 and 1000 mg/kg groups were observed, when compared to controls. In the liver, hepatocellular hypertrophy was seen in all test animals, and changes in hepatic fatty tissue deposition were seen in males from the high dose group and all the test females. Increased incidence of bile duct production was seen in males from the mid dose group and in females from the low and mid dose groups. Minimal hypertrophic changes in the follicular epithelium of the thyroid gland were observed in 4 males from the high dose group, 2 males from the low dose group, and 1 male from the mid dose group. The NOAEL was determined to be > 1000 mg/kg. No deaths or significant changes related to the test material were observed in a short-term oral toxicity study in which CD rats received 0, 20, 150, or 1000 mg/kg/d Trimethylsiloxyphenyl Dimethicone, in corn oil, via gavage, for 4 wk. The NOAEL was determined to be 1000 mg/kg/d. In an inhalation study, no mortality occurred in 1 cat, 2 guinea pigs, 2 rabbits, and 4 rats exposed, whole body, to a mist of Phenyl Methicone (67.4 mg/min) contained in a chamber, at a concentration of 0.52 mg/l, for 7 h/d, over 10 d. In the absence of control data, moderate degenerative changes in the livers of the cats and guinea pigs were considered only circumstantially associated with siloxane exposure.

Groups of Sprague-Dawley rats (10/sex/group) received 0, 100, 500, or 1000 mg/kg bw/d Diphenylsiloxy Phenyl Trimethicone, in corn oil, via gavage 2 wk prior to mating, and until 4 d postpartum, in a reproductive and developmental toxicity study. No treatment-related effects on reproductive endpoints in the parents, including testis weight, epididymis weight, mean gestation length, mean number of corpora lutea, mean number of implantation sites, mean mating and fertility indices, nor changes in gross pathology, mean litter size, mean litter weight, or mean ratio live births/litter size of the pups were observed. The NOAEL for reproductive (male and female) and developmental toxicity was determined to by ≥ 1000 mg/kg bw/d. In a 4-wk study of the effects of Phenyl Trimethicone on testicular histology and weight, male Wistar rats were dosed with up to 1000 mg/kg Phenyl Trimethicone 5d/wk, via gavage. No visible changes, body weight fluctuations, deaths, or changes in testicle histology or weight were observed. The NOAEL for effects on body weight, testicle weight, and histology was determined to be > 1000 mg/kg.

In an Ames test, Diphenylsiloxy Phenyl Trimethicone was tested at concentrations up to 5000 µg/plate, using *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* WP2. No increase in revertant colonies was observed in the presence or absence of metabolic activation. The genotoxic potential of Diphenylsiloxy Phenyl Trimethicone, tested at up to 5 µl/ml for 4, 18, or 28 h, with and without metabolic activation, was evaluated in a mammalian chromosomal aberration test, using the Chinese hamster lung cell line. Cell numbers below 50% of the controls or poor metaphase quality were observed in cells treated in the absence of metabolic activation with ≥ 0.15 µl/ml of the test substance for 18 h. No statistically significant increase in the frequency of cells with chromosome aberrations was induced in either the absence or presence of metabolic

activation. Trimethylsiloxyphenyl Dimethicone was not genotoxic when tested at up to 100 µl/plate with and without metabolic activation in an Ames test using *S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538.

Diphenyl Dimethicone (100% pure and applied neat) was not irritating to New Zealand white rabbit skin in a primary dermal irritation test. In another primary dermal irritation test, Diphenylsiloxy Phenyl Trimethicone was considered not irritating to New Zealand white rabbit skin. Diphenylsiloxy Phenyl Trimethicone was not irritating and slightly irritating or non-irritating, in 2 separate, 4-h, semi occlusive patch tests made to New Zealand white rabbit skin, when tested neat. In the second test, very slight erythema persisted in all animals until 24 h after patch removal, and in 1 animal at the 48-h reading; all effects were reversible within 72 h. Trimethylsiloxyphenyl Dimethicone and a mixture of 72 - 82% Phenyl Trimethicone and 18 - 22% Polysilicone-11 were not irritating to New Zealand white rabbit skin in 2 separate acute dermal irritation tests. A lip color formulation containing 9.06% Diphenyl Dimethicone, an ampoule formulation containing 0.5% Diphenylsiloxy Phenyl Trimethicone, an eye primer formulation containing 10% Phenyl Trimethicone, and a shine gloss formulation containing 5% Trimethylsiloxyphenyl Dimethicone were deemed non-irritating in separate 24-hr single insult occlusive patch tests. A SPF cream formulation containing 3.2363% Phenyl Trimethicone and a serum formulation containing 2% Trimethylsiloxyphenyl Dimethicone were not irritating in a 14-d cumulative irritation test and 15-d cumulative irritation test, respectively.

A product containing 15% Diphenyl Dimethicone (tested at concentrations of 2.5, 5, 10, 25, or 50% in acetone:olive oil (4:1 v/v)) was not sensitizing in a LLNA in groups of 4 female CBA mice; 2 of the animals from the 10% group died on day 3 and 1 of the animals in the 50% group died on day 6, but these deaths were not attributed to the test article. Diphenyl Dimethicone (100%) was not sensitizing in a Buehler test using male and female Hartley albino guinea pigs. In two LLNAs using female mice, the topical application of 25, 50, or 100 % w/w Diphenylsiloxy Phenyl Trimethicone in acetone and olive oil (4:1 v/v) was not considered sensitizing. Trimethylsiloxyphenyl Dimethicone, tested at 50% in FCA during intradermal injection (both applied neat during challenge), was not irritating or sensitizing in a guinea pig maximization test. A formulation containing 2% Diphenyl Dimethicone was neither irritating nor sensitizing in a Marzulli-Maibach HRIPT completed in 111 subjects. Similarly, an ampoule formulation containing 0.5% Diphenylsiloxy Phenyl Trimethicone and a lip balm containing 11% Diphenylsiloxy Phenyl Trimethicone were neither irritating or sensitizing in 2 separate occlusive HRIPTs performed in 112 and 109 subjects, respectively. A formulation containing 0.2% Phenyl Methicone was neither irritating or sensitizing in a Marzulli-Maibach HRIPT performed in 107 subjects. An occlusive HRIPT of a product containing 20% Phenyl Trimethicone (53 subjects), a semi-occlusive HRIPT of a product containing 28.67% Phenyl Trimethicone (203 subjects), a maximization assay of a concealer formulation containing 26.18% Phenyl Trimethicone (26 subjects), and 3 separate HRIPTs of a cream formulation containing 3% Trimethylsiloxyphenyl Dimethicone (103 subjects), a product containing 38% Trimethylsiloxyphenyl Dimethicone (205 subjects), and 100% pure Trimethylsiloxyphenyl Dimethicone (51 subjects) all yielded negative results.

A lotion containing 7.5% Phenyl Trimethicone was not considered to be a potential photosensitizer in a photocontact allergenicity assay of 27 subjects. The repeated dermal application of a serum containing 2% Trimethylsiloxyphenyl Dimethicone was not contraindicated with sunlight exposure in a test of photoallergic potential in 26 subjects.

The ocular irritation potential of Diphenyl Dimethicone was tested in albino rabbit eyes; the maximal irritation score (8 of out of 110) was observed within 4 h in 1 animal from the group with eyes washed after 2 s; any signs of irritation resolved by the second or third day. Under these conditions, the test article was considered slightly, and transiently irritating to rabbit eyes. In an acute ocular irritation study, rabbit eyes were treated with undiluted Diphenylsiloxy Phenyl Trimethicone for 72 h; the test article was deemed slightly irritating to rabbit eyes based on Kay and Calandra criteria, but was not deemed irritating according to the Globally Harmonized System of classification. Phenyl Methicone was slightly irritating at 4 and 8 h after being instilled in rabbit eyes; subsequently, the irritation subsided. A mixture of 78 - 82% Phenyl Trimethicone and 18 - 22% Polysilicone-11 produced an MMTS of 0 when tested for acute irritancy in the eyes of New Zealand white rabbits; the test article was deemed a non-irritant. In another acute ocular irritation study, Trimethylsiloxyphenyl Dimethicone was deemed slightly irritating to male New Zealand white rabbit eyes; the mean values for opacity to the cornea, congestion to the iris, and chemosis and enanthema to the conjunctiva were 0, 0.5, 0.5, and 1.39, respectively.

Total daily systemic exposure to Diphenylsiloxy Phenyl Trimethicone was evaluated in an Australian exposure assessment. The simultaneous use of cosmetic products applied via varied routes of exposure was estimated to be 7.68 mg/kg bw/d, assuming 30% concentration in all cosmetic products, with the exception of aerosols (in which a maximum concentration of 3% was used).

DISCUSSION

This assessment reviews the safety of 7 phenyl-substituted methicones, as used in cosmetic formulations. The Panel concluded that these ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment, with the exception that the available data are insufficient to make a determination of safety for these in products that may be incidentally inhaled.

The Panel noted that the toxicological profile for these ingredients is mostly comprehensive, with multiple routes and durations of exposure, with the exception that there is a lack of inhalation toxicity data. Negative studies for genotoxicity and

developmental and reproductive toxicity were considered to be robust. Furthermore, no evidence of dermal irritation or sensitization were found for these ingredients. Transient signs of irritation were observed in a 15-d cumulative irritation study, in which a serum containing 2% Trimethylsiloxyphenyl Dimethicone, was tested using 28 subjects. The Panel discussed that there was no further evidence of these ingredients causing irritation or sensitization, even when tested at higher concentrations. Thus, the Panel reasoned that these results may not be attributable to the ingredient alone and were possibly influenced by the formulation and product type as well.

The Panel considered the available method of manufacturing and impurities data as appropriate read-across for the remaining ingredients in this group. Namely, the Panel considered data for Diphenyl Dimethicone and Phenyl Trimethicone as suitable read-across for Phenyl Dimethicone and Phenyl Methicone, while data on Diphenylsiloxy Phenyl Trimethicone was considered suitable read-across for Diphenylsiloxy Phenyl/Propyl Trimethicone and Trimethylsiloxyphenyl Dimethicone.

The Panel reviewed data received in response to the second IDA that was issued at its March 2023 meeting, including correspondence from the Silicones, Environmental, Health, and Safety Center (SEHSC) and a CAS number review for Phenyl Trimethicone conducted by the Council. The Panel acknowledged that although the SEHSC stated the data they submitted are representative of Phenyl Trimethicone, the test article in those studies is associated with CAS No. 70131-69-0, which is no longer connected to Phenyl Trimethicone in the wINCI *Dictionary*. Therefore, it is unclear to the Panel as to whether data submitted for the test article under the name Phenyl Trimethicone, but with CAS No. 70131-69-0, refer to the ingredient included in this report, and if those data are applicable to this safety assessment. Accordingly, the Panel determined those data should not be included due to this uncertainty.

Furthermore, the Panel agreed that data on short-term intermittent-exposure inhalation toxicity and on the particle size distribution and concentrations of use for these ingredients in products which may be incidentally inhaled remain lacking. Consequently, the additional data needs are:

- Clarification of the identity and chemical nomenclature for the test article referred to as Phenyl Trimethicone in the SEHSC data submission
- Additional respiratory toxicity data at, or above, the reported maximum concentration of use in products that could be incidentally inhaled (i.e., Phenyl Trimethicone is reported to be used at up to 7.5% in aerosol sprays)
    - Preferably, the protocol should be similar to the short-term inhalation toxicity study described in the original report on Phenyl Trimethicone (i.e., a 4-wk study in which rats were exposed twice daily to a 30-s burst of an aerosol containing 3% Phenyl Trimethicone, followed by a 15-min chamber exposure).

The Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings) notes that airbrush technology presents a potential safety concern, and that no data are available for consumer habits and practices thereof. As a result of deficiencies in these critical data needs, the safety of cosmetic ingredients applied by airbrush delivery systems cannot be determined by the Panel. Therefore, the Panel has concluded the data are insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 7 phenyl-substituted methicone ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment, with the exception that the available data are insufficient to make a determination of safety for these ingredients in products that may be incidentally inhaled.

