Amended Safety Assessment of Dimethicone, Methicone, and Substituted-Methicone Polymers as Used in Cosmetics

Status:	Draft Final Amended Report for Panel Review
Release Date:	November 10, 2021
Panel Meeting Date:	December 6-7, 2021

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.; Daniel C. Liebler, Ph.D.; Lisa A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. Previous Panel member involved in this assessment: James G. Marks, Jr., M.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Preethi S. Raj, Senior Scientific Analyst/Writer, CIR.

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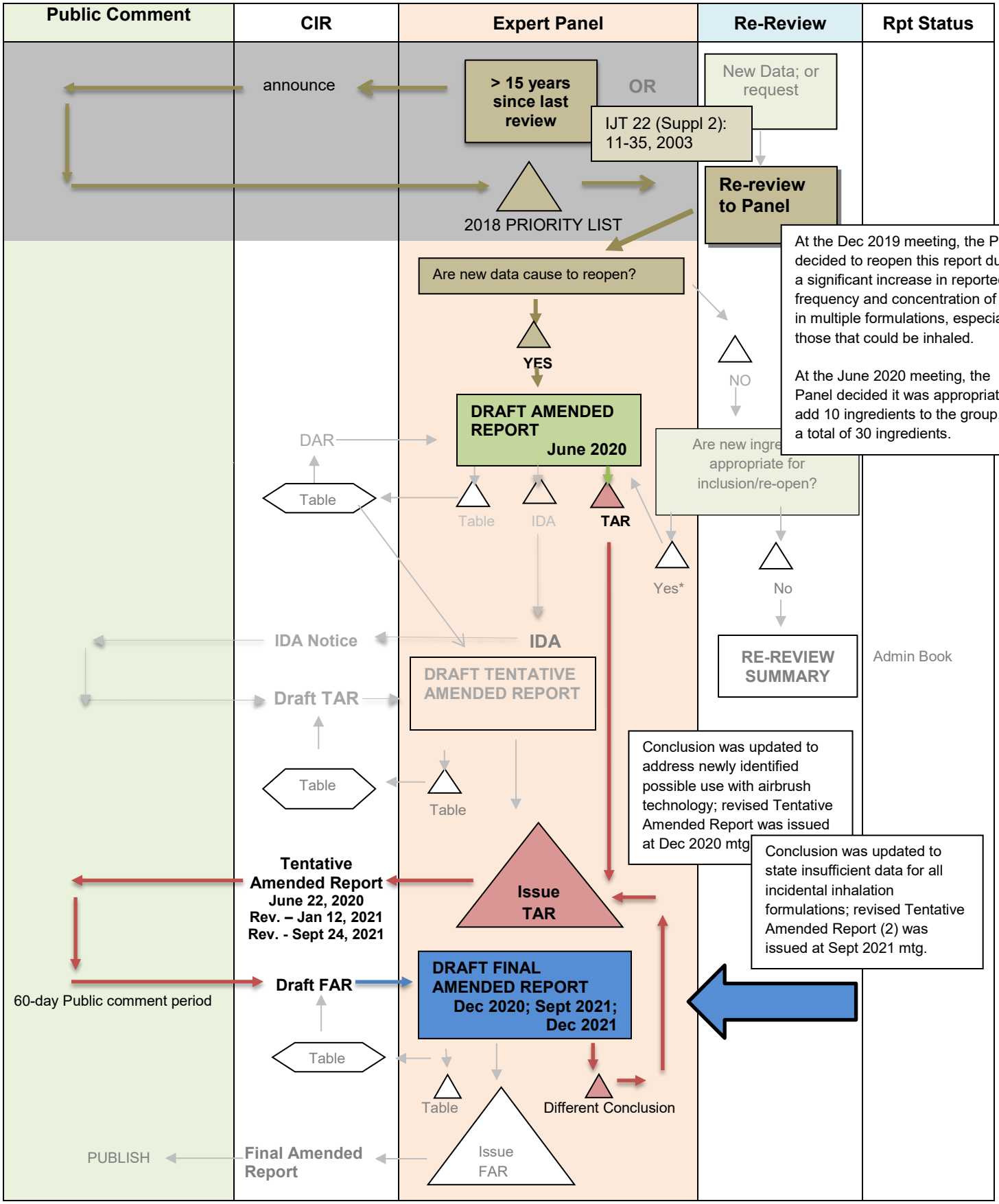
RE-REVIEW FLOW CHART

INGREDIENT/FAMILY Dimethicone-, Methicone-, and Substituted-Methicone Polymers

MEETING December 2021



Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Preethi S. Raj, M.Sc., Senior Scientific Writer/Analyst, CIR
Date: November 10, 2021
Subject: Amended Safety Assessment of Dimethicone-, Methicone-, and Substituted-Methicone Polymers as Used in Cosmetics

A Draft Final Amended Report of the Amended Safety Assessment of Dimethicone-, Methicone-, and Substituted-Methicone Polymers as Used in Cosmetics is enclosed for your review (*report_Methicones_122021*). The Expert Panel for Cosmetic Ingredient Safety (Panel) first published a safety assessment of Dimethicone-, Methicone-, and substituted-methicone polymer ingredients in 2003, with the conclusion that the 20 ingredients named in that report are safe as used in cosmetic products. At the June 2020 Panel meeting, the Panel approved the addition of 10 ingredients. The original report is included for your use (identified as *originalreport_Methicones_122021* in the pdf).

At the December 2020 meeting, a Draft Final Amended Report was first presented to the Panel. At that meeting, correspondence from the Women's Voices of Earth (WVE) acknowledging the potential use of these ingredients in cosmetic products applied via airbrush technology posed a new challenge to the Panel (*WVE1comments_Methicones_122021*; although this information has been informally presented to the Panel before, it is included in this package for comprehensiveness and transparency). In the absence of the necessary data, the Panel issued a Revised Tentative Amended Report, containing a split conclusion of safe in cosmetics in the present practices and concentrations of use and concentration when formulated to be non-irritating, with the exception that the available data are insufficient to make a determination of safety for the utilization of these ingredients with airbrush use.

Similarly, a second Draft Final Amended Report was presented at the September 2021 meeting, during which the WVE submitted data and references suggesting the potential for incidental inhalation from cosmetic and deodorant sprays. Per Panel request, an annotated version of this memo has been included for review (*WVE2comments-annotated_Methicones_122021*) (This same document is included with the Inhalation Resource Document (and the Silicates report); it is also being included here for ease of access for this review). In response, the Panel asserted the need for more information on current uses, concentrations, particle size distributions, duration and types of exposures for cosmetic sprays, as well as the devices and technologies used for these applications, to make a determination of safety for products that could be incidentally inhaled. Consequently, the Panel issued a second Revised Tentative Amended Report, containing a split conclusion of safe in cosmetics in the present practices of use and concentration as described in the safety assessment when formulated to be non-irritating, with the exception that the available data are insufficient to make a determination that these ingredients are safe for use in products that may be incidentally inhaled.

Additionally, comments on the second Revised Tentative Amended Report (*PCPCcomments_Methicones_122021*) received from the Council are attached, and have been considered. A comments response checklist also follows (*response-PCPCcomments_Methicones_122021*).

Transcripts from recent and previous meetings (*transcripts_Methicones_122021*), a flow chart (*flow_Methicones_122021*), the history of these ingredients (*history_Methicones_122021*), 2021 FDA VCRP data (*VCRP_Methicones_122021*), and a search strategy document (*search_Methicones_122021*) are also included, as is a data profile identifying the presence of information in the original and current report (*dataprofile_Methicones_122021*).

The Panel should carefully consider the newly added data, the Abstract, Discussion, and Conclusion, and be prepared to issue a Final Amended Report.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: October 7, 2021

SUBJECT: Revised Tentative Report: Amended Safety Assessment of Dimethicone, Methicone, and Substituted-Methicone Polymers as Used in Cosmetics (report released September 24, 2021)

The Personal Care Products Council respectfully submits the following comments on the revised tentative report, Amended Safety Assessment of Dimethicone, Methicone, and Substituted-Methicone Polymers as Used in Cosmetics.

Acute, Inhalation, old report summary – Please clarify what kg represents in "10 mg/kg", is this kg body weight?

Sensitization, Animal, Dimethicone – It is not clear what is meant by "radioisotopic hypersensitivity". Generally, radioactivity is used to measure cell proliferation.

Ocular Irritation, Dimethicone – Please revise: "a saline balanced salt solution" (saline and salt is redundant)

Discussion – Rather than saying that the Panel was made aware of use in airbrush products "through alternative sources", it should be more specific and state that Women's Voices for the Earth identified information on the internet that indicates that these ingredients are reported to be used in cosmetic products applied using airbrush devices. Rather than saying "consumer products" it should state "cosmetics". The Discussion states: "The Panel is considering the available physio-chemical properties data on airborne particles…". The Panel is considering particle size information about cosmetics applied using an airbrush. What "chemical" properties are being considered?

Methicones - December 6-7, 2021 Panel Meeting – Preethi Raj			
Comment Submitter: Personal Care Products Council **Date of Submission: October 7, 2021 (Comments on rev TAR posted after Sept 2021 meeting)**			
#	**Report section/Comment**	**Response/Action**	**Needs Panel Input**
1	Acute, Inhalation, old report summary --Clarification of '10 mg/kg'	Cannot find where this is located, not sure how to address	
2	Sensitization, Animal, Dimethicone – clarification of 'radioisotopic hypersensitivity'	Provided more detail and rephrased	
3	Ocular Irritation, Dimethicone – revise 'a saline balanced salt solution'	Deleted salt (editorial)	
4	Discussion – directly state the source which identified incidental inhalation data	Typically, external sources are not named in CIR reports.	
5	Discussion – replace 'consumer products' with 'cosmetics'	Since we haven't received data from industry on cosmetic airbrush use, it is better to keep the definition broad.	
6	Discussion - define 'physico-chemical properties' which the Panel is considering (i.e. mainly concerned with particle size distribution)	Rephrased	✓

FYI

From: Alexandra Gorman Scranton <alexs@womensvoices.org>
Sent: Tuesday, June 2, 2020 5:36 PM
To: CIRINFO <cirinfo@cir-safety.org>
Cc: Bart Heldreth <heldrethb@cir-safety.org>
Subject: New data for methicones assessment for July 8-9 CIR meeting

To the CIR:

I have raised the concern previously about airbrush makeup products and the potential for very small particle sizes in the airbrush aerosol, with very long exposure times (10 – 40 minutes) directly to the user's face. The CIR has discussed these products but concluded that they could not assess the hazards – because there was very little data on the particle sizes of the aerosols produced by these devices. I was pleased to find that relevant research has now been published. The recent study (Pearce et.al. 2019) measured particle size from the use of a commercially available makeup airbrush and found that the vast majority of particles emitted by airbrush makeup guns are less than 1.3 microns in diameter – and thus pose a potential inhalation hazard.

This information is currently relevant to the methicones assessment, as methicones are ingredients used in airbrush makeup liquids. Discussion of the inhalation hazards of methicones should include the potential hazards posed by these products.

This study should also be useful for the future discussion of inhalation hazards of cosmetic aerosols by the CIR as well.

Details on the study:

Citation: Pearce K, Goldsmith WT, Greenwald R, Yang C, Mainelis G, Wright C. Characterization of an aerosol generation system to assess inhalation risks of aerosolized nano-enabled consumer products. Inhal Toxicol. 2019;31(9-10):357-367. doi:10.1080/08958378.2019.1685613

The study (Pearce et. al. 2019) looked specifically at measuring particle sizes from realistic applications of airbrush makeup.

The study explains:
"The system mimicked consumer application and potential exposure by spraying the liquid powder cosmetic via a commercial airbrush/nebulizer that consumers use (Model #: BC-200R, Luminess Direct, LLC., Stafford, TX). The product was sprayed from a distance of 6", as recommended by commercial airbrush/nebulizer manufacturers, onto a mannequin's face (Model #: 50023, Giell.com, Flowery Branch, GA) that was fitted with stainless steel sampling lines placed in the mannequin's nostrils and also directly above the top of the mannequin's head."

"A spray duration of 20 minutes was chosen for experiments based on the amount of time to apply even coverage of the products on the mannequin face in preliminary studies."

"…aerosols were monitored using both a scanning mobility particle sizer (SMPS) that measured particle

size distributions between 10–435nm and an optical particle sizer (OPS) that measured size distributions between 0.3–10 microns. Additionally, a water-based condensation particle counter (CPC) was used to obtain total particle number concentration during aerosol generation sessions."

"*The micron-sized particles found were well within the accepted respirable particle size range of 1-10 microns, which confirms a fraction of these particles could be inhaled and may give rise to potential adverse respiratory health effects."*

The study also addressed the issue of potential agglomeration of particles during consumer use. This is an issue the CIR has brought up in previous conversations about the potential hazards of aerosols, under the assumption that the agglomerations of smaller particles were likely to be greater than 10 microns in diameter. However, this study found that it was the nano-sized particles with diameters less than 50 nm (50 nm = .05 microns) were agglomerating to larger masses that were up to 1.3 microns in diameter. So, the researchers did observe likely agglomeration, but the resulting particles were still much smaller than 10 microns, and thus inhalable.

Airbrush makeup products can include methicones.

Here are some examples of the ingredients of currently available airbrush makeup products containing methicones:

https://www.maccosmetics.com/product/7407/921/pro/proproduct-grid/pro-performance-hd-airbrush-makeup

MAC Pro Performance HD Airbrush Makeup

Ingredients: Isododecane, Trisiloxane, Water\Aqua\Eau, Dimethicone, Polysilicone-6, Silica, Octyldodecyl/ Ppg-3 Myristyl Ether Dimer Dilinoleate, Dimethicone Silylate, Butylene Glycol, Peg-10 Dimethicone, Tocopheryl Acetate, Ascorbyl Palmitate, Retinyl Palmitate, Caprylyl Glycol, Hexylene Glycol, Cetyl Peg/Ppg-10/1 Dimethicone, Diethylhexyl Malate, Methicone, Polyglyceryl-4 Isostearate, Polysilicone-11, Hexyl Laurate, Triethoxycaprylylsilane, Trimethylsiloxysilicate, Sodium Chloride, Phenoxyethanol, [+/- Mica, Iron Oxides (Ci 77491, Ci 77492, Ci 77499), Titanium Dioxide (Ci 77891), Bismuth Oxychloride (Ci 77163), Blue 1 Lake (Ci 42090), Carmine (Ci 75470), Chromium Oxide Greens (Ci 77288), Chromium Hydroxide Green (Ci 77289), Red 6 (Ci 15850), Red 6 Lake (Ci 15850), Red 7 Lake (Ci 15850), Red 21 (Ci 45380), Red 22 Lake (Ci 45380), Red 28 Lake (Ci 45410), Red 30 Lake (Ci 73360), Red 33 Lake (Ci 17200), Ultramarines (Ci 77007), Yellow 5 Lake (Ci 19140), Yellow 6 Lake (Ci 15985)]

https://www.airbasemakeup.com/about/silicone-based-foundation/airbase-foundation
Airbase Ultra Foundation

Ingredients: Cyclomethicone, Aqua, Dimethicone, Cyclopentasiloxane, Talc, Isododecane, Trimethylsiloxysilicate, Phenyl Trimethicone, Butylene Glycol, Triethoxysilylethyl Polydimethylsiloxyethyl Dimethicone, Silica, Titanium Dioxide(Nano), Caprylic/Capric Triglyceride, Cyclomethicone, Sorbitan Sesouioleate, PEG/PPG-18/18 Dimethicone, Octyldodecanol, PEG-30, Dipolyhydroxystearate, Isononyl Isononanoate, Glycerin, Sodium Chloride, Disteardimonium Hectorite, Propylene Carbonate, Polysorbate 20, PEG-40 Sorbitan Peroleate, Stearic Acid, Aluminium Hydroxide, Xanthan Gum,

Tocopheryl Acetate, Retinyl Palmitate, Trisodium EDTA, Phenoxyethanol, Ethylhexylglycerin.