Diphenyl Dimethicone
Diphenylsiloxy Phenyl Trimethicone
Diphenylsiloxy Phenyl/Propyl Trimethicone
Phenyl Dimethicone
Phenyl Methicone
Phenyl Trimethicone
Trimethylsiloxyphenyl Dimethicone

TABLES

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

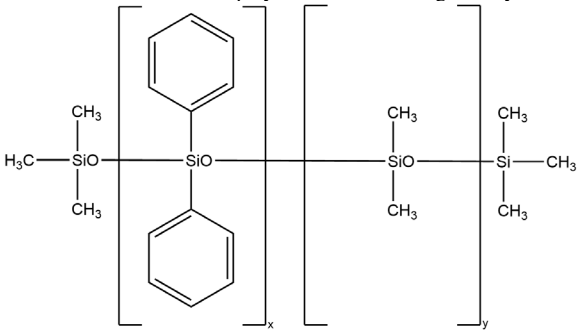
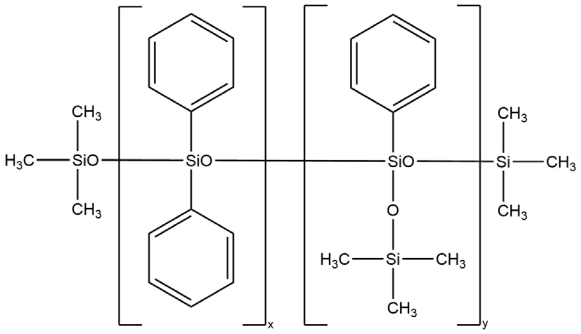
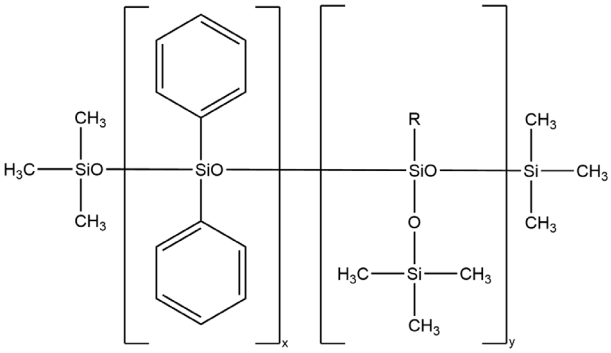
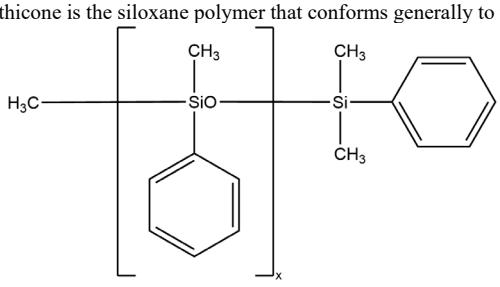
Ingredient/CAS No.	Definition	Function(s)
Diphenyl Dimethicone 68083-14-7	Diphenyl Dimethicone is a siloxane polymer that conforms generally to the structure: 	Antifoaming agents; Skin-conditioning agents - occlusive
Diphenylsiloxy Phenyl Trimethicone 352230-22-9	Diphenylsiloxy Phenyl Trimethicone is the silicone compound that conforms to the structure: 	Antifoaming agents; Hair conditioning agents; Skin-conditioning agents-miscellaneous
Diphenylsiloxy Phenyl/Propyl Trimethicone	Diphenylsiloxy Phenyl/Propyl Trimethicone is the silicone compound that conforms to the structure:  wherein R represents either a phenyl or propyl group.	Hair conditioning agents; Skin conditioning agents - emollient
Phenyl Dimethicone 9005-12-3	Phenyl Dimethicone is the siloxane polymer that conforms generally to the structure: 	Antifoaming agents; Skin-conditioning agents - occlusive

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

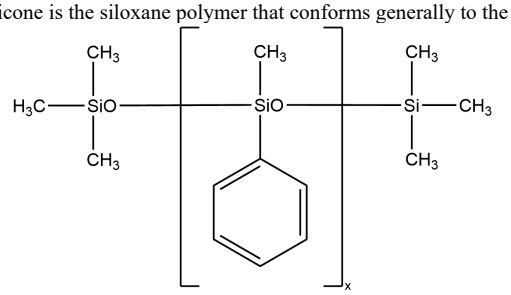
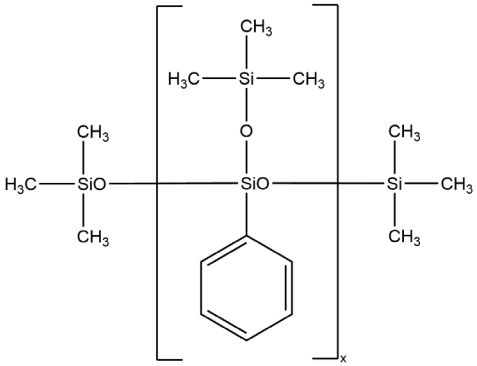
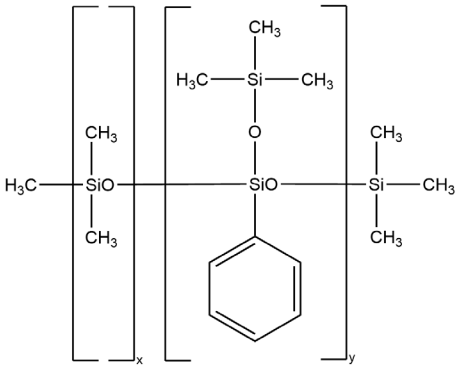
Ingredient/CAS No.	Definition	Function(s)
Phenyl Methicone 31230-04-3 63148-58-3	Phenyl Methicone is the siloxane polymer that conforms generally to the structure: 	Skin-conditioning agents - emollient
Phenyl Trimethicone 195868-36-1 2116-84-9 73559-47-4	Phenyl Trimethicone is the siloxane polymer that conforms generally to the structure: 	Antifoaming agents; Hair conditioning agents; Skin-conditioning agents - occlusive
Trimethylsiloxyphenyl Dimethicone 73138-88-2	Trimethylsiloxyphenyl Dimethicone is the siloxane polymer that conforms generally to the structure: 	Hair conditioning agents

Table 2. Frequency (2023/2002) and concentration (2023/2004) of use according to duration and exposure for Phenyl Trimethicone

	# of Uses		*Max Conc of Use (%)*	
	2023[15]	**2002[4]**	**2022[16]**	**2004[4]**
Totals*	**705**	**279**	**0.1 – 59.5**	**0.0075-36**
summarized by likely duration and exposure**				
Duration of Use				
Leave-On	659	*264*	*0.1 – 24.8*	*0.0075 - 36*
Rinse-Off	46	*14*	*0.75 – 59.5*	*0.3 - 4*
Diluted for (Bath) Use	NR	*1*	*NR*	*NR*
Exposure Type				
Eye Area	102	83	0.75 - 17	0.008 - 15
Incidental Ingestion	96	34	1 - 13.8	0.08 - 36
Incidental Inhalation-Spray	57; 121[a]; 55[b]	24; 56[a]; 7[b]	0.1 -7.5; 6[a]	0.1 – 18; 0.2 – 11[a]; 0.2 -18[b]
Incidental Inhalation-Powder	31; 55[b]; 3[c]	10; 7[b]	1.2 – 15.6; 1.7 – 13[c]	0.1 – 8; 0.2 -18[b]
Dermal Contact	426	175	0.1 – 24.8	0.0075 - 22
Deodorant (underarm)	1[a]	1[a]	spray: 2.2; not spray: 1.8 – 10.2	NR
Hair - Non-Coloring	174	69	0.5 – 59.5	0.1 - 18
Hair-Coloring	9	NR	NR	NR
Nail	NR	NR	3	0.5
Mucous Membrane	97	36	1 – 13.8	0.08 - 36
Baby Products	3	NR	6.5	NR
as reported by product category				
Baby Products				
Baby Lotions/Oils/Powders/Creams	3	NR	NR	NR
Other Baby Products	NR	NR	6.5	NR
Bath Preparations (diluted for use)				
Bath Oils, Tablets, and Salts	NR	1	NR	NR
Eye Makeup Preparations				
Eyebrow Pencil	2	NR	8.8	NR
Eyeliner	10	1	3.4-16.5	2-6
Eye Shadow	70	77	2.4-17	4-13
Eye Lotion	1	NR	NR	0.008-1
Mascara	NR	1	NR	0.1-0.4
Other Eye Makeup Preparations	19	4	0.75	6-15
Fragrance Preparations				
Cologne and Toilet Water	NR	NR	NR	0.5
Perfumes	1	1	3	NR
Powders (dusting/talcum, excl aftershave talc)	NR	1	NR	NR
Other Fragrance Preparation	2	NR	0.5	0.5
Hair Preparations (non-coloring)				
Hair Conditioner	32	8	0.75-3	0.3-2
Hair Spray (aerosol fixatives)	48	23	0.5-7.5	0.1-18
Hair Straighteners	5	NR	NR	NR
Shampoos (non-coloring)	2	NR	59.5	1
Tonics, Dressings, and Other Hair Grooming Aids	57	31	0.51-9 (not spray); 2 (pump spray); 7 (aerosol)	5-11
Other Hair Preparations	30	7	3	0.5-2
Hair Coloring Preparations				
Hair Tints	4	NR	NR	NR
Hair Rinses (coloring)				
Hair Color Sprays (aerosol)	5	NR	NR	NR
Makeup Preparations				
Blushers (all types)	22	1	5.2	2-15
Face Powders	31	9	1.2-15.6	0.1-18
Foundations	67	17	7-12	2-22
Leg and Body Paints	NR	NR	NR	2
Lipstick	96	34	1-13.8	0.08-36
Makeup Bases	22	8	NR	NR
Rouges	4	2	2-4.8	NR
Makeup Fixatives	2	NR	NR	NR
Other Makeup Preparations	34	13	12.1-24.8	0.0075-22
Manicuring Preparations (Nail)				
Nail Creams and Lotions	NR	NR	NR	0.5
Nail Polish and Enamel	NR	NR	3	NR
Other Manicuring Preparations				
Personal Cleanliness Products				
Deodorants (underarm)	1	1	1.8-10.2 (not spray); 2.2 (aerosol)	NR
Feminine Deodorants	1	NR	NR	NR
Shaving Preparations				
Aftershave Lotion	NR	1	NR	0.5-2

Table 2. Frequency (2023/2002) and concentration (2023/2004) of use according to duration and exposure for Phenyl Trimethicone

	# of Uses		*Max Conc of Use (%)*	
	2023[15]	**2002[4]**	**2022[16]**	**2004[4]**
Beard Softeners	1		NR	
Preshave Lotions (all types)	NR	1	2.5	2
Other Shaving Preparations	NR	NR	NR	0.5
Skin Care Preparations				
Cleansing	1	4	NR	2-4
Face and Neck (exc shave)	39	3	3.4-13 (not spray)	4-6
Body and Hand (exc shave)	15	4	1.7 (not spray)	0.2-18
Moisturizing	56	15	0.8-22.7 (not spray)	0.8-3
Night	2	NR	NR	2
Paste Masks (mud packs)	2	NR	NR	NR
Skin Fresheners	6	NR	NR	NR
Other Skin Care Preparations	11	NR	0.5-4.9	2
Suntan Preparations				
Suntan Gels, Creams, and Liquids	1	2	0.1 (aerosol); 0.5 (pump spray)	0.5-9
Indoor Tanning Preparations	NR	8	NR	0.2-5
Other Suntan Preparations	NR	NR	6	2

NR – not reported

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

**likely duration and exposure are derived 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. Frequency (2023)[15] and concentration (2021)[17] 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 (%)**
	Diphenyl Dimethicone		**Diphenylsiloxy Phenyl Trimethicone**		**Diphenylsiloxy Phenyl/Propyl Trimethicone**	
Totals*	**150**	**0.1 – 24.1**	**275**	**0.3 – 19.9**	**NR**	**5.3**
summarized by likely duration and exposure**						
Duration of Use						
Leave-On	*148*	*0.1 – 24.1*	*268*	*0.3 – 19.9*	NR	*5.3*
Rinse-Off	*2*	*NR*	*7*	*1 – 8.8*	NR	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	NR	*NR*
Exposure Type						
Eye Area	12	NR	44	4.4 – 19.9	NR	NR
Incidental Ingestion	84	1.9 - 24.1	62	9.4 – 15.2	NR	NR
Incidental Inhalation-Spray	1; 15[a]; 2[b]	0.1 - 1	40[a]; 16[b]	0.3 – 5; 3.5[a]	NR	NR
Incidental Inhalation-Powder	2[b]	0.42[c]	13; 16[b]	5.7; 0.4 – 0.5[c]	NR	NR
Dermal Contact	64	0.42 – 1.3	213	0.4 – 19.9	NR	5.3
Deodorant (underarm)	NR	NR	NR	spray: 0.5 not spray: 0.5	NR	NR
Hair - Non-Coloring	2	0.9 - 1	NR	1.2 – 3.5	NR	NR
Hair-Coloring	NR	0.1	NR	0.3 – 8.8	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	84	1.9 – 24.1	62	9.4 – 15.2	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
as reported by product category						
Baby Products						
Baby Lotions/Oils/Powders/Creams						
Other Baby Products						
Bath Preparations (diluted for use)						
Bath Oils, Tablets, and Salts						
Eye Makeup Preparations						
Eyebrow Pencil			NR	4.4		
Eyeliner			1	19.9		
Eye Shadow	12	NR	30	15		
Eye Lotion			5	NR		
Mascara						
Other Eye Makeup Preparations			8	NR		
Fragrance Preparations						
Cologne and Toilet Water						
Perfumes						
Powders (dusting/talcum, excl aftershave talc)						
Other Fragrance Preparation						
Hair Preparations (non-coloring)						
Hair Conditioner	1	NR	NR	1.2		

Table 3. Frequency (2023)[15] and concentration (2021)[17] 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 (%)
Hair Spray (aerosol fixatives)	1	0.9-1				
Hair Straighteners						
Shampoos (non-coloring)						
Tonics, Dressings, and Other Hair Grooming Aids			NR	3.5		
Other Hair Preparations						
Hair Coloring Preparations						
Hair Tints			NR	8.8		
Hair Rinses (coloring)			NR	1		
Hair Color Sprays (aerosol)	NR	0.1	NR	0.3		
Makeup Preparations						
Blushers (all types)	2	NR	19	4.7		
Face Powders			13	5.7		
Foundations	1	0.6-1.3	29	3.3-7.5		
Leg and Body Paints						
Lipstick	84	1.9-24.1	62	9.4-15.2		
Makeup Bases	NR	NR	1	NR	NR	5.3
Rouges	26	NR	11	NR		
Makeup Fixatives			1	NR		
Other Makeup Preparations	1	NR	30	NR		
Manicuring Preparations (Nail)						
Nail Creams and Lotions						
Nail Polish and Enamel						
Other Manicuring Preparations						
Personal Cleanliness Products						
Deodorants (underarm)			NR	0.5 (aerosol) 0.5 (not spray)		
Feminine Deodorants						
Shaving Preparations						
Aftershave Lotion						
Beard Softeners						
Preshave Lotions (all types)						
Other Shaving Preparations						
Skin Care Preparations						
Cleansing	1	NR	5			
Face and Neck (exc shave)	1	0.42 (not spray)	11	0.4-0.5 (not spray)		
Body and Hand (exc shave)	1	NR	5	5 (spray)		
Moisturizing	13	NR	36	1.7 (not spray)		
Night			4	NR		
Paste Masks (mud packs)			2	NR		
Skin Fresheners	2	NR				
Other Skin Care Preparations	4	NR	2	2-9		
Suntan Preparations						
Suntan Gels, Creams, and Liquids						
Indoor Tanning Preparations						
Other Suntan Preparations						
	Phenyl Dimethicone		**Phenyl Methicone**		**Trimethylsiloxyphenyl Dimethicone**	
Totals*	**3**	**0.0096 – 19.5**	**15**	**0.28**	**37**	**0.2 - 23**
summarized by likely duration and exposure**						
Duration of Use						
Leave-On	*3*	*0.0096 – 19.5*	15	*0.28*	*36*	*0.2 - 23*
Rinse-Off	*NR*	*NR*	NR	*NR*	*1*	*0.5*
Diluted for (Bath) Use	*NR*	*NR*	NR	*NR*	*NR*	*NR*
Exposure Type*						
Eye Area	NR	2.1	1	NR	6	14
Incidental Ingestion	NR	19.5	NR	NR	17	18 - 23
Incidental Inhalation-Spray	2[a]	NR	4[a]; 2[b]	NR	1[b]	5[a]
Incidental Inhalation-Powder	NR	NR	2[b]	0.28[c]	1[b]	3.5
Dermal Contact	1	2.1	12	0.28	19	3.5 - 20
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	2	NR	NR	NR	1	0.5 - 5
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	0.0096	3	NR	NR	0.2
Mucous Membrane	NR	19.5	NR	NR	17	18 – 23
Baby Products	NR	NR	NR	NR	NR	NR
as reported by product category						
Baby Products						
Baby Lotions/Oils/Powders/Creams						
Other Baby Products						

Table 3. Frequency (2023)[15] and concentration (2021)[17] 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 (%)
Bath Preparations (diluted for use)						
Bath Oils, Tablets, and Salts						
Eye Makeup Preparations						
Eyebrow Pencil					1	
Eyeliner					1	NR
Eye Shadow	NR	2.1			3	14
Eye Lotion			1	NR		
Mascara						
Other Eye Makeup Preparations					1	NR
Fragrance Preparations						
Cologne and Toilet Water						
Perfumes						
Powders (dusting/talcum, excl aftershave talc)						
Other Fragrance Preparation						
Hair Preparations (non-coloring)						
Hair Conditioner					1	0.5
Hair Spray (aerosol fixatives)						
Hair Straighteners						
Shampoos (non-coloring)						
Tonics, Dressings, and Other Hair Grooming Aids	2	NR			NR	5
Other Hair Preparations					NR	5
Hair Coloring Preparations						
Hair Tints						
Hair Rinses (coloring)						
Hair Color Sprays (aerosol)						
Makeup Preparations						
Blushers (all types)						
Face Powders					NR	3.5
Foundations			3	NR	1	NR
Leg and Body Paints						
Lipstick	NR	19.5			17	18-23
Makeup Bases	1	NR				
Rouges						
Makeup Fixatives						
Other Makeup Preparations			2	NR	11	NR
Manicuring Preparations (Nail)						
Nail Creams and Lotions						
Nail Polish and Enamel	NR	0.0096	2	NR	NR	0.2
Other Manicuring Preparations			1	NR		
Personal Cleanliness Products						
Deodorants (underarm)						
Feminine Deodorants						
Shaving Preparations						
Aftershave Lotion						
Beard Softeners						
Preshave Lotions (all types)						
Other Shaving Preparations						
Skin Care Preparations						
Cleansing						
Face and Neck (exc shave)			2	0.28 (not spray)	1	NR
Body and Hand (exc shave)						
Moisturizing			2	NR	NR	20 (not spray)
Night			2	NR		
Paste Masks (mud packs)						
Skin Fresheners						
Other Skin Care Preparations						
Suntan Preparations						
Suntan Gels, Creams, and Liquids						
Indoor Tanning Preparations						
Other Suntan Preparations						

NR – not reported

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

**likely duration and exposure are derived 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 4. Acute toxicity studies

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	LD_{50}/LC_{50}/Results	Reference
DERMAL						
Diphenylsiloxy Phenyl Trimethicone	Wistar Han rats	5/sex	none	OECD TG 402. Semi-occlusive application of 2000 mg/kg bw for 24 h.	LD_{50} >2000 mg/kg. Slight crust formation in 1 female rat on the fourteenth and fifteenth day of observation. There were no signs of systemic or clinical toxicity.	6,7
Trimethylsiloxyphenyl Dimethicone	Sprague-Dawley rats	5/sex	none	OECD TG 402. Occlusive application of 2000 mg/kg bw for 24 h.	LD_{50} > 2000 mg/kg bw. No mortality nor pathological clinical signs were noted.	20
ORAL						
Diphenyl Dimethicone	Rats (strain not specified)	3/sex	none	Rats were administered 8190, 16,380, 32,770, or 65,540 mg/kg bw of the test article, intragastrically. Animals were observed for 14 d before necropsy.	LD_{50} > 65,550 mg/kg bw, computed via the Miller and Taint method. Abdominal pain was observed after administration, followed by excessive laxation and urinary incontinence. One rat/group from the three highest dose groups died (3 or more days after dosing) and diffuse pulmonary hemorrhage and petechial hepatic hemorrhage was observed. No gross abnormalities were found at necropsy.	21
Diphenyl Dimethicone	Albino rats	5/sex	none	Animals were given 5000 mg/kg bw of the test article, via gavage. Animals were observed for 14 d prior to necropsy.	LD_{50} > 5000 mg/kg	22
Diphenylsiloxy Phenyl Trimethicone	Female Wistar Han rats	3/group	corn oil	OECD TG 423. The animals were given 2000 mg/kg bw of the test article, via gavage.	LD_{50} > 2000 mg/kg. Slightly ruffled fur was observed in 1 male and 1 female for up to 3 h after administration. No mortality or other abnormalities occurred.	6,7
Phenyl Trimethicone	Female Wistar rats	3/group	corn oil	OECD TG 423. Two groups were administered 2000 mg/kg bw (no control group), via gavage and were observed for 14 d prior to necropsy.	$LD_{50} \geq$ 2000 mg/kg. No mortality or clinical abnormalities were observed.	5
Phenyl Trimethicone	Rats (strain not specified)	NR (both males and females)	NS	OECD TG 401. Animals were administered 1000, 2500, or 5000 mg/kg bw of the test article, via gavage and observed for 7 d (necropsy not performed).	LD_{50} > 5000 mg/kg. No mortality or clinical abnormalities were observed.	5
78 - 82% Phenyl Trimethicone and 18 - 22% Polysilicone-11	Wistar-derived albino rats	5/sex	none	The animals were given 5000 mg/kg bw of the test article, via gavage.	LD > 5000 mg/kg. No mortality or clinical abnormalities were observed.	23
Trimethylsiloxyphenyl Dimethicone	CD rats	5/sex	corn oil	Animals were administered a 2000 mg/kg bw dose, via gavage, at a constant volume-dosage of 10 ml/kg,	LD_{50} > 2000 mg/kg bw	12

Table 4. Acute toxicity studies

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	LD_{50}/LC_{50}/Results	Reference
INHALATION						
Diphenyl Dimethicone	Albino rats	5/sex/group	none	Whole body exposure. The test article was vaporized during 5-min intervals, at 370 °C on an electric hot plate, housed within a bell jar (maintained at 25 - 30 °C) connected to an animal exposure chamber. Fresh air mixed with the heated vapors entered the exposure chamber at an airflow rate of 5 lb/in^2. Animals were exposed to either 5, 10, 23, 24, 42, 90, 101, 168, or 214 mg/l of the vaporized test article for 1 h. Exposure concentrations were calculated based on the volume of the chamber and the amount of Diphenyl Dimethicone being vaporized. Animals were observed for 14 d after exposure.	LC_{50}: 18 mg/l (estimated). Little or no respiratory distress was observed during the exposure period. One animal each from the 42 mg/l and 101 mg/l group died during the exposure period. Within 24 h after exposure, the following deaths occurred: 5 mg/l: none 10 mg/1: 3 animals 23 mg/l: 6 animals 24 mg/l: 7 animals 42 mg/l: 6 animals 90 mg/l: 8 animals 101 mg/l: 7 animals 168 mg/l: 3 animals 214 mg/l: 1 animal At higher volumes of dispensation (≥ 101 mg/l), residues accumulated on the hot plate. The lower conductivity of these concentrations was suspected to modify temperature and vaporization, thus, resulting in lower mortality than at intervening dose levels. Granular livers were seen in ~ 30% of the animals exposed to ≥ 24 mg/l. Severe and diffuse pulmonary hemorrhages accounted for most of the deaths. Pulmonary consolidation, varying from pinkish orange petechia to major involvement, was found in surviving animals.	[21]

N/A - not applicable; NR - none reported; OECD - Organisation for Economic Cooperation and Development; TG - test guideline

Table 5. Repeated dose toxicity studies

Test Article	Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
ORAL							
Diphenyl Dimethicone, 15%	10% polyethylene glycol 660 hydroxystearate, in purified water	Sprague-Dawley rats (10/sex)	90 d	0, 5, 20, or 80 mg/kg/d, via gavage	Subchronic oral toxicity study. The animals were observed daily for mortality and clinical abnormalities; body weights and food consumption were recorded weekly. Animals were killed at the end of treatment; post-mortem evaluation of animal organs and hematological parameters, including glucose, triglycerides, white blood cell counts, and prothrombin time, as well as urinalysis, were performed.	No deaths related to treatment with the test article occurred and no changes were observed in body weight and food consumption. Higher absolute and relative liver weights in animals given 80 mg/kg were considered to be treatment-related and were correlated with slight hepatocellular hypertrophy seen in 8 males and 10 females in the 80 mg/kg group; both effects were considered toxicologically significant. Liver enlargement was noted in 3 males from the 80 mg/kg group, which was attributed to treatment with the test article. Higher liver weight was noted in females from the 5 and 20 mg/kg/d groups, but these effects were not related to relevant microscopic findings and were therefore not considered toxicologically significant. Other statistically significant differences (including higher prothrombin time in males given 80 mg/kg and lower mean leukocyte counts in all the test group females) were not considered toxicologically-significant, as they were minimal, without a dose-response relationship, did not exhibit any trend between the sexes, and individual values were within the expected historical range. The NOAEL was determined to be 20 mg/kg/d.	[24]