May Contain: Titanium Dioxide (Cl 77891), Iron Oxides (Cl 77489, Cl 77491, Cl 77492, Cl 77499) Yellow 5 Lake (CI 19140), Red 7 Lake (CI 15850).

http://beautyhdcosmetics.com/product/second-skin-silicone-based-airbrush-foundations-30ml/

Second Skin Silicone-Based Airbrush Foundation

Ingredients:
Aqua (water), Glycerin, Propylene Glycol, Copolymer, PEG-12, Phenoxyethanol, Trisodium EDTA, Dimethicone, Cyclopentasiloxane, Sericite, Titanium Dioxide, Zinc Oxide. May contain: Iron Oxides, Micas.

Thank you for your consideration of this information.

Alexandra Scranton
Director of Science and Research
Women's Voices for the Earth

WOMEN'S VOICES FOR THE EARTH

OUR HEALTH. OUR FUTURE. TOXIC FREE.

By email: cirinfo@cir-safety.org

September 9, 2021

To: Cosmetic Ingredient Review Expert Panel Members and Liaisons,

I am writing on behalf of Women's Voices for the Earth to provide comments on the Methicones and Silicates safety assessments.

In both the Safety Assessment for Methicones and the Safety Assessment for Silicates, a draft conclusion has been made that the data is "safe in cosmetics in the present practices and concentrations of use", but "insufficient to make a determination of safety for the utilization of these ingredients with airbrush use". This appears based on discussions at previous meetings by CIR panel members that the new paper indicating that significant proportions of airbrush particle sizes are respirable did not constitute enough to be considered "sufficient data". This is in contrast to the CIR's often-used claim that 95-99% of particles from cosmetic sprays are not respirable, for which the CIR assumes there is sufficient data.

In reviewing the available data, it appears however, that there is actually an equivalent amount of data on the particle size distributions from cosmetic pump sprays and cosmetic aerosol sprays, as there is on particle sizes from cosmetic airbrush sprays.

Specifically, the CIR's respiratory exposures document (boilerplate) states:

"The CIR Expert Panel noted that, in practice, 95% to 99 % of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters greater than 10 µm."

The data cited in this document to back up this statement include the following four citations:

CIR staff annotation: The above statement WVE cited is not exactly what appears in CIR Respiratory Exposure Resource Document (the Document). The original version is shown as the following:

"*The CIR Expert Panel has previously noted that in practice, 95% to 99% of the droplets/particles released from cosmetic **pump** and **propellant hair sprays** have aerodynamic equivalent diameters greater than 10 µm. While **a larger fraction** of respirable particles would release from **propellant deodorant sprays**, the realistic consumer exposure is generally many times lower compared to the amount calculated with the in silico models.*" (see page 5 at https://www.cir-safety.org/sites/default/files/RespiratoryExposure%20-

%20Zhu%20-%202019.pdf)

Thus, the statement in the Document intends to distinguish pump, propellant hair sprays with propellant deodorant sprays, and clearly indicates more particles in the respirable size range (a larger fraction of respirable particles) would release during usage of propellant deodorant sprays. Given new data regarding particle size distribution of aerosolized nano-enabled consumer products, e.g., airbrush makeup foundation, have been incorporated into the revised Document, such statement has been removed and additional caveat language has been added.

Citation 1. Rothe H, Fautz R, Gerber E, et al. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. Toxicol Lett. 2011;205(2):97-104.

Citation 10. Rothe H. Special aspects of cosmetic spray safety evaluation. 2011. Unpublished information presented to the 26 September CIR Expert Panel. Washington D.C. .

Citation 17: Bremmer HJ, Prud'homme de Lodder LCH, van Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. Bilthoven, Netherlands 2006 2006. RIVM 320104001/2006. http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf. Accessed 8/24/2011. Pages 1-77.

Citation 23: Delmaar JE, Bremmer HJ. The ConsExpo Spray Model. 2009 2009. RIVM 320104005/2009. http://www.rivm.nl/bibliotheek/rapporten/320104005.pdf

However, if you examine these four citations, they all make claims about cosmetic particle size distributions which are sourced originally from the same single study:

"Tuinman, I.L., (2004) Aerosols from spray cans and trigger sprays. Particle size distributions and spreading in a closed environment. TNO-report: PML2004-C106."

Specifically:

Citation 1 is a paper by Rothe which discusses principles of inhalation risk assessment. With respect to particle size distribution data it states on page 3,

"*Typically, propellant gas sprays may produce proportionate respirable particles or droplets <10um particle size (Bremmer et al., 2006a; Eickmann, 2007a), whereas pump sprays emit larger droplets in a non-respirable range >10 um particle size."*

The "Bremmer et al. 2006a" citation refers to the same report as CIR's citation 23.

CIR staff annotation: Citation 1 is an important review paper that compiles common principles for inhalation risk assessment of cosmetic spray. It also covers some particle size data from previous studies.

Eickmann, 2007a is not a paper in English and thus not cited by CIR Respiratory Exposure Resource Document.

WVE claims herein "*The 'Bremmer et al. 2006a' citation refers to the same report as CIR's citation 23.*", which

is **NOT** correct.

CIR's citation 23 refers to "*23. Delmaar JE, Bremmer HJ. The ConsExpo Spray Model. 2009. RIVM 320104005/2009. http://www.rivm.nl/bibliotheek/rapporten/320104005.pdf.*" (see page 9 at https://www.cir-safety.org/sites/default/files/RespiratoryExposure%20-%20Zhu%20-%202019.pdf), while "*Bremmer et al., 2006a"* refers to the following document:

Bremmer, H.J., Pruˇıd homme de Lodder, L.C.H., van Engelen, J.G.M., **2006a**.Cosmetics Fact Sheet to assess the risk for the consumer. Updated version for ConsExpo 4.
RIVM report 320104001/2006, http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf. "

To be clear, *"Bremmer et al., 2006a"* is a RIVM (Netherlands National Institute for Public Health and the Environment) report published in 2006, which covers some particle size data of various types of sprays, including the data on deodorant sprays that was provided by "*Tuinman, I.L., (2004) Aerosols from spray cans and trigger sprays. Particle size distributions and spreading in a closed environment. TNO-report: PML2004-C106.",* as mentioned by WVE. While CIR's citation 23 refers to a different RIVM report (published in 2009), which introduced the ConsExpo spray model that can be used to estimate the human exposure resulting from the use of propellant sprays and trigger sprays. In addition to *Tuinman, I.L., (2004)*, CIR's citation 23 covers additional data regarding the mass generation rates and particle size distributions of spray cans and trigger sprays, which were provided by the following report:

***Tuinman, I.L. (2007)**. Particle size distributions of aerosols from spray cans and trigger sprays. TNO report august 2007.*

Such data are combined with the dataset from *Tuinman, I.L., (2004)* and used to derive new default values for the ConsExpo Spray Model. As discussed in *New Default Values for the Spray Model (*RIVM, March 2010; at https://www.rivm.nl/sites/default/files/2018-11/New_defaults_for_the_spray_model.pdf), "all deodorants, of which particle size distributions were measured (Tuinman, I.L. 2004; Tuinman, I.L. 2007), were grouped together; every size of the particle size distribution was regarded as a statistical sample of the 'new default' deodorant particle distribution." That is, CIR's citation 23 covers particle size data of deodorant sprays not only from *Tuinman, I.L. 2004*, but also *Tuinman, I.L. 2007*.

Actually, the citation "*Bremmer et al. 2006a*" refers to another RIVM report as CIR's citation 17.

Citation 10 refers to a presentation given to the CIR by the author (Rothe) of Citation 1 in the same year that Citation 1 was published. I think it's safe to assume the presentation was based on the paper that was published that year – which, as noted above, was based on Citation 23.

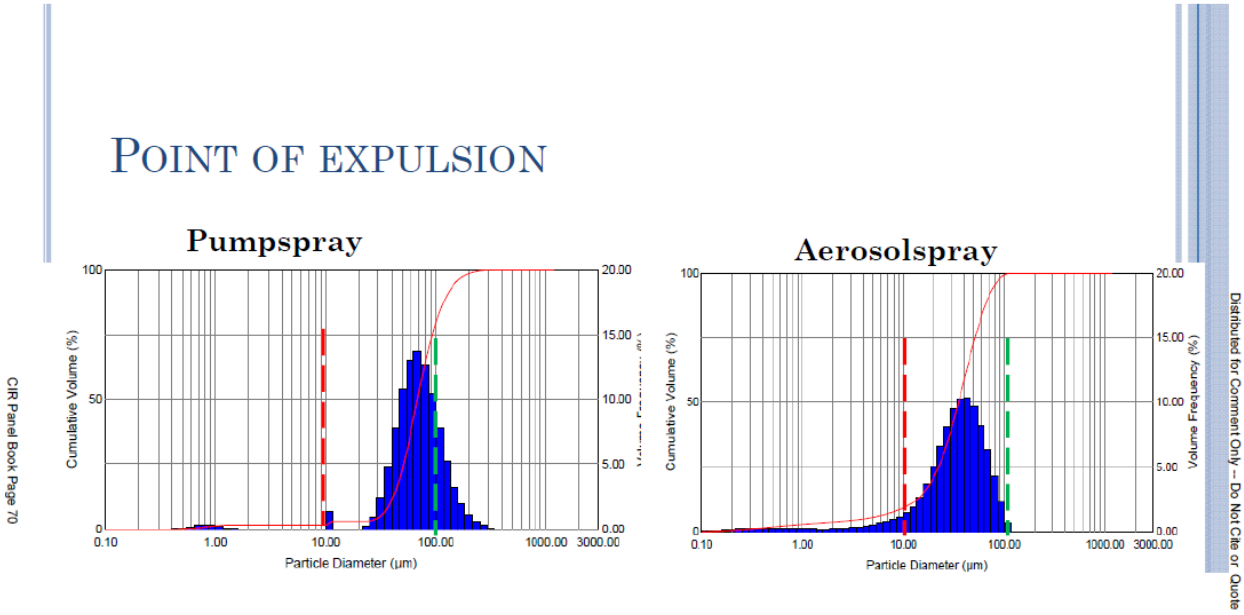
CIR staff annotation: WVE's assumption is **NOT** correct. Dr. Helga Rothe gave a presentation at the September 2011 Panel meeting, namely *Special Aspects of Cosmetic Spray Safety Evaluation*.

Slides of this presentation are available at: https://www.cir-safety.org/sites/default/files/aerosols_w_tabs.pdf

Transcripts of this presentation are available at: https://www.cir-safety.org/sites/default/files/092611-CIR.pdf

When comparing the records of the presentation with Citation 1 of the Document, we may find that the presentation was **NOT** based on the paper that Dr. Helga Rothe published in 2011. Specifically, Dr. Rothe presented additional data to the Panel at the September 2011 meeting with regard to the particle size distribution of pump spray and aerosol spray (propellant); however, such data were not included and discussed in her 2011 paper. As indicated in the presentation, these data sourced from *FEA Guide on Particle Size Measurement from aerosol products*, which can be accessed at https://www.aerosol.org/publications-news/publications/guidance/.

The key particle size data presented in Dr. Rothe's 2011 presentation are shown below:



From FEA Guide on Particle Size Measurement from aerosol products

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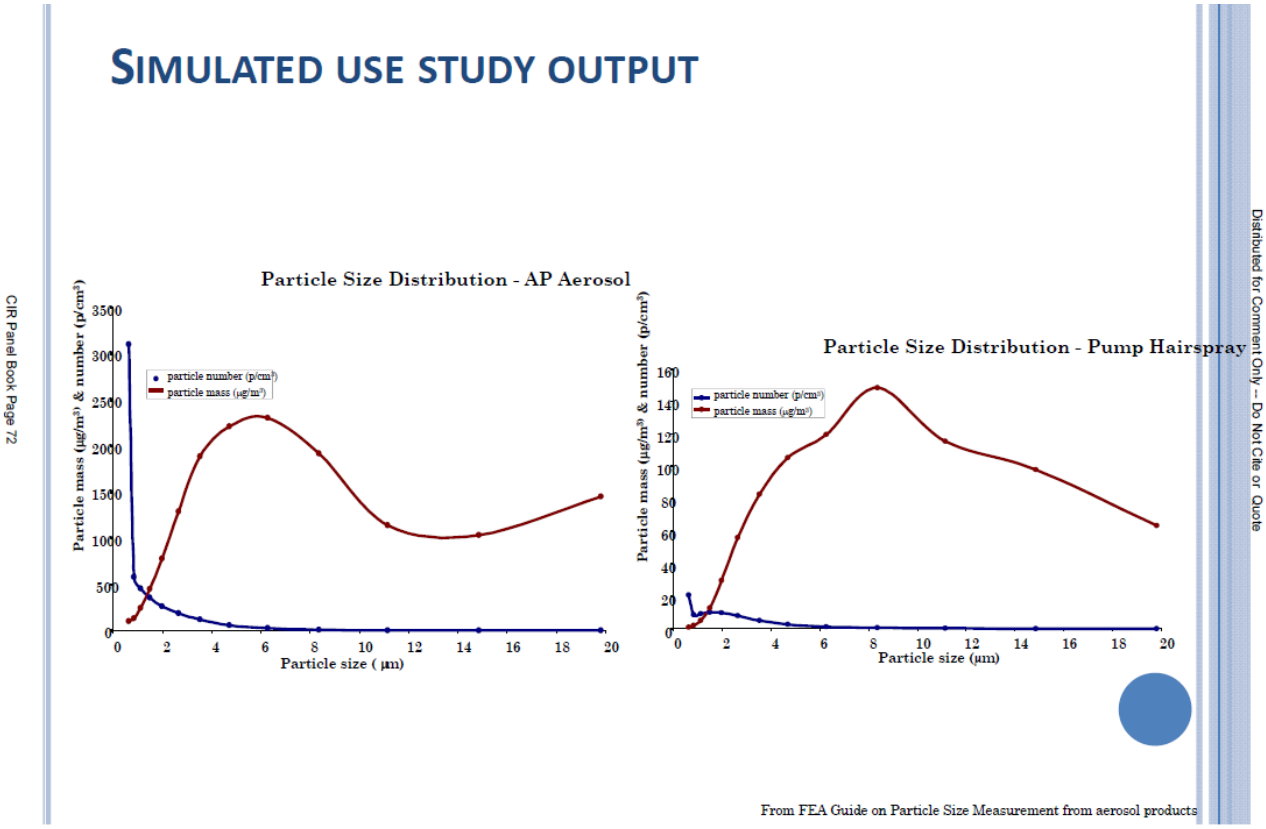
When showing this slide, Dr. Rothe said: "So when we think about the particle size which is then inhaled, we use for these assumptions here the measurement by the point of expulsion. That means the real particle size distribution pattern which comes out of the can at a distance of about 10 to 20 centimeters. You see here the numbers for pump spray and a aerosol spray, and what you can see here, the red line is the 10 micrometers and the 100 micrometers is the green line. And **the mean distribution of a pump spray is larger** -- it depends really from product to product. It's always **in the range between 60 and 80** I would say in the mean. The **aerosol spray is a little bit smaller**. It depends also again from product to product and for the