Table 5. Repeated dose toxicity studies

Test Article	Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
Diphenylsiloxy Phenyl Trimethicone	corn oil	Wistar Han rats (5/sex)	28 d	0, 200, 600, or 1000 mg/kg bw, via gavage	OECD TG 407. Short-term oral toxicity study	A statistically significant reduction in body weight gain occurred in male rats from the 1000 mg/kg group (18 - 19%, when compared to controls) on day 8 and day 15 of observation. Significant reduction in body weight gain (48%, compared to controls) also occurred in female rats from the 600 and 1000 mg/kg groups on day 8. There were no reported treatment-related changes to food consumption in test animals. No treatment-related changes in hematology, clinical chemistry, urinalysis, or deaths occurred. Compared to controls, relative liver weights increased by 12, 22, and 18% for low-, mid-, and high-dose groups for the male rats, respectively, while relative liver weights increased by 23, 29, and 43% for low-, mid-, and high-dose groups for the female rats, respectively. Treatment-related microscopic liver changes, such as the following, were observed: hepatocellular hypertrophy (ranging from minimal to moderate degrees) in all test animals, increased incidence or severity of change in fatty tissue deposition in the livers of males from the high dose group and in all of the test females, and the increased incidence of bile duct production in males from the mid dose group and females from the low and mid dose groups. Minimal hypertrophic changes in the follicular epithelium of the thyroid gland were observed in 2 males from the low-dose group, 1 male from the mid-dose group, and 4 males from the high-dose group. The authors considered the hepatic hypertrophy adaptive, and the thyroid changes as secondary, and a result of the metabolic turnover of thyroid hormones. The NOAEL was determined to be > 1000 mg/kg.	[6,7]
Trimethylsiloxyphenyl Dimethicone	corn oil	CD rats (5/sex/group)	4 wk	0, 20, 150, 1000 mg/kg/d, via gavage	The test article was administered at a constant volume of 5 ml/kg bw. The animals were monitored for mortality, food and water consumption, and body weight throughout the study period. Hematological and blood chemistry samples were taken on day 29. Upon necropsy, the organ weights of the adrenals, liver, kidneys, and testes were calculated relative to bodyweight gain. Gross and histopathological examination of the adrenals, heart, kidneys, liver, spleen, and testes was performed.	No deaths or significant changes related to the test material were observed. The NOAEL was determined to be 1000 mg/kg/d.	[25]

Table 5. Repeated dose toxicity studies

Test Article	Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
INHALATION							
Phenyl Methicone, 9.2 cSt, 25 °C	N/A	1 cat, 2 guinea pigs, 2 rabbits, and 4 rats	10 d, for 7 h/d	67.4 mg/min, at a concentration of 0.52 mg/l	Animals were exposed, whole body, to the test article.	No animals died during and after exposure. Histopathological examination did reveal moderate degenerative changes in the livers of cats and guinea pigs. However, in the absence of control data, moderate degenerative changes in livers of the cats and guinea pigs were considered only circumstantially associated with siloxane exposure.	[26]

N/A - not applicable; NOAEL - no-observable-adverse-effect-level; OECD - Organisation for Economic Cooperation and Development; TG - test guideline

Table 6. Developmental and reproductive toxicity studies

Test Article	Vehicle	Animals/Group	Dose/Concentration	Procedure	Results	Reference
ORAL						
Diphenylsiloxy Phenyl Trimethicone	corn oil	Sprague-Dawley rats (10/sex)	0, 100, 500, or 1000 mg/kg bw/d, via gavage	OECD TG 422. Males and females were treated with the test substance 2 wk prior to, and during, mating. One group which received no treatment served as negative controls. Males were treated for 92 d and were killed at the end of the treatment period, while dams were treated up until postpartum day 3. Males, pups, and dams which delivered were killed on day 4 postpartum; mated females which did not deliver were killed on day 25 or 26 of gestation.	No statistically significant changes in body weight, food consumption, or organ weights were observed. (Statistically significant changes in body weight for females during week 2 of gestation were not toxicologically significant.) No treatment-related effects were apparent for reproductive endpoints in the parents, including testis weight, epididymis weight, mean gestation length, mean number of corpora lutea, mean number of implantation sites, mean mating and fertility indices, nor were there effects observed in the offspring for gross pathology, mean litter size, mean litter weight, or mean ration live births/litter size. The NOAEL for reproductive (both sexes) and developmental toxicity was determined to be ≥ 1000 mg/kg bw/d.	[6]
Phenyl Trimethicone	oil	Male Wistar rats (20/group)	0, 100, 300, or 1000 mg/kg bw, via gavage	The test article was administered 5 d/wk, over 4 wk. Animals were killed 24 h after the final dose, and testicles were weighed and examined microscopically.	No visible changes, body weight fluctuations, or deaths occurred during the course of the study. No effects on testicle weight or histology were observed. The NOAEL for effects on body weight, testicle weight, and histology was determined to be > 1000 mg/kg.	[5]

NOAEL - no-observable-adverse-effect-level; OECD - Organisation for Economic Cooperation and Development; TG - test guideline

Table 7. Genotoxicity studies

Test Article	Vehicle	Concentration/Dose	Test System	Procedure	Results	Reference
IN VITRO						
Diphenylsiloxy Phenyl Trimethicone	ethanol	Up to 5000 µg/plate, with and without metabolic activation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2 strains	OECD TG 471. Ames test	Not genotoxic	[6,7]
Diphenylsiloxy Phenyl Trimethicone	ethanol	Without metabolic activation: 0.025 – 0.3 µl/ml (4 h) 0.006 – 0.2 µl/ml (18 h) 0.013 – 0.1 µl/ml (28 h) With metabolic activation: 0.003 – 0.2 µl/ml (4 h) 0.040 – 5 µl/ml (4 h)	Chinese hamster lung (V79) cell line	OECD TG 473. Mammalian chromosomal aberration study. Appropriate positive and negative controls were used. Cells were treated prior to harvest with a metaphase-arresting substance, stained, and analyzed microscopically for induced cytotoxicity or the presence of chromatid-type and chromosome-type aberrations in cells undergoing metaphase.	Non-clastogenic. Cell numbers below 50% of the controls or poor metaphase quality were observed in cells treated with ≥ 0.15 µl/ml of the test substance in the absence of metabolic activation for 18 h. No statistically significant increase in the frequency of cells with chromosome aberrations was induced in either the absence or presence of metabolic activation.	[6,7]
Trimethylsiloxy Phenyl Dimethicone	10% Tween 80 solution	1, 5, 10, 50, or 100 µl/plate	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538 strains, with or without metabolic activation	Ames test.	Not genotoxic	[27]

OECD - Organisation for Economic Cooperation and Development; TG - test guideline

Table 8. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
IRRITATION						
ANIMAL						
Diphenyl Dimethicone, 100% pure	N/A	0.5 ml, applied neat	6 New Zealand white rabbits	Primary dermal irritation test. The test article was simultaneously applied to an abraded and unabraded test site, under occlusion, for 24 h. Mean scores from 24 and 72 h after application were used to determine the PII. Under study conditions, the test article was not considered to be a primary dermal irritant.	Not irritating; PII = 0.28	[28]
Diphenylsiloxy Phenyl Trimethicone, 100% pure	N/A	0.5 ml, applied neat	3 New Zealand white rabbits	OECD TG 404; primary skin irritation test. A semi-occlusive patch application of the test article was made for 4 h, and test sites were scored at 1, 24, 48, and 72 h after patch removal.	Not irritating	[29]

Table 8. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
Diphenylsiloxy Phenyl Trimethicone	N/A	NS, applied neat	1 male and 2 female New Zealand white rabbits	OECD TG 404; dermal irritation study. A semi-occlusive patch application of the test article was made for 4 h, and test sites were scored at 24, 48, and 72 h after patch removal. Mean scores for erythema/eschar and edema were calculated for each animal from scores taken at the 3 time points.	Slightly irritating; non-irritating in another description. Very slight to well-defined erythema was noted in all 3 animals 1 h after patch removal. Mean erythema/eschar scores were 0.33 for both animal 1 and 2, and 0.67 for animal 3; no edema was observed. Very slight erythema persisted in all animals until the 24-h reading, and was still present in 1 animal at the 48-h reading. The noted effects were reversible and no longer evident at the 72 h. In another description of the same study, GHS criteria were not met, and the test article was deemed non-irritating.	6,7
72 - 82% Phenyl Trimethicone 18 - 22% Polysilicone-11	N/A	0.5 ml, applied neat	6 New Zealand white rabbits	In an acute skin irritation test, an occlusive application of the test material was made to intact and abraded skin on the shaved trunk (approximately 6 cm^2) for 24 h. Upon removal of the patch, test sites were gently wiped, and were scored for erythema and edema at 24 and 72 h after application.	Not irritating; PII = 0	30
Trimethylsiloxyphenyl Dimethicone	N/A	0.5 ml, applied neat	6 New Zealand white rabbits	OECD 404.; primary skin irritation test. A semi-occlusive application of the test article was made for 4h. Test sites were scored 1, 24, 48, and 72 hr after patch removal. Mean values were calculated from the evaluation of erythema and edema lesions at 24, 48, and 72 h.	Not irritating; mean values for erythema = 0.06; edema = 0	31
				HUMAN		
Lip color containing 9.06% Diphenyl Dimethicone	N/A	NS, applied neat	20 subjects	24-h, SIOPT. Irritation scores were made on a scale of 0 - 4 and PIIs were calculated. A liquid lip color was tested in tandem.	Not irritating; PII = 0	32
Ampoule containing 0.5% Diphenylsiloxy Phenyl Trimethicone	N/A	not specified, applied neat	20 subjects	24-h, SIOPT. Irritation scores were made on a scale of 0 - 4 and PIIs were calculated. A serum was tested in tandem.	Not irritating; PII = 0.03	33
SPF cream containing 3.2363% Phenyl Trimethicone	N/A	0.05 ml, applied neat	25 subjects	14-d cumulative irritation test. Occlusive, 15 mm^2 applications of the test material were made to a site on the upper arm or back for 14 d. Positive and negative control sites comprised 0.05 ml of 0.25% SLS or plain cotton, respectively. Test sites were graded daily after patch removal on a scale of 0 - 5.	Not irritating. Cumulative score and CII = 0. Control results were as expected.	36
Eye primer containing 10% Phenyl Trimethicone	N/A	not specified, applied neat	21 subjects	24-h, SIOPT. Performed as described previously. A mousse foundation was tested in tandem.	Not irritating; PII = 0	34
Shine gloss containing 5% Trimethylsiloxyphenyl Dimethicone	N/A	not specified, applied neat	18 subjects	24-h, SIOPT. Performed as described previously. A frizz shine spray was tested in tandem.	Not irritating; PII = 0	35

Table 8. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
Serum containing 2% Trimethylsiloxyphenyl Dimethicone	N/A	200 µl, applied neat	28 subjects	15-d cumulative irritation test. Occlusive, 24-h applications of the test material (2 cm^2) were made to the back for 15 d. Positive and negative control sites comprised 200 µl of 0.25% SLS or plain cotton, respectively. Test sites were graded daily after patch removal on a scale of 0 - 4.	Not irritating. No reactions were observed in 27 subjects. Grade 1 reactions (mild redness) occurred twice in one participant, yielding a CII = 0.002 (negligible/non-significant irritation). Control results were as expected.	37
SENSITIZATION						
			ANIMAL			
Product containing 15% Diphenyl Dimethicone	acetone: olive oil (4:1 v/v)	25 ml; 2.5, 5, 10, 25, or 50%	Groups of 4 female CBA mice	OECD TG 429; LLNA. The test article was topically applied on days 1, 2, and 3 to one ear, while acetone:olive oil (vehicle control) was applied to the other ear. One group which received 25% α-hexylcinnamaldehyde in the acetone:olive oil mixture served as positive controls. Animals were observed for clinical and gross abnormalities for up to 6 d before being killed. Stimulation indices (SI) were calculated.	Not sensitizing. Two of 4 of animals in the 10% group died on day 3 and 1 of the animals in the 50% group died on day 6. These deaths were not attributed to the test article. No positive lymphoproliferative response (SI > 3) were noted at any tested concentration.	38
Diphenyl Dimethicone, 100% pure	N/A	NS, applied neat	6 male and 6 female Hartley albino guinea pigs	Buehler test. Animals received 3 topical, occluded applications of the test article over the 3-wk induction period. Five males and 5 females served as the control group (which received no treatment during induction). After 2 wk, a challenge application of the test article was made to an untreated site on both the test and control animals. Reactions were scored 7 and 24 h after each induction and challenge application, and also at 48 h following the challenge application. The test article was deemed a non-sensitizer.	Not sensitizing	28
Diphenylsiloxy Phenyl Trimethicone, 100% pure	acetone: olive oil (4:1 v/v)	25, 50, or 100% w/w	Groups of 4 female mice	LLNA. The test article was applied topically to the back of both left and right ear lobes for 3 consecutive days. A control group was treated only with the acetone:olive oil mixture. Five days after the first topical application the mice were intravenously injected with radio-labelled thymidine. The animals and were killed and lymph nodes were excised for evaluation approximately 5 h after injection.	25% group SI = 1 50% group SI = 2 100% group SI = 2.4 (An SI < 3 is non-sensitizing) No deaths occurred during the study period, and no clinical signs were observed in controls or animals in the 25% group. All mice in the 100% group exhibited slight ear swelling at both ear lobes on day 2, which persisted for 4 d. All mice in the 50 and 100% groups exhibited such results on day 3, which persisted for 3 d.	29