hairsprays it's **usually around 30, 40, 50, 25**, something in this range. But the important point here is the particle size, which is **below 10 microns**. And you can see for the **pump spray** it's **really below one percent**. It's really extremely small but you still see some of it. **For an aerosol spray it's also very, very small.** It's usually **in the range of two percent, one percent, two and a half percent**. It's always small but I would say **never above five percent**. So nothing I have ever seen is above five percent but I wouldn't exclude that there is sometimes something."(see page 20 – 21, at https://www.cir-safety.org/sites/default/files/092611-CIR.pdf)



When showing this slide, Dr. Rothe said: "So another option is the simulated use studies to do a measurement in the breathing zone…The output you get here is the respirable dose and the inhalable dose, but as I said at the beginning, all the different kinds of measurements, the different methods, have advantages and disadvantages and have their **limitations** here. So, you see here the outcome of such a study and don't get confused here. The scale on the X-axis is going **only** to 20 microns, so **it's not really the whole distribution pattern.** So, when you remember what I showed you at the beginning, **the distribution pattern which was going up to 150 microns**, you **see here only the very, very small portion which is below 20 microns.** So that's important to note. And also, when you look at the Y-axis, so you have here an ADPO aerosol on the left hand side and a pump hairspray on the right hand side, but **the scale is more than one magnitude of order lower for the pump spray**. So, but what you can measure here is not the percentage of mass volume, so the particle size distribution. What you measure here **is really the particle number or the**

particle mass in (inaudible) cubic centimeter. And what you can see here is that the particle number by itself is extremely low in all -- in both cases. And 16 depending on the chemical you are looking to, then the particle mass is showing a peak."(see page 21 – 23, at https://www.cir-safety.org/sites/default/files/092611-CIR.pdf)

Citation 17 is a fact sheet written by RIVM, (The National Institute for Public Health and the Environment in the Netherlands) which reports on particle size distribution on three samples of an aerosol hair spray and three samples of aerosol deodorant spray. The data in the fact sheet is referenced as coming from

"Tuinman, I.L., (2004) Aerosols from spray cans and trigger sprays. Particle size distributions and spreading in a closed environment. TNO-report: PML2004-C106."

Citation 23 is a more lengthy report written by RIVM which both reports and displays the same hair spray and aerosol deodorant spray data mentioned in the fact sheet (Citation 17) and again cites the data as "described in detail in Tuinman (2004)".

The particle size distribution data from Tuinman (2004), as displayed in Citation 23 is the following:

rivm

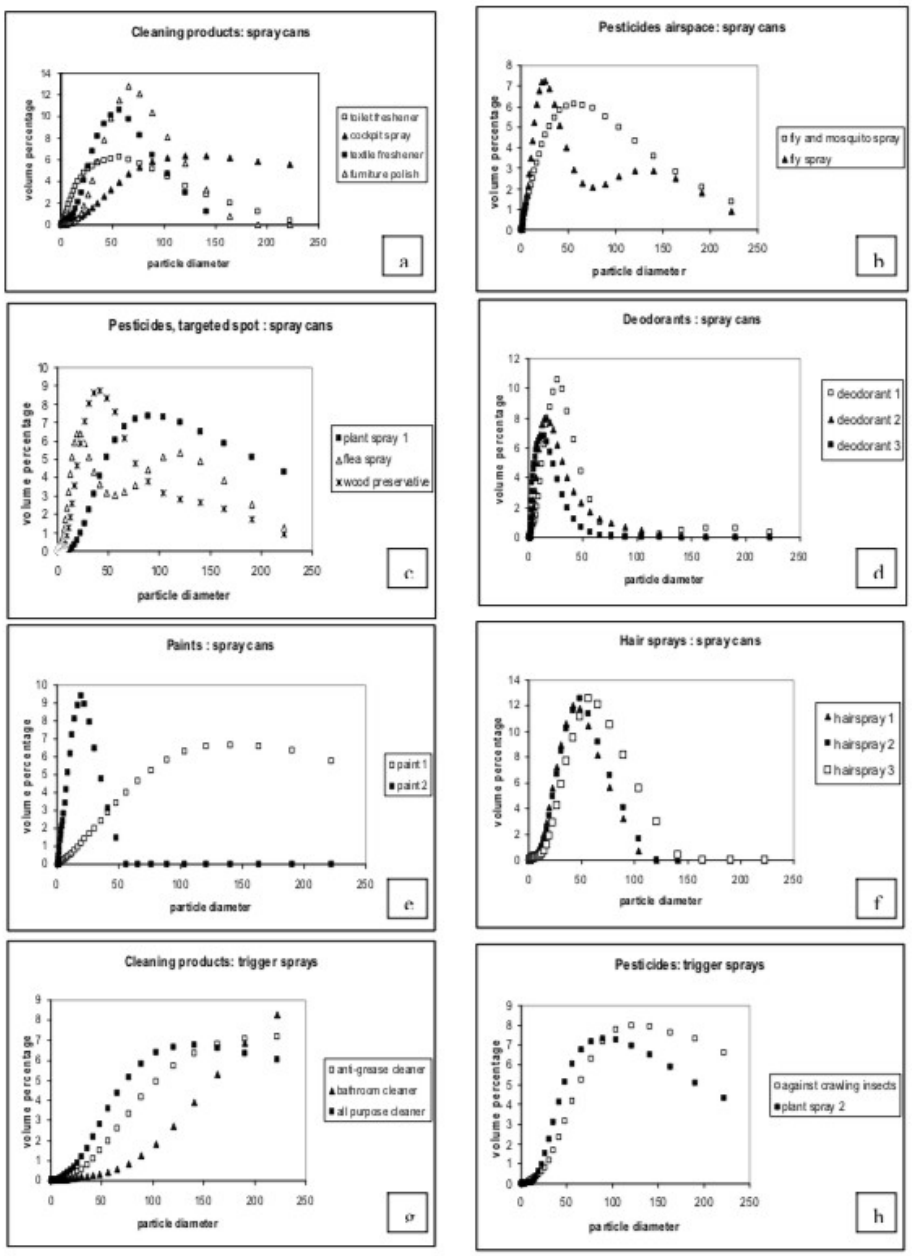


Figure 1a-h: Experimental particle size distributions for consumer products in spray cans and trigger sprays grouped according to product category, use category and container type (spray can or trigger spray).

Note that the scale of these particle size distribution graphs is in microns. One can see that for the three hairspray samples, the bulk of the curve represents particles larger than 10 microns. But forthe deodorant sprays, about half of the curve falls below the 10 micron particle size.

To repeat, all of the data cited in the CIR's respiratory exposures document (with respect to cosmetic spray particle size) are sourced from this data from this single paper.

CIR staff annotation: As described above, CIR's citation 17 refers to "Bremmer et al. 2006a", which provided part of the particle size data of deodorant sprays, while more data were covered in CIR's citation 23, i.e., the final spray parameters of deodorants applied in the ConsExpo Spray Model analysis, including measured particle size distributions as well as mass generation rates of deodorant sprays, are the combination of the original dataset (Tuinman, I.L., 2004) with the data obtained from Tuinman, I.L., 2007. More discussion on the data source and their applications can be found in a RIVM document, titled *New Default Values for the Spray Model (*RIVM, March 2010; at https://www.rivm.nl/sites/default/files/2018-11/New_defaults_for_the_spray_model.pdf).

What's more, particle/droplet size data were also provided by industry survey, e.g., the following data have already included in the previous version of the Document:

"*Propellant deodorant/antiperspirant sprays have consistently smaller median particle/droplet size than propellant hair sprays. The mean (SD) values of Dv90, Dv50 and Dv10 of droplets/particles released from propellant deodorant/antiperspirant sprays are 4.1 (2.6), 23 (33.2), and 35.3 (7.6) µm, respectively. In addition, the percentage of respirable particles/droplets (% < 10 µm) is 3.24 ± 4.48 and 26.6 ± 13.4 (mean ± SD) for propellant hair sprays and deodorant/antiperspirant sprays, respectively.* " (see page 4 at https://www.cir-safety.org/sites/default/files/RespiratoryExposure%20-%20Zhu%20-%202019.pdf)

In sum, considering additional data regarding particle properties of diverse sprayers were provided by Tuinman, I.L., 2007 report, by industry survey, as well as by Dr. Rothe's 2011 presentation (supporting data came from *FEA Guide on Particle Size Measurement from aerosol products)*, WVE's judgement that "*data cited in the CIR's respiratory exposures document are sourced from this data from this single paper"* is **NOT** right.

To contrast, there is the Pearce (2019) paper, previously submitted to the CIR, which reported data on cosmetic airbrush spray particle size distribution.

Pearce K, Goldsmith WT, Greenwald R, Yang C, Mainelis G, Wright C. Characterization of an aerosol generation system to assess inhalation risks of aerosolized nano-enabled consumer products. Inhal Toxicol. 2019 Aug-Aug;31(9-10):357-367. doi: 10.1080/08958378.2019.1685613.

I have copied here the particle size distribution data presentations from this paper as well.

Particle size distribution cosmetic airbrushes from Pearce (2019)

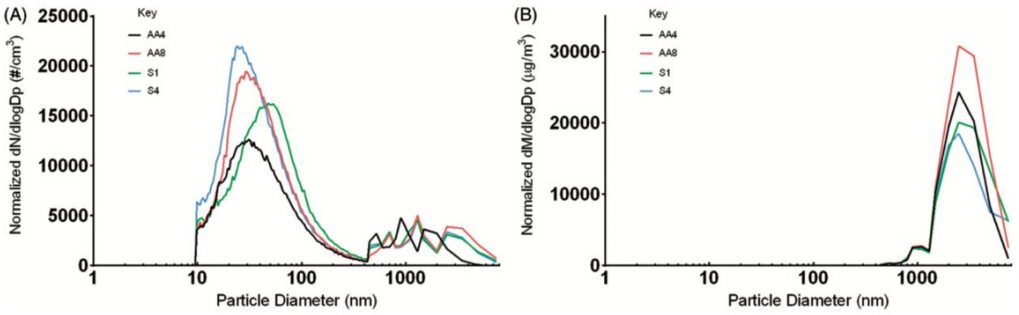


Figure 2. Mean size distribution of aerosols generated by the investigated original products as determined by a scanning mobility particle sizer (SMPS) and an optical particle sizer (OPS) over 20 minutes using the 10 mg/m^3 target level. Panel A displays the size distribution by number and Panel B displays the size distribution by mass.

Based on this side-by-side comparison, I do not understand why the Expert Panel claims thatthe information on particle size distribution for airbrush technology is insufficient, while the information on particle size distribution for other cosmetic sprays is sufficient.

CIR staff annotation: The Panel last reviewed the Respiratory Exposure Resource Document at the September 2019 meeting, while the Pearce 2019 paper was published after October 2019.

In addition, the following Pearce 2020 paper has been identified by CIR staff:

Pearce KM, Okon I, Watson-Wright C. Induction of Oxidative DNA Damage and Epithelial Mesenchymal Transitions in Small Airway Epithelial Cells Exposed to Cosmetic Aerosols. *Toxicol Sci.* 2020;177(1):248-262.

In this paper, aerosol monitoring data generated from Pearce 2019 study were further utilized to determine potential inhaled dose in human lungs as well as in vitro concentrations for epithelial cell treatment, using multiple path particle dosimetry (MMPD) model. That is, both Pearce 2019 and 2020 papers are based on the **same set** of particle size measurements, i.e., the aerosol properties of four airbrush makeup products, including a light and dark shade of foundation from each expensive or inexpensive cosmetic line respectively, have been examined during simulated realistic makeup application utilizing a fully automated aerosol generation system. Data presented in these two papers suggested that a fraction of airborne particles/agglomerates resulting from airbrush delivery are respirable (i.e., the majority of particles with diameters ≤ 100 nm, and the majority of the collected aerosols contained agglomerates sized < 2 µm), and all of the four investigated airbrush makeup products may have similar size distributions. What's more, Pearce 2020 paper revealed that collected aerosols during airbrush application can induce oxidative DNA damage and epithelial mesenchymal transition in vitro (within human small airway epithelial cells).

These "newly" identified data have been incorporated into the next iteration of CIR Respiratory Exposure Resource Document, which is about to be reviewed at the coming December 2021 Panel meeting. Safety concerns as well as relevant regulatory issues regarding inhalation exposure to nanosized metal oxide during the use of airbrush makeup devices, such as TiO_2 and Fe_2O_3, have been discussed therein. Meanwhile, it is worthy to note that neither Methicones nor Silicates were examined or discussed in both Pearce 2019 and 2020 papers. The safety concerns raised by these two studies are mainly related to the incorporated metal nanoparticles in the original airbrush makeup products, which are now found can be emitted into the consumer breathing zone during the airbrush applications.

If the CIR is interested in incorporating additional sources of data on non-airbrush cosmetic sprays, there are two other papers that may be of interest:

Nazarenko Y, Han TW, Lioy PJ, Mainelis G. Potential for exposure to engineered nanoparticles from nanotechnology-based consumer spray products. J Expo Sci Environ Epidemiol. 2011;21(5):515-528. doi:10.1038/jes.2011.10

(This paper was submitted to the CIR several years ago and resulted in a presentation by Dr. Nazerenko to the CIR.)

Halbert MK, Mazumder MK, Bond RL. Size-distribution analysis of respirable particulates in cosmetic aerosols: a methodological comparison. Food Cosmet Toxicol. 1981 Feb;19(1):85-8. doi: 10.1016/0015-6264(81)90308-4. PMID: 7262736.

CIR staff annotation: Nazarenko et al. 2011 paper examined the inhalation exposure to nanotechnology-based consumer spray products, which covers four types of cosmetic sprays, i.e., regular hair spray vs. hair nanospray, as well as regular facial spray vs. facial nanospray; while the rest consumer products under investigation were not cosmetics, e.g., silver nanospray used for against bacteria, disinfectant nanospray used as sanitizer and deodorizing cleaner for use on hard surfaces, wheel nanocleaner to quickly penetrate and remove tough brake dust from wheel surfaces, etc. The data from this paper indicated that the use of nanotechnology-based spray and regular spray products may result in inhalation exposures to single nanosized particles and multi-sized agglomerates (size ranging from 13 nm to 20 μm), including complex nanoparticle-containing composites. As WVE mentioned, this paper was once submitted to the CIR and resulted in a presentation by Dr. Nazerenko to the CIR. Note that Dr. Nazerenko's presentation at the September 2017 Panel meeting covered the particle size data from this paper, which had been cited in CIR Respiratory Exposure Resource Document as citation 28 (Dr. Nazerenko's presentation slides are available at https://www.cir-safety.org/sites/default/files/nazarenko_presentation.pdf). While this paper did not clearly clarify how to define/categorize Hair Nanospray as well as Facial Nanospray, the relevant particle size data has been added to the updated Document and for the following discussion:

"However, given the use of nanotechnology-based cosmetics can lead to respiratory exposure to single and agglomerated nanoparticles, the knowledge of the external, the systemic and in particular respiratory tract exposure of potential toxicities and their doses is necessary for the determination of safe exposure levels."