Table 8. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
Diphenylsiloxy Phenyl Trimethicone	acetone: olive oil (4:1 v/v)	25, 50, or 100% w/w	Groups of 4 female CBA mice	OECD TG 429; LLNA. The test item was topically administered for an unspecified duration. Vehicle controls received the acetone:olive oil mixture, while animals treated previously with α-hexylcinnamide served as positive controls. Lymphocyte proliferative responses (measured as DPM/lymph node) and SIs (test/control ratio) were calculated for each group.	No evidence of induction of a lymphocyte proliferative response indicative of skin sensitization to the test substance was observed. Slight ear swelling was observed in test animals exposed to 100% of the test article on the second day of application. Animals exposed to 50 and 100% of the test article also exhibited slight erythema of the ear on the third day of application, which persisted until the end of the study.	[6,7]
Trimethylsiloxyphenyl Dimethicone	FCA	Intradermal injections during induction: -test article, as supplied -50% FCA in isotonic solution -50% test article in FCA and isotonic solution Intradermal challenge: 0.5 ml, applied neat Challenge: 0.5 ml, applied neat	Dunkin Hartley guinea pigs (10/sex/group)	OECD TG 406. On day 1, animals received 2 lots of 0.1 ml intradermal injections. Additionally, a 48-h, occlusive application of the undiluted test substance was made. As this application did not cause irritation, 0.5 ml of SLS (10% in paraffin oil) was applied to the skin on day 8. On day 9, a 48-h, occlusive application of the test article was made to an 8 cm^2 area where the injections were delivered. On day 22, an occlusive, 24-h challenge application of the undiluted test article was made to a 2 cm^2 area. Challenge sites were scored 24 and 48 h after patch removal. Controls received water during induction, and were challenged with the test article.	Not sensitizing	[39]
				HUMAN		
Product containing 2% Diphenyl Dimethicone	N/A	0.02 ml, applied neat	111 subjects	Modified Marzulli-Maibach HRIPT. Nine occlusive applications were made to a 50 mm^2 area of the back using Finn chambers over a 3-wk period for 48- or 72-h. After a 13-d non-treatment period, a single 48-h challenge application was made to the induction site and a previous untreated site. Reactions were scored on a 0 - 4 irritation scale between 15 and 30 min of patch removal during both the induction and challenge phases; challenge phase reactions were additionally evaluated 48 h after application. An MII was calculated by dividing the sum of the quotations of the 9 induction readings by the number of subjects and readings performed. The test article did not demonstrate potential to produce irritation or cutaneous sensitization.	Not irritating or sensitizing; MII = 0.01	[40]
Ampoule containing 0.5% Diphenylsiloxy Phenyl Trimethicone	N/A	0.2 g, applied neat	112 subjects	HRIPT. Nine occlusive, 24-h applications of the test material were made over 3 wk. After a 2-wk non-treatment period, a 24-h challenge application was made to a previously untreated site in the same manner as the induction applications, and reactions were scored 24, 48, 72, and 96 h after application.	Not sensitizing Two subjects exhibited low level reactions during induction and 2 other subjects exhibited low level reactions during challenge.	[41]
Lip balm containing 11% Diphenylsiloxy Phenyl Trimethicone	N/A	~ 0.1 - 0.15g, applied neat	109 subjects	HRIPT. Similar procedure as described above. The 24-h challenge application was scored 24 and 72 h after application.	Not irritating or sensitizing	[42]

Table 8. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
Product containing 0.2% Phenyl Methicone	N/A	not specified, applied neat	107 subjects	Marzulli-Maibach HRIPT. Nine occlusive, 48-h induction applications were made using 8 mm Finn chambers to the same site over a 3-wk period. Induction sites were evaluated for dermal reactions immediately prior to application of the next patch. After a 2-wk non-treatment period, challenge applications were made to the original test site and a previously untreated site in the same manner as the induction applications. Challenge sites were scored 48, 72, and 96 h after application.	Not irritating or sensitizing	[43]
Product containing 20% Phenyl Trimethicone	N/A	0.1 - 0.15 g, applied neat	53 subjects	HRIPT. Nine occlusive, 24-h applications of the test material were made over 3 wk. After a 2-wk non-treatment period, a 24-h challenge application was made to a previously untreated site in the same manner as the induction applications, and reactions were scored 24 and 72 h after application.	Not irritating or sensitizing	[44]
Concealer containing 26.18% Phenyl Trimethicone	N/A	0.05 ml, applied neat	26 subjects	Maximization assay. Five, occlusive induction applications were made. Prior to each induction application, a 24-h application of 0.05 ml of 0.25% aqueous SLS was made. After removal of the SLS-pre-treatment patch, 0.5 ml of the test material was applied for 48 - 72 h using an occlusive patch. After a 10-d non-treatment period, subjects were pre-treated with 0.05 ml of 1 % aqueous SLS for 1 h on a novel site, prior to a 48-h challenge application, in the same manner as the induction applications. Challenge reactions were scored immediately after patch removal and 24 h later.	Not sensitizing No instances of contact allergy or irritation were observed.	[45]
Product containing 28.67% Phenyl Trimethicone	N/A	0.2 g, applied neat	203 subjects	HRIPT. The test material was applied to the skin using a 2 cm^2 absorbent pad for semi-occlusive, 24-h induction and challenge applications. Challenge reactions were scored 48 and 72 h after application.	Not sensitizing	[46]
Cream containing 3% Trimethylsiloxyphenyl Dimethicone	N/A	0.2 g, applied neat	103 subjects	HRIPT. The test material was applied using a 0.75 in^2 absorbent pad for the occlusive, 24-h induction and challenge applications. Challenge reactions were scored 24 and 72 h after application. The test material did not demonstrate a potential for eliciting dermal irritation or allergic contact sensitization.	Not irritating or sensitizing	[47]
Product containing 38.006% Trimethylsiloxyphenyl Dimethicone	N/A	0.2 g, applied neat	205 subjects	HRIPT. The test material was applied using a 2 cm^2 absorbent pad for 24-h occlusive induction and challenge applications. Challenge reactions were scored 48 and 72 h after application.	Not sensitizing	[48]
Trimethylsiloxyphenyl Dimethicone, 100% pure	N/A	0.2 ml, applied neat	51 subjects	HRIPT. The test material was applied using a 0.75 in^2 absorbent pad for the 24-h induction and challenge applications. Challenge reactions were scored 24 and 72 h after application. The test material did not demonstrate a potential for eliciting dermal irritation or allergic contact sensitization.	Not irritating or sensitizing	[49]

CII - cumulative irritation index; DCNB - 1-chloro-2, 4-dinitrobenzene; DPM - disintegrations per minute; FCA – Freund's Complete Adjuvant; GHS - Globally Harmonized System of classification; HRIPT - human repeat insult patch test; LLNA - local lymph node assay; MII - mean irritation index; N/A - not applicable; PDII - primary dermal irritation index; PII - primary irritation index; SI - stimulation index; SIOPT - single insult occlusive patch test; SLS - sodium lauryl sulfate

Table 9. Ocular irritation studies

Test Article	Vehicle	Concentration/Dose	Test Population	Procedure	Results	Reference
ANIMAL						
Diphenyl Dimethicone	N/A	0.1 ml, undiluted	Groups of 3 albino rabbits	Ocular irritation test. Each animal had the test material instilled in the conjunctival sac of one eye. Treated eyes remained unwashed in the first group, were washed 2 s after exposure with 20 ml water in the second group, and were washed 4 s after exposure with 20 ml water in the third group. The eyes were examined and irritation was scored 4 h, and 1, 2, 4, and 7 d after exposure.	Slightly, but transiently, irritating. A maximum score of 8 (out of the potential maximum of 110), indicating slight irritation, was observed only within 4 h in 1 animal from the second group. By the second or third day the eyes appeared normal, regardless of rinsing status.	[21]
Diphenylsiloxy Phenyl Trimethicone	N/A	0.1 ml, undiluted	1 male and 2 female New Zealand white rabbits	OECD TG 405; Acute ocular irritation study. Rabbit eyes were treated with the undiluted test article for 72 h.	Not irritating (according to GHS classification); slightly irritating according to Kay and Calandra criteria. Mild ocular changes, including reddening of the conjunctivae and sclerae, discharge, and chemosis were observed 1 h after instillation, but resolved within 24 h.	[6,7]
Phenyl Methicone	N/A	not specified	Rabbits (strain and number not specified)	Ocular irritation test. The test article (35 and 75 cSt viscous) was directly instilled into rabbit eyes and the eyes were observed for irritation from application for up to 48 h.	Not irritating Slight irritation, observed 4 and 8 h after exposure, subsequently subsided.	[26]
78 - 82% Phenyl Trimethicone 18 - 22% Polysilicone-11	N/A	0.1 ml, undiluted	6 New Zealand white rabbits	Ocular irritation test. The test material was instilled on the everted lower lid of one eye, and the upper and lower eye lids were gently held together for 1 s before releasing. The contralateral, untreated eye served as control. The cornea, iris, and conjunctivae were evaluated according to the Draize method at 24 and 72 h post-instillation. A 2% fluorescein sodium solution, followed by saline solution wash was utilized as necessary.	Not irritating; MMTS = 0	[52]
Trimethylsiloxyphenyl Dimethicone	N/A	0.1 ml, undiluted	6 male New Zealand white rabbits	OECD TG 405. The test material was instilled as supplied, without rinsing, to the right eye. The left eye served as the untreated control. Eyes were examined 1, 24, 48, and 72 h after instillation. Mean values were calculated for ocular lesions in the conjunctiva, iris, and cornea 24, 48, and 72 h after instillation.	Slightly irritating; Mean values: Opacity to the cornea: 0 Congestion to the iris: 0.5 Chemosis and enanthema to the conjunctiva: 0.5 and 1.39	[53]

cSt – centistoke; GHS – Globally Harmonized System of classification; MMTS- maximum mean total score; OECD- Organisation for Economic Cooperation and Development; TG- test guideline; UV- ultraviolet

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4

Final Report on the Safety Assessment of Phenyl Trimethicone

Phenyl Trimethicone is a silicon polymer used in a variety of cosmetic products at concentrations up to 5%.

In acute oral studies, Phenyl Trimethicone was relatively nontoxic in rats and was nontoxic in acute and subchronic dermal studies. Phenyl Trimethicone was nonirritating to the skin of rabbits under both intact and abraded conditions and was not a sensitizer to guinea pigs. The ingredient was not an eye irritant when evaluated by the Draize ocular irritation test.

Phenyl Trimethicone was nonmutagenic both with and without metabolic activation when evaluated in the Ames assay. Phenyl Trimethicone was not teratogenic in rats and rabbits when applied dermally at doses of up to 500 mg/kg per day, although an increase in the number of resorptions was noted in two of three studies (statistically significant in only one). A dose of 200 mg/kg per day indicated that a fetotoxic dose was being approached. The doses tested are comparatively greater than the concentrations used in cosmetic products.

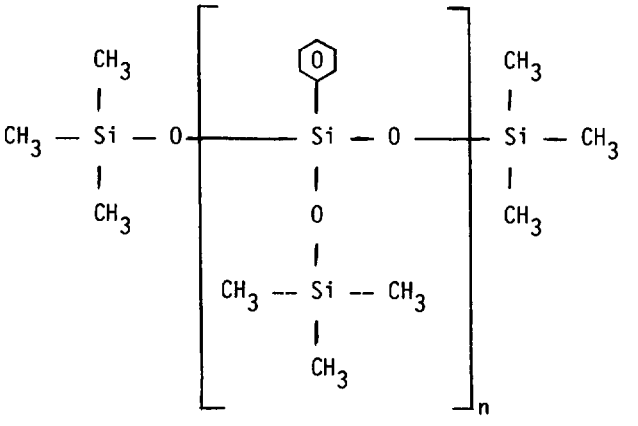
Phenyl Trimethicone is neither an irritant nor a sensitizer to humans. No photosensitization data are available on Phenyl Trimethicone; however, the UV absorption spectrum indicated only weak absorbance at 327 nm.