Halbert et al. 1981 paper evaluated one pressurized hair spray and four types of antiperspirant sprays, including a pump spray, a fluorocarbon propelled spray, an isobutane-propane propellant spray, and a spray powder. The data showed that the pressurized aerosol products produced particulates with count median diameters of 0.6 - 1.5 µm and mass median diameters of 2.2 - 3.2 µm. However, due to the limited description of the experimental design, it is not clear to what extent such study mimicked the realistic consumer use conditions. Considering it is a paper published thirty years ago, the cosmetic formulations, the spraying devices as well as particle characterization equipment have undergone significant development in the past several decades, this paper is not included in the updated CIR Respiratory Exposure Resource Document. But if the Panel requested, it would be covered.

However, it is worth noting neither paper supports the CIR's assertion that 95-99% of particles from cosmetic sprays are not respirable, but rather that much greater proportions of particles may be inhaled more deeply into the lungs.

Thank you for your consideration of these comments, and hope they are helpful to your discussion.

Sincerely,

Alexandra Scranton
Director of Science and Research
Women's Voices for the Earth

CIR History of

Dimethicone, Methicone, and Substituted-Methicone Polymers (formerly 20, now, 30 ingredients)

August 1998: Scientific Literature Review published

June 1999 Panel Meeting: The first draft report was assessed, and the Panel issued an IDA for methods of manufacture, UV absorption data, and dermal reproductive and developmental toxicity data.

September 1999 Panel Meeting: The Panel unanimously concluded that the ingredients in the Methicone ingredient family are safe for use in cosmetics, with the understanding that forthcoming reports would include discussion on cautionary elements (such as the potential for inhalation exposure), and information on chemistry, delivery systems, and Dimethicone use levels. The issuance of a Tentative Report was approved.

September 1999: Tentative Report published

February 2000 Panel Meeting: The Panel requested for clarification of minor differences between the reported use of Dimethicone polymers by the cosmetics industry and the FDA. A skin irritation study describing necrosis was attributed to mineral spirits, and not Dimethicone, and was hence removed. The Panel voted unanimously in favor of issuing a Final Report with a safe as used conclusion.

February 2000: Final Report published

December 2019: A Re-Review was presented to the Panel. Due to substantial increases in frequency of use and concentrations of use for these ingredients, the Panel unanimously agreed to reopen this report.

June 2020: A Draft Amended Report was presented to the Panel, along with 11 additional ingredient suggestions (including Simethicone), from the CIR Scientific Support Committee. The Panel approved the addition of 10 ingredients, excluding Simethicone, and issued a Tentative report.

July 2020: Council comments on the Tentative report were received.

October 2020: Concentration of use data for 10 Methicones add-on ingredients were received.

December 2020: A Draft Final Amended Report was presented to the Panel. In light of positive ocular irritation data for concentrations nearing those of present use, the Panel decided that these ingredients are safe when formulated to be non-irritating. Upon knowledge of these ingredients being used in airbrush cosmetics, which are potentially respirable, the Panel saw the need for the following data to determine safety for ingredients in products delivered via airbrush technology:

- particle size distribution, present concentrations of use, and if the particles are considered of respirable size, respiratory toxicity data
- information on methods of use, including exposure duration and frequency (e.g., daily, brief foundation application, compared to periodic, but longer suntan spray exposure).

The Panel therefore issued a revised Tentative Amended Report, with a split conclusion, of safe as used at the present concentrations and practices of use, when formulated to be non-irritating, but that the data are

insufficient to support the safety of products containing these ingredients when applied via airbrush technology. None of the requested data was received.

January 2021: Updated VCRP data were received from the FDA and have been incorporated in the report.

September 2021: A Draft Final Amended Report was presented to the Panel. Upon receiving a memo with data and references suggesting respirable particle sizes resulting from cosmetic sprays and deodorants, the Panel asserted the need for more data on current uses, concentrations, and particle size distributions of these ingredients in products that could be incidentally inhaled. Additionally, with the rise of non-professional, personal use, the Panel requested more information on the relevant parameters of devices used to apply cosmetics via airbrush, and other technologies creating potentially respirable particles. The Panel reasoned that these additional data are necessary to make a determination of safety for this product category.

Thus, the Panel issued a revised Tentative Amended Report, with the conclusion that these ingredients are safe as used in the present practices of use and concentration as described in the safety assessment when formulated to be non-irritating; however, the Panel also concluded that the data are insufficient to support the safety of products that may be incidentally inhaled.

October 2021: Council comments on the revised Tentative Amended Report were received

December 2021: A Draft Final Amended Report is being presented to the Panel.

Methicones Data Profile* – December 6-7, 2021 – Preethi S. Raj																														
	Use				Toxico-kinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	New Rpt	Old Rpt	Method of Mfg	Impurities	log P/log K_{ow}	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Amino Bispropyl Dimethicone	X																													
Aminopropyl Dimethicone	X																													
Amodimethicone	X	O																												
Amodimethicone Hydroxystearate																														
Behenoxy Dimethicone	X	O																												
C20-24 Alkyl Dimethicone	X																													
C20-24 Alkyl Methicone																														
C24-28 Alkyl Dimethicone																														
C24-28 Alkyl Methicone	X	O																												
C26-28 Alkyl Dimethicone	X																													
C26-28 Alkyl Methicone																														
C30-45 Alkyl Dimethicone	X	O		X				X								X					X									
C30-45 Alkyl Methicone	X																													
C30-60 Alkyl Dimethicone																														
C32 Alkyl Dimethicone																														
Capryl Dimethicone	X																													
Caprylyl Methicone	X				X	X	X	X	X			X			X	X	X				X			X				X		
Cetearyl Methicone	X	O																												
Cetyl Dimethicone	X	O	O	O																										
Dimethicone	X	O	O	O	O	OX	OX	OX	OX	OX	OX	OX	O	O	O	OX		O	OX		OX	O		OX	OX			OX		X
Dimethoxysilyl Ethylenediaminopropyl Dimethicone	X																													
Hexyl Dimethicone	X																													
Hexyl Methicone										O																				
Hydroxypropyldimethicone																														
Methicone	X	O						O	O	O																		O		
Stearamidopropyl Dimethicone																														
Stearoxy Dimethicone	X	O	O	O																										
Stearyl Dimethicone	X	O	O	O																										
Stearyl Methicone	X																													
Vinyldimethicone	X							O	O	O											O				O			O		

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

[Methicones (years 1998 forward)- 10/19/2021]