Based on the animal and human data included in this report, it is concluded that Phenyl Trimethicone is safe as a cosmetic ingredient in the present practices of use and concentration.

CHEMICAL AND PHYSICAL PROPERTIES

Definition and Structure

Phenyl Trimethicone is a water white, almost odorless, fluid silicone polymer.[1] It conforms to the formula[2]:



This compound is a tris(trimethylsiloxy)-phenylsilane and is also known as Dow Corning® 556 fluid (defined as mixed oligomers).[2-4] The ultraviolet (UV) spectrum for Phenyl Trimethicone indicates weak absorbance centered at approximately 327 nm.[5] No data on impurities were available. The chemical and physical characteristics of Phenyl Trimethicone are presented in Table 1.

Analytical Method

Identification is by infrared spectroscopy.[1] The compound can also be detected by analysis for silicon using optical emission spectroscopy[6] or atomic absorption spectrophotometry.[7] Smith[8] has published a reference book for silicone analysis.

TABLE 1. Physicochemical Properties of Phenyl Trimethicone

Property	*Value*	*Reference*
Structural formula	$(CH_3)_3SiO[(CH_3)_3SiOSi(C_6H_5)O]_nSi(CH_3)_3$	2
Boiling point at 760 mm Hg (°C)	265	6
Flash point, minutes (°F)	250	6
Specific gravity 25°: 25°C	0.970	6
Refractive index at 25°C	1.459	1
Total acid number	0.25 maximum	1
Methyl:phenyl ratio	5.00–7.14	1
Kinematic viscosity	5–30 centistokes	1
UV absorbance	Weak absorbance at 327 nm	5

Method of Manufacture

Silicones may be considered to be organic derivatives of silica, SiO_2, with organic groups replacing some of the oxygens in the polymeric silica molecule. One industrial process first converts silica to tetraethoxysilane. The ethoxy groups are replaced with the desired organic group by the Grignard reaction. The resulting organosilanes are hydrolyzable to organo-substituted silicic acids, called "silanols," which rapidly condense with each other to produce the silicon–oxygen–silicon framework of the silicone polymers. In these silicone structures, the organic radicals are firmly bonded to the silicon through a carbon–silicon linkage. Each silicon atom is linked to neighboring silicon atoms through an oxygen atom.[9]

COSMETIC USE

Phenyl Trimethicone is used in cosmetics intended for human skin contact. Some of its cosmetic uses are as a lubricant, water-repellent, and vehicle.[10–12] The types of products in which this ingredient is used, as well as the concentrations used, are presented in Table 2. The information in the table was obtained from FDA's computerized information file containing product formulation data submitted to FDA in 1981 by companies participating in the voluntary cosmetic registration program.[13,14]

Phenyl Trimethicone was reported as an ingredient in 113 cosmetic formulations at concentrations of ≤0.1% (27 products), >0.1–1% (53 products), >1–5% (32 products), and >5–10% (1 product). The maximum reported use was in aerosol hair sprays (25 products). The greatest concentration of use was in an outdoor tanning preparation (5–10%).[13] Voluntary filing of product formulation data with FDA by cosmetic manufacturers and formulators conforms to the prescribed format of preset concentration ranges and product categories as described in Title 21 part 720.4 of the Code of Federal Regulations. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the concentration reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA. The fact that data are only submitted within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration.

Cosmetic products containing Phenyl Trimethicone may contact all external body surfaces, hair, and lungs, as well as conjunctivae and vaginal and other mucous membranes (Table 2). These products may be used daily or occasionally over a period of up to several years. The frequency and duration of application could result in continuous exposure.

TABLE 2. Product Formulation Data on Phenyl Trimethicone[13]

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)			
			>5–10	>1–5	>0.1–1	≤0.1
Baby products	15	1	–	–	1	–
Bath oils, tablets, and salts	237	1	–	–	1	–
Other bath preparations	132	2	–	2	–	–
Eye shadow	2582	1	–	1	–	1
Mascara	397	1	–	–	1	–
Other eye makeup preparations	230	1	–	–	1	–
Hair conditioners	478	10	–	1	7	2
Hair sprays (aerosol fixatives)	265	25	–	–	7	18
Hair straighteners	64	1	–	1	–	–
Hair rinses (noncoloring)	158	1	–	–	1	–
Tonics, dressings, and other hair grooming aids	290	9	–	2	6	1
Wave sets	180	2	–	1	1	–
Other hair preparations (noncoloring)	177	1	–	–	1	–
Blushers (all types)	819	11	–	11	–	–
Face powders	555	2	–	–	2	–
Makeup foundations	740	2	–	2	–	–
Lipstick	3319	2	–	2	–	–
Makeup bases	831	2	–	1	–	1
Nail polish and enamel	767	7	–	–	7	–
Preshave lotions (all types)	29	6	–	3	3	–
Face, body, and hand skin care preparations (excluding shaving preparations)	832	8	–	–	6	2
Moisturizing skin care preparations	747	7	–	1	4	2
Night skin care preparations	219	1	–	–	–	1
Other skin care preparations	349	1	–	1	–	–
Suntan gels, creams, and liquids	164	6	–	2	4	–
Indoor tanning preparations	15	1	1	–	–	–
Other suntan preparations	28	1	–	1	–	–
1981 TOTALS		113	1	32	53	27

BIOLOGY

Structure and Activity

Bennet et al.,[15] Hayden and Barlow,[16] Hobbs et al.,[6] LeFevre et al.,[17] LeVier and Jankowiak,[18] and Palazzolo et al.[19] have studied the relative activities and structure–activity relationships of various silicones and silanes.* Certain phenyl-substituted silicones have been shown to be active androgen depressants.[15] Those studies pertinent to Phenyl Trimethicone are presented in the following sections. They indicate that this ingredient does not affect the function of either male or female sex organs in rats.

ANIMAL TOXICOLOGY

A general review of silicone toxicity has been published by Rowe et al.[9]

Oral Studies

Acute Oral Toxicity

The acute oral toxicity of Phenyl Trimethicone was evaluated in Spraque-Dawley albino rats.[20] Single doses of undiluted Phenyl Trimethicone ranging from 10.2 to 34.6 g/kg were administered by intubation to groups of four rats (two male, two female). The animals were observed for 14 days and then necropsied. One rat receiving 34.6 g/kg Phenyl Trimethicone died; the others at this dose had hypoactivity, muscular weakness, diarrhea, diuresis, ruffed fur, and weight loss. There were no significant gross lesions in the tissues and organs examined. Phenyl Trimethicone was considered nontoxic (Table 3).

Samples taken from 54 production lots of Phenyl Trimethicone were administered to male Sprague-Dawley rats. Phenyl Trimethicone was administered at 3.3 mg/kg per day orally for 7 days to groups of 10 fasted rats. Doses were calculated on the basis of initial body weight and administered by gavage without an oil vehicle. Control groups were treated with saline solution. No significant effects were observed with reference to mortality, body weight changes, behavioral changes, or gross pathological alterations[6] (Table 3).

Phenyl Trimethicone and a series of low molecular weight organosiloxanes were assayed for uterine weight changes using immature female Wistar rats weighing 30–40 g. The rats were bilaterally ovariectomized and allowed 3 days to recover before treatment. On the fourth day, the animals were randomly distributed into treatment groups of six animals each. The test material was administered by oral intubation in a sesame oil vehicle. Doses of 10.0, 1.0, 0.1, and 0.01 mg/kg were administered in a final oil volume of 2 g/kg. Animals were dosed once daily for 3 days. Controls received the oil vehicle only. Animals were nec-

*In this series of publications in *Toxicology and Applied Pharmacology*, Volume 21, 1972, Dow Corning® 556 fluid was designated as the monomer, but, in fact, the product tested in the reported studies was the mixed oligomers.[4]

TABLE 3. Oral Toxicity of Phenyl Trimethicone

Ingredient	*Test*	*Dose*	*Animal*	*Comments*	*Reference*
Phenyl Trimethicone 100%	Acute	10.2–34.6 g/kg (single dose)	8 male rats 8 female rats	One rat at the high dose died; considered non-toxic; hypoactivity, muscular weakness, diarrhea, diuresis, ruffed fur, and weight loss noted at high dose	20
Phenyl Trimethicone 100%	Acute	3.3 mg/kg per day for 7 days	540 male rats	No significant effects	6
Phenyl Trimethicone in sesame oil	Assay for uterine weight change	0.01, 0.1, 1.0, and 10 mg/kg per day for 3 days	6 female rats per group	No significant uterine effects	16
Phenyl Trimethicone 10% in a product	Acute	Single dose of 10 ml/kg	10 mice	No deaths	21
Phenyl Trimethicone 10% in a product	Acute	Single dose of 10 ml/kg	10 mice	No deaths	22
Phenyl Trimethicone 10% in a product	Acute	Single dose of 10 ml/kg	10 mice	No deaths	23
Phenyl Trimethicone 5% in a foundation cream	Acute	Single 5.0 ml/kg dose	10 rats	No deaths	24

ropsied 24 h after the final dose. No toxic effects were observed in Phenyl Trimethicone-treated animals. Statistically significant increases were observed in the uterine weights of some animals treated with other phenyl-substituted organosiloxanes[16] (Table 3).

The acute toxicity of three cosmetic products containing 10% Phenyl Trimethicone was determined for male CD-1 albino mice. Treatment groups of 10 mice each were dosed by gavage once with 10 ml/kg of the products. No deaths were reported during the 14-day observation period[21-23] (Table 3).

A foundation cream containing 5% Phenyl Trimethicone was administered to five male and five female Sprague-Dawley rats. The selected dose was the same as the dose (per kilogram body weight) that would be received by a 10 kg child ingesting the entire contents of the largest marketed container. A single 5.0 ml/kg dose resulted in leg weakness, transient vasodilation of the ears, and hypoactivity. These signs disappeared within 6 h posttreatment, and no deaths were reported during the 2-week study[24] (Table 3).

Dermal Studies

Acute Dermal Toxicity

The acute dermal toxicity of Phenyl Trimethicone was evaluated in 10 albino rabbits. The trunk of each animal was clipped before application, and the skin of half of the rabbits was abraded. Single 24-h doses of 2.0 g/kg Phenyl Trimethicone were applied by means of an occlusive sleeve. No deaths or behavioral reactions were observed during 14 days postexposure. Phenyl Trimethicone was considered nontoxic[20] (Table 4).

Subchronic Dermal Toxicity

Phenyl Trimethicone was assayed for dermal toxicity in 10 adult male New Zealand rabbits. The exposure sites on the back, approximately 10% of the body surface, were shaved 24 h before application of the test material. A 200 mg/kg dose of Phenyl Trimethicone was distributed, without rubbing, over the entire clipped site. Applications were made daily for 28 days. Each animal was caged individually and fitted with a collar to prevent licking of the test site. Observations were made daily, and necropsy was performed at the end of the test period. No significant adverse effects were noted in any of the control or test animals with reference to body weight, mortality, behavioral reactions, testicular histology, and spermatogenic activity. Phenyl-substituted cyclosiloxanes were positive for testicular atrophy in similar studies[6] (Table 4).

Samples taken from five production lots of Phenyl Trimethicone were tested for biological activity. Treatment groups of four rabbits received dermal applications of 50 ml/kg per day for 20 days. No adverse effects were observed[6] (Table 4).

Phenyl Trimethicone was evaluated for dermal toxicity in three groups of 10 New Zealand albino rabbits (5 males and 5 females). The rabbits were dosed daily for 20 consecutive days with doses of 2, 6, and 20 mg/kg Phenyl Trimethicone. Solutions in polypropylene glycol-2-methyl ether corresponding to 1.0, 3.0, and 10.0% (w/v), respectively, were used to maintain a constant volume of test solution (0.2 ml/kg per day) in the three dose groups. Treated (with polypro-

TABLE 4. Dermal Toxicity of Phenyl Trimethicone

Ingredient	*Test*	*Dose*	*Animal*	*Comments*	*Reference*
Phenyl Trimethicone 100%	Acute	2.0 g/kg	10 rabbits	Nontoxic	20
Phenyl Trimethicone 100%	Subchronic	200 mg/kg per day for 28 days	10 rabbits	No significant adverse effects	6
Phenyl Trimethicone 100%	Subchronic	50 mg/kg per day for 20 days	20 rabbits	No significant adverse effects	6
Phenyl Trimethicone in polypropylene glycol-2-methyl ether	Subchronic	2, 6, and 20 mg/kg for 20 days (actual dose)	30 rabbits	No significant adverse effects	25
Phenyl Trimethicone 2.5% in a moisturizer	Subchronic	5.5 and 8.4 mg/cm^2/ 8.4% body surface area	20 rabbits	Some irriation and inflammation at application site; no other adverse effects	26

pylene glycol-2-methyl ether) and untreated control groups were also used. Test sites of all rabbits were shaved weekly, and in two males and two females of each group the skin was abraded before compound application. The solutions of Phenyl Trimethicone were applied gently without rubbing, and the rabbits were fitted with collars to prevent ingestion of the test material. The rabbits were observed daily during the application period and for 14 days thereafter. No deaths or unusual behavioral reactions were noted. Local skin reactions were characterized by slight desquamation at the application site among rabbits of all test groups as well as the treated controls. No toxic effects were noted in body weight, hematological values, blood chemistry, urine analyses, and gross or microscopic pathological findings of the test or control groups[25] (Table 4).

A 3-month toxicity study was conducted in rabbits to investigate the effects of daily dermal exposure to a skin moisturizer containing 2.5% Phenyl Trimethicone. Two treatment groups and one control group each consisted of 10 New Zealand White rabbits. Two doses, 5.5 and 8.4 mg/cm^2 per 8.4% body surface area, were administered to the clipped back of the animals. Collars were fitted to prevent ingestion of the test material. These doses represented multiples of 7.5 and 12 of the anticipated human exposure of 2.2 mg/cm^2 per 2.8% body surface area. The moisturizer caused persistent erythema, slight edema, and slight desquamation; these changes appeared slightly more severe at the higher dose during the first month of exposure, but no differences between dose groups were observed by the second month. Signs of irritation were nearly maximum in the first week of exposure, declined slightly and remained unchanged for 2 months. The dermal irritation increased gradually in severity in the last month of exposure. No adverse hematological or clinical chemistry findings were reported. There were no significant differences between the organ weights (testes but not seminal vesicles were examined) of treated and control animals. At histopathological examination, no treatment-related changes other than inflammation were observed at the application sites[26] (Table 4).

Skin Irritation

Phenyl Trimethicone was evaluated for primary skin irritation in six albino rabbits. The rabbits were clipped free of hair, and the skin of three was abraded. A 0.5 ml sample of undiluted Phenyl Trimethicone was applied for 24 h to each animal using an occlusive patch. Sites were scored upon patch removal and 48 h later. Phenyl Trimethicone had a Primary Irritation Index (PII) of 0.7 (max = 8) and was considered nonirritating[20] (Table 5).

A foundation cream containing 5% Phenyl Trimethicone was applied to six rabbits for 14 days. A 0.5 ml dose was applied to the clipped back of the animal for 18 h on 14 consecutive days. The rabbits were fitted with collars to prevent licking of the test material. Slight erythema, slight edema, and desquamation were observed. The cream had a PII of 1.9 (max = 8) and was considered mildly irritating[24] (Table 5).

Primary irritation tests of three cosmetic products containing 10% Phenyl Trimethicone were conducted with groups of six male New Zealand white rabbits. Using single insult patch procedures, 0.5 ml of the test product was applied via an occlusive patch to the clipped back of each rabbit. Patches remained in

TABLE 5. Irritation and Sensitization of Phenyl Trimethicone

Ingredient	*Test*	*Dose*	*Animal*	*Comments*	*Reference*
Phenyl Trimethicone 100%	Single insult occlusive patch	0.5 ml/24 h	6 rabbits 3 intact 3 abraded	PII[a] = 0.7; nonirritating	20
Phenyl Trimethicone Induction 5% Booster 20% Challenge 10, 20%	Magnusson-Kligman Maximization Test	See text	20 guinea pigs	No sensitization	31
Phenyl Trimethicone 5% in a foundation cream	Irritation	0.5 ml/18 h for 14 consecutive days	6 rabbits	PII = 1.9; mildly irritating	24
Phenyl Trimethicone 10% in a product	Single insult occlusive patch	0.5 ml/24 h	6 rabbits	PII = 0.58; slightly irritating	27
Phenyl Trimethicone 10% in a product	Single insult occlusive patch	0.5 ml/24 h	6 rabbits	PII = 0.71; slightly irritating	28
Phenyl Trimethicone 10% in a product	Single insult occlusive patch	0.5 ml/24 h	6 rabbits	PII = 0.37; slightly irritating	29

[a]PII, Primary Irritation Index (max = 8).

place for 24 h, and sites were scored at 24 and 72 h. The products had group PIIs (max = 8) of 0.585,[27] 0.71,[28] and 0.375[29] and were considered slightly irritating (Table 5).

Skin Sensitization

The contact sensitization potential of Phenyl Trimethicone was assessed using the Magnusson-Kligman Maximization Test.[30] In the induction phase of the test, 10 female guinea pigs received 0.05 ml intradermal injections each of 50% aqueous Freund's Complete Adjuvant, 5% Phenyl Trimethicone in propylene glycol, and 5% Phenyl Trimethicone in 50% Freund's Complete Adjuvant. One week after induction injections, a topical booster of 20% Phenyl Trimethicone in petrolatum was applied to the induction site. (A 5% solution of sodium lauryl sulfate in petrolatum had been applied 24 h earlier to produce minor irritation.) The sites were then placed under occlusive patches for 48 h. Two weeks after the topical booster, the animals were challenged with topical applications of 10 and 20% Phenyl Trimethicone in petrolatum to the shaved sides of the guinea pigs, and application sites were covered by occlusive patches for 24 h. The challenge sites were scored 48 and 72 h after challenge application. No sensitization was observed in any of the Phenyl Trimethicone-treated animals, and the investigators concluded that Phenyl Trimethicone did not produce an allergic response in guinea pigs[31] (Table 5).

Ocular Studies

Phenyl Trimethicone was evaluated for ocular irritation in six albino rabbits. A 0.1 ml sample of undiluted Phenyl Trimethicone was instilled into one eye of each rabbit; the other eye served as the untreated control. Reactions were scored according to Draize at 24, 48, and 72 h. The total score was 21 (max = 110) at 24 h and 0 thereafter. Phenyl Trimethicone was not considered an eye irritant[29] (Table 6).

Eye irritation studies were conducted with three cosmetic products containing 10% Phenyl Trimethicone. Six adult, male albino rabbits were used for each test material, and a 0.10 ml dose was instilled into one eye; the other eye served as control. The eyes were graded according to the standard Draize eye irritation scale.[32] There were no positive reactions; the products were not considered eye irritants[33-35] (Table 6).

Six albino rabbits were given instillations (into the conjunctival sac) of 0.10 ml of a foundation cream containing 5% Phenyl Trimethicone. Slight conjunctivitis occurred. There was no evidence of corneal dullness or iritis[24] (Table 6).

Inhalation Studies

An aerosol formulation containing 3% Phenyl Trimethicone in propellants was evaluated for inhalation toxicity in five male and five female rats. An aerosol without Phenyl Trimethicone was used as the control. A single exposure consisted of a 30-second burst followed by a 15-minute exposure within a 350 L inhalation chamber. This exposure was repeated twice daily, 5 days per week, for 4 weeks (40 exposures). The animals were observed for deaths, behavioral reac-

TABLE 6. Ocular Irritation of Phenyl Trimethicone

Ingredient	*Test*	*Dose*	*Animal*	*Comments*	*Reference*
Phenyl Trimethicone 100%	Draize	0.1 ml	6 rabbits	Score of 21 (max = 110) at 24 h, score of 0 thereafter; not an eye irritant	20
Phenyl Trimethicone 10% in a cosmetic product	Draize	0.1 ml	6 male rabbits	No positive reactions; not an eye irritant	33
Phenyl Trimethicone 10% in a cosmetic product	Draize	0.1 ml	6 male rabbits	No positive reactions; not an eye irritant	34
Phenyl Trimethicone 10% in a cosmetic product	Draize	0.1 ml	6 male rabbits	No positive reactions; not an eye irritant	35
Phenyl Trimethicone 5% in a foundation cream	--	0.1 ml	6 rabbits	Slight conjunctivitis; no evidence of corneal dullness or iritis	24

tions, and body weight changes. Hematological and blood chemistry as well as urine analyses were conducted. The animals exposed to the Phenyl Trimethicone areosol gained slightly less weight than the controls; no other toxic effects were noted.[36]

Mutagenicity

Phenyl Trimethicone was evaluated for mutagenicity in the Ames bacterial assay using *Salmonella* strains both with and without metabolic activation. Phenyl Trimethicone was not mutagenic when tested either with or without activation.[36]

Teratogenicity/Reproductive Effects

Phenyl Trimethicone was evaluated for teratogenicity in three groups of 26 rats each and three groups of 15 rabbits each. Doses of 50 and 500 mg/kg body weight (0.05 and 0.5 ml/kg) were applied topically to two groups of the rats and rabbits on Days 6–16 and 6–18 of gestation, respectively. The third group of each species served as the untreated control. Doses were applied by syringe onto the shaved dorsal area of each animal. The rats and rabbits were killed on Day 20 and 30, respectively, and the fetuses were removed by cesarean section. Approximately one half of the fetuses were examined microscopically, and the remaining fetuses were examined for skeletal abnormalities.[37]

The mean number of implantation sites and the mean number of live fetuses derived from rats of the control and test groups were comparable and within

normal limits. No gross lesions were found in any group. All fetuses had the normal number of ribs, but 10 and 3 fetuses from the low and high test group, respectively, had incompletely developed sternebrae. A greater number of fetuses derived from the test groups had bipartite sternebrae and lack of closure of the coronal suture.[37]

Of the rabbits on test, one died from the control and two from the low-dose groups died. The control group had a greater mean number of implantation sites than the test groups, although the mean number of live fetuses from all three groups was comparable. None of the dead fetuses delivered from the control (8), low (9), and high (2) dose groups were abnormal; most showed signs of immaturity. All live pups had fully developed sternebrae and normal ribs. No abnormalities were found in soft tissues. The investigators concluded that Phenyl Trimethicone had no adverse effects on resorptions, in utero mortality, or gross fetal development in rats and rabbits. The delayed ossification found in both test groups of rats was not seen in rabbits and was considered a species variation.[37]

Phenyl Trimethicone was evaluated for teratogenicity in two studies using New Zealand albino rabbits. In both studies, 200 mg/kg of the test material was applied to the shaved back of each animal on Days 6–18 of gestation. The rabbits were killed on Day 29, and the fetuses were removed by cesarean section. All fetuses were examined for viability, abnormalities, and skeletal deformities.[38,39]

One study was conducted with three groups of 10 rabbits each: the first group received Phenyl Trimethicone suspended in corn oil, the second received an equal volume of corn oil, and the third served as an untreated control. No deaths, unusual behavioral reactions, or adverse effects on maternal body weight were noted. A slight but significant increase in the number of resorption sites and a decreased viability of the Phenyl Trimethicone-exposed fetuses were observed. The investigators concluded that Phenyl Trimethicone, at a dose of 200 mg/kg, was not teratogenic[38] (Table 7).

The other study was conducted 1 year later with three groups of 15 rabbits each: the first group received Phenyl Trimethicone, the second received an equal volume of sesame oil, and the third served as an untreated control. No deaths or unusual reactions were observed. No adverse effects were noted on maternal body weight, external or internal development of 84/85 fetuses, or on viability.

An increase in the number of resorption sites was noted in the Phenyl Trimethicone test group (21.3% compared to 7.5 and 6.0% in the treated and untreated control groups, respectively). No skeletal abnormalities were found. The investigators concluded that Phenyl Trimethicone, at a dose of 200 mg/kg, was not teratogenic[39] (Table 7).

CLINICAL ASSESSMENT OF SAFETY

Dermal Absorption

Dermal absorption of Phenyl Trimethicone was evaluated in a panel of five male volunteers. During a 25-day pretest period, silicon baseline analysis of 24-h urine samples was conducted. Samples of home drinking water and various brands of beer consumed during the test were analyzed for silicon content. Dur-

TABLE 7. Teratogenicity Studies on Phenyl Trimethicone

Ingredient	*Method*	*Dose*	*Animal*	*Comments*	*Reference*
Phenyl Trimethicone 100%	Dermal application to shaved skin on Days 6–16 of gestation	0,50, and 500 mg/kg per day	3 groups of 26 rats	No adverse effects on resorptions, in utero mortality, or gross fetal development; not teratogenic	37
Phenyl Trimethicone 100%	Dermal application to shaved skin on Days 6–18 of gestation	0, 50, and 500 mg/kg per day	3 groups of 15 rabbits	No adverse effects on resorptions, in utero mortality, or gross fetal development; not teratogenic	37
Phenyl Trimethicone suspended in corn oil	Dermal application to shaved skin on Days 6–18 of gestation	200 mg/kg per day	3 groups of 10 rabbits (including treated and untreated controls)	Slight but significant increase in number of resorptions and decreased viability—approaching fetotoxic dose; not teratogenic	38
Phenyl Trimethicone 100%	Dermal application to shaved skin on Days 6–18 of gestation	200 mg/kg per day	3 groups of 15 rabbits (including treated and untreated controls)	Increase in number of resorptions indicating approaching fetotoxic dose; no other adverse effects; not teratogenic	39

ing the 10-day test period, 50 mg/kg Phenyl Trimethicone was applied once daily over the entire surface of the back. The test material remained in contact with the back for a period of 20 h, after which time any excess material was removed by washing. No special covering other than clothing was used. Blood and urine samples were taken for analysis on Days 1, 3, 6, 8, and 10.[6]

Blood and urine silicon concentrations were determined using optical emission spectroscopy. The procedure is applicable to determination of silicon in the 5 to 100 μg/ml range, with a detectability of 5 μg/ml. There were no statistically significant increases in blood or urinary silicon concentrations[6] (Table 8).

Irritation and Sensitization

A Repeated Insult Patch Test (RIPT) evaluated the irritation and sensitization of Phenyl Trimethicone using a panel of 50 subjects (36 males and 14 females). The induction phase consisted of nine occlusive patches applied for 24 h on alternate days. The patches were coated with Phenyl Trimethicone and always applied to the same skin site. Two weeks after the last induction patch, a challenge

TABLE 8. Clinical Assessment of Safety

Ingredient	*Test*	*No. of panelists*	*Results*	*Reference*
Phenyl Trimethicone 100%	Dermal absorption	5 males	No detectable concentration in blood and urine	6
Phenyl Trimethicone 100%	RIPT[a]	50 (36 males, 14 females)	No irritation or sensitization	40
Phenyl Trimethicone 10% in each of 17 products	RIPT (modified 4 applications on consecutive days)	8 per group (80 total)	Highest total score of 5.0 (max = 256) and highest individual score of 1.0 (max = 8); minimally irritating	41–50
Phenyl Trimethicone 5% in a foundation	RIPT	189	No irritation or sensitization	51
Phenyl Trimethicone 2.5% in a moisturizer	RIPT	239	No irritation or sensitization	52
Phenyl Trimethicone 2.5% in a moisturizer	Cumulative Irritation test	9	Cumulative irritation score of 13 (max = 630); classified as a mild material (essentially no experimental irritation)	54

[a]RIPT, Repeated Insult Patch Test.

patch was applied to an adjacent site. All sites, both induction and challenge, were scored upon patch removal. No signs of erythema or edema were observed; all scores were 0. It was concluded that Phenyl Trimethicone was not irritating, fatiguing, or sensitizing[40] (Table 8).

RIPTs were conducted to evaluate the irritancy of 17 cosmetic products, each containing 10% Phenyl Trimethicone. For each product, four overnight patches were applied on 4 consecutive days to eight panelists. Sites were scored upon patch removal. The products were at most minimally irritating, as the highest total score was 5.0 (max = 256) and the highest individual score was 1.0 (max = 8)[41–50] (Table 8).

Two modified Draize-Shelanski RIPTs were conducted to evaluate the irritation and sensitization of a cosmetic foundation product and a moisturizer containing 5 and 2.5% Phenyl Trimethicone, respectively. The panels consisted of 189 and 239 individuals for the 5 and 2.5% products, respectively. Ten 24-h patches were applied during the 23-day induction period. Following a 2-week nontreatment period, a 48-h challenge patch was applied to a previously untreated site. No irritation or sensitization was observed in any of the subjects[51,52] (Table 8).

A moisturizer containing 2.5% Phenyl Trimethicone was tested for cumulative irritation by the methods of Phillips et al.[53] Using an occlusive patch, 0.3 ml of the product was applied to the back of nine panelists for 23 h on 21 consecutive days. Applications were made to the same site for the duration of the test. The cumulative irritation score was 13 (max = 630), and the product was classified as a mild material (essentially no experimental irritation)[54] (Table 8).

One case of allergic contact dermatitis to a sunscreen preparation containing Phenyl Trimethicone has been reported. A 64-year-old woman developed contact dermatitis 4 weeks after she had begun using a sunscreen on a regular basis. After patch testing with individual active and vehicular ingredients of the sunscreen, the patient reacted (at 72 h) to 2% Phenyl Trimethicone in petrolatum. Five control subjects patch tested with this mixture had no reactions.[10]

SUMMARY

Phenyl Trimethicone is a fluid, water white, almost odorless silicone polymer used in a variety of cosmetic products. It is generally used at a concentration of <5%.

In acute oral studies, Phenyl Trimethicone was relatively nontoxic for rats. Cosmetic products containing up to 10% Phenyl Trimethicone when administered orally were also relatively nontoxic for mice and rats.

Phenyl Trimethicone was nontoxic for rabbits in acute and subchronic dermal toxicity studies. Doses of up to 200 mg/kg applied once daily for up to 28 days caused no adverse effects. Topical application for 3 months of a moisturizer containing 2.5% Phenyl Trimethicone produced no treatment-related changes in rabbits other than inflammation at the application site.

Phenyl Trimethicone was nonirritating to the intact and abraded skin of rabbits. A cosmetic product containing 5% Phenyl Trimethicone was mildly irritating to rabbits when applied for 14 consecutive days, and cosmetic products

containing 10% Phenyl Trimethicone were slightly irritating to rabbits after a single application of the product.

Phenyl Trimethicone evaluated with the Magnusson-Kligman Maximization Test was not a sensitizer in guinea pigs.

Phenyl Trimethicone evaluated by the Draize Ocular Irritation Test was not irritating. Cosmetic products containing up to 10% Phenyl Trimethicone were also essentially nonirritating to eyes of rabbits.

An aerosol formulation containing 3% Phenyl Trimethicone tested by inhalation produced no significant adverse effects in rats.

Phenyl Trimethicone evaluated by the Ames assay was nonmutagenic both with and without metabolic activation.

Phenyl Trimethicone applied dermally at doses of up to 500 mg/kg per day was not teratogenic in rats and rabbits. An increase in the number of resorptions was noted in two studies (statistically significant in only one) at a dose of 200 mg/kg per day.

A clinical trial of Phenyl Trimethicone dermal absorption in five panelists was negative. A 50 mg/kg dose was applied once daily for 10 days. Using a spectroscopic method with a detection limit of 5 μg of silicone per ml, detectable amounts of silicone were not found in the blood and, compared to controls, only insignificant changes were seen in the urine.

Phenyl Trimethicone evaluated by RIPT using a panel of 50 subjects produced no irritation or sensitization. In clinical studies, cosmetic products containing Phenyl Trimethicone produced essentially no cumulative irritation (2.5% Phenyl Trimethicone) over 21 days and minimal irritation at most when applied for 4 consecutive days (10% Phenyl Trimethicone). In RIPTs, cosmetic products containing 5 and 2.5% Phenyl Trimethicone produced no irritation or sensitization in the 189 and 239 people, respectively. One case of allergic contact dermatitis to Phenyl Trimethicone in a sunscreen has been reported.

DISCUSSION

No photosensitization data were available on Phenyl Trimethicone. These were not considered essential for the evaluation of the safety of Phenyl Trimethicone in cosmetic products as the UV spectrum indicated only weak absorbance at 327 nm. It was considered unnecessary to request clinical photosensitization data. An increase in the number of resorption sites was noted in two of three teratogenicity/reproductive studies, but the results were statistically significant in only one study. The doses tested in these studies were comparatively greater than the concentrations used in cosmetics, and the Panel did not believe that additional data were required for evaluation of the safety of Phenyl Trimethicone in cosmetics.

CONCLUSION

Based on the data from animal and human studies included in this report, the CIR Expert Panel concludes that Phenyl Trimethicone is safe as a cosmetic ingredient in the present practices of use and concentration.

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PHENYL TRIMETHICONE

In 1986, the CIR Expert Panel found that Phenyl Trimethicone is safe as a cosmetic ingredient in the present practices of use and concentration (Elder 1986). A review of the recent literature uncovered no new studies regarding Phenyl Trimethicone,

but the Panel did consider updated information regarding uses and use concentrations. The Panel determined to not reopen the safety assessment.

Phenyl Trimethicone uses have increased from 169 in 1981 to 279 in 2002, based on industry voluntary reports provided to FDA (Elder 1986; FDA 2002). An industry survey in 2003 indicated that use concentrations range from 0.0075% to 36% (CTFA 2004). The maximum value in that range is higher than the maximum use concentration of 5% reported in 1981 (Elder 1986). Table 17 presents the available use and concentration information for Phenyltrimethicone. The most recent information now represents the present practice of use and concentration.

The Panel considered the increased use concentrations in the context of the reproductive and developmental toxicity data in the original safety assessment. Phenyl Trimethicone was not teratogenic at 500 mg/kg/day in rats and rabbits. For a 70-kg person, this dose corresponds to 35 g/day. At the current maximum use in lipsticks and the amount of lipstick used in a typical day, a dose of Phenyl Trimethicone was estimated to be 10 mg/day. This dose was 3500× lower than the observable effect level.

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PROPYLENE CARBONATE

A safety assessment of Propylene Carbonate was published in 1987 with the conclusion that it is safe as a cosmetic ingredient in the present practices of use and concentration (Elder 1987). Studies published since the last assessment were reviewed along with updated information concerning frequency of use and use concentrations. The CIR Expert Panel determined to not reopen the safety assessment.

Based on voluntary reports provided by industry to FDA, there were 295 reported uses in 1981 (Elder 1987) and 178 reported uses in 2002 (FDA 2002). Use concentrations from an industry survey (CTFA 2003) ranged from 0.003% to 6%, not very different from the use concentration range reported in 1981 of ≤0.1% to >5% (Elder 1987).

Table 18 presents the available use and concentration information for Propylene Carbonate. The most recent information constitutes present practices of use and concentration.

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POLYVINYLPYRROLIDONE/VINYL ACETATE COPOLYMER

In 1983, the CIR Expert Panel concluded that this ingredient is safe as a cosmetic ingredient under the present practices of product and concentration use (Elder 1983). New studies available since that review have been considered by the Expert Panel,

[18] Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

[19] Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036-4702, USA.

TABLE 17
Historical and current cosmetic product uses and concentrations for Phenyl Trimethicone

Product category	1981 uses (Elder 1986)	2002 uses (FDA 2002)	1986 concentrations (Elder 1986) %	2003 concentrations (CTFA 2004) %
Baby Care	1*	—	>0.1–1*	—
Bath				
Oils, tablets, and salts	1	1	>0.1–1	—
Other bath	2	—	>1–5	—
Eye Makeup				
Eyeliners	—	1	—	2–6
Eye shadow	1	77	≤0.1–5	4–13
Eye lotions	—	—	—	0.008–1
Mascara	1	1	>0.1–1	0.1–0.4
Other eye makeup	1	4	>0.1–1	6–15
Fragrances				
Colognes and toilet waters	—	—	—	0.5
Perfumes	—	1	—	—
Powders	—	1	—	—
Other fragrances	—	—	—	0.5
Noncoloring hair care				
Conditioners	10	8	≤0.1–5	0.3–2
Sprays	25	23	≤0.1–1	0.1–18
Straighteners	1	—	>1–5	—
Rinses	1	—	>0.1–1	—
Shampoos	—	—	—	1
Tonics, dressings, etc.	9	31	≤0.1–5	5–11
Wave sets	2	—	>0.1–5	—
Other noncoloring hair care	1	7	>0.1–1	0.5–2
Makeup				
Blushers	11	1	>1–5	2–15
Face powders	2	9	>0.1–1	0.1–8
Foundations	2	17	>1–5	2–22
Leg and body paints	—	—	—	2
Lipsticks	2	34	>1–5	0.08–36
Makeup bases	2	8	≤0.1–5	—
Rouges	—	2	—	—
Other makeup	—	13	—	0.0075–22
Nail care				
Creams and lotions	—	—	—	0.5
Polishes and enamels	7	—	>0.1–1	—
Personal hygiene				
Underarm deodorants	—	1	—	—
Other personal hygiene	—	1	—	—
Shaving				
Aftershave lotions	—	1	—	0.5–2
Preshave lotions	6	1	>0.1–5	2
Other shaving	—	—	—	0.5
Skin care				
Cleansing creams, lotions, etc.	—	4	—	2–4
Face and neck skin care	8**	3	≤0.1–1**	4–6
Body and hand skin care		4		0.2–18
Moisturizers	7	15	≤0.1–5	0.8–3
Night skin care	1		≤0.1	2
Other skin care	1		>1–5	2
Suntan				
Suntan gels, creams, liquids and sprays	6	2	—	0.5–9
Indoor tanning	1	8	—	0.2–5
Other suntan	1		>1–5	2
Total uses/ranges for Phenyl Trimethicone	**113**	**279**	**≤0.1–5**	**0.0075–36**

*Product categories within the group not given.

**These categories were combined originally, but are now separate.