Ingredient	CAS #	Info Base	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Amino Bispropyl Dimethicone	**189959-16-8** 999002112 243842-22-0	✓	1/0	NR	NR	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Aminopropyl Dimethicone	977185264 **99363-37-8**	✓	1/0	NR	NR	✓*	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Amodimethicone	977091647 106842-44-8 **68554-54-1** 71750-79-3	✓	2/0	1?	NR	✓*	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Amodimethicone Hydroxystearate	NR	✓	1/0	NR	NR	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Behenoxy Dimethicone	**977136745 193892-43-2**	✓	1/0	NR	NR	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
C20-24 Alkyl Dimethicone	**200074-76-6**	✓	0/0	NR	NR	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
C24-28 Alkyl Dimethicone	**192230-29-8**	✓	4/0	NR	NR	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
C26-28 Alkyl Dimethicone	NR	✓	0/0	NR	NR	NR	NR	NR	NR	NR	NR	✓*	NR	NR	NR	NR	NR	NR	
C30-60 Alkyl Dimethicone	NR	✓	0/0	NR	NR	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
C32 Alkyl Dimethicone	NR	✓	0/0	NR	NR	✓*	NR	NR	NR	NR	NR	NR	✓*	NR	NR	NR	NR	NR	
C20-24 Alkyl Methicone	**200074-77-7**	✓	0/0	NR	NR	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
C24-28 Alkyl Methicone	**189378-12-9** 158061-44-0	✓	1/0	NR	NR	NR	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
C26-28 Alkyl Methicone	**189378-12-9**	✓	0/0	NR	NR	✓*	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
C30-45 Alkyl Methicone	977144016 **189378-12-9** 246864-88-0	✓	1/0	NR	NR	NR	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
C30-45 Alkyl Dimethicone	**170831386**	✓	1/0	NR	NR	NR	NR	NR	NR	NR	NR	✓	NR	NR	NR	NR	NR	NR	
Capryl Dimethicone	NR	✓	0/0	1/0	NR	✓*	NR	NR	NR	NR	NR	NR	✓*	NR	NR	NR	NR	NR	
Caprylyl Methicone	**17955-88-3**	✓	0/0	0/0	NR	✓*	✓	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Cetearyl Methicone	**977183359**	✓	1/0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Cetyl Dimethicone (Cetyl dimethicone 25)	977114263 **191044-49-2**	✓	11/1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Dimethicone (Dimethylpolysiloxane, Dimethylsilicone fluid/oil, Polydimethylsiloxane)	9016-00-6 **9006-65-9**	✓	23/5	✓	NR	NR	NR	NR	NR	✓	NR	✓*	NR	✓*	NR	✓	NR	NR	
Dimethoxysilyl Ethylenediaminopropyl Dimethicone	**71750-80-6**	NR	1/0	NR	NR	NR	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Hexyl Dimethicone	NR	✓	9/0	1/0	NR	✓*	NR	NR	NR	NR	NR	NR	✓*	NR	NR	NR	NR	NR	

Ingredient	CAS #	Info Base	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Hexyl Methicone	**1873-90-1**	✓	1/0	NR	NR	NR	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Hydroxypropyldimethicone	**102782-61-6**	✓	2/0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Methicone	63148-57-2 **9004-73-3**	✓	2/1	NR	NR	NR	NR	NR	NR	NR	NR	✓*	NR	NR	NR	NR	NR	NR	
Stearamidopropyl Dimethicone	110475-03-1	✓	1/0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Stearoxy Dimethicone	**68554-53-0**	✓	1/0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Stearyl Dimethicone	977094464 **67762-83-8**	✓	2/0	✓*	NR	NR	NR	NR	NR	NR	NR	✓*	NR	NR	NR	NR	NR	NR	
Stearyl Methicone	**977130247** 67762-83-8	✓	2/0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Vinyldimethicone	**53529-60-5**	NR	1/0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	

Bolded CAS number -number most recognized by
NR – not reported or available
✓ - data is available
✓*- in database, but data is not available or relevant
total # of hits/total # useful

Search Strategy

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

[*In PubMed*- 622/4]

Group search; note: also searched for ingredients individually

((((((((((((((((((((stearoxy dimethicone) OR dimethicone) OR dimeticone) OR methicone) OR amino bispropyl dimethicone) OR aminopropyl dimethicone) OR amodimethicone) OR amodimethicone hydroxystearate) OR behenoxy dimethicone) OR c24-28 alkyl methicone) OR c30-45 alkyl methicone) OR c30-45 alkyl dimethicone) OR cetearyl methicone) OR cetyl dimethicone) OR dimethoxysilyl ethylenediaminopropyl dimethicone) OR hexyl methicone) OR hydroxypropyldimethicone) OR stearamidopropyl dimethicone) OR stearyl dimethicone) OR stearyl methicone) OR vinyl dimethicone) AND [search terms listed below]

Pubmed search on 06/24/2021

Methicone toxicity – 15/2

((((((((((((((((((((((((((((amino bispropyl dimethicone) OR (aminopropyl dimethicone)) OR (amodimethicone)) OR (amodimethicone hydroxystearate)) OR (behenoxy dimethicone)) OR (c20-24 alkyl dimethicone)) OR (c20-24 alkyl methicone)) OR (c24-28 alkyl dimethicone)) OR (c24-28 alkyl methicone)) OR (c26-c28 alkyl dimethicone)) OR (c26-28 alkyl methicone)) OR (c30-45 alkyl dimethicone)) OR (c30-45 alkyl methicone)) OR (c30-60 alkyl dimethicone)) OR (c32 alkyl dimethicone)) OR (or capryl dimethicone)) OR (caprylyl methicone)) OR (cetearyl methicone)) OR (cetyl dimethicone)) OR (dimethicone)) OR (dimethoxysilyl ethylenediaminopropyl dimethicone)) OR (hexyl dimethicone)) OR (hexyl methicone)) OR (hydroxypropyldimethicone)) OR (methicone)) OR (stearamidopropyl dimethicone)) OR (stearoxy dimethicone)) OR (stearyl dimethicone)) OR (stearyl methicone)) OR (vinyl dimethicone)) AND (toxicity) – 18/1

Search for add-on ingredients in Pubmed and TOXNet (10/10/2020):

((((((((((((((c20-24 alkyl dimethicone) OR (200074-76-6)) OR (c24-28 alkyl dimethicone)) OR (192230-29-8)) OR (c26-28 alkyl dimethicone)) OR (c30-60 alkyl dimethicone)) OR (c32 alkyl dimethicone)) OR (200074-77-7)) OR (c20-24 alkyl methicone)) OR (189378-12-9)) OR (c26-28 alkyl methicone)) OR (capryl dimethicone)) OR (17955-88-3)) OR (caprylyl methicone)) OR (hexyl dimethicone)) AND (toxicity) – 1/0

tox [subset] AND c20-24 alkyl dimethicone -0/0;
OR c24-28 alkyl dimethicone – 1/0;
OR c26-c28 alkyl dimethicone -0/0;
OR c30-60 alkyl dimethicone – 0/0;
OR c32 alkyl dimethicone - 0/0;
OR c20-24 alkyl methicone – 0/0;
OR c26-28 alkyl methicone – 0/0;
OR capryl dimethicone – 1/0;
OR caprylyl methicone – 0/0;
OR hexyl dimethicone – 9/0

Updated search on 10/12-10/19/2021
((((((((((((((((((((((((((((amino bispropyl dimethicone) OR (aminopropyl dimethicone)) OR (amodimethicone)) OR (amodimethicone hydroxystearate)) OR (behenoxydimethicone)) OR (c20-24 alkyl dimethicone)) OR (c20-24 alkyl methicone)) OR (c24-28 alkyl dimethicone)) OR (c24-28 alkyl methicone)) OR (c26-28 alkyl dimethicone)) OR (c26-28 alkyl methicone)) OR (c30-45 alkyl dimethicone)) OR (c30-45 alkyl methicone)) OR (c30-60 alkyl dimethicone)) OR (c32 alkyl dimethicone)) OR (capryl dimethicone)) OR (caprylyl methicone)) OR (cetearyl methicone)) OR (cetyl dimethicone)) OR (dimethicone)) OR (dimethoxysilyl ethylenediaminopropyl dimethicone)) OR (hexyl dimethicone)) OR (hexyl methicone)) OR (hydroxypropyldimethicone)) OR (methicone)) OR (stearamidopropyl dimethicone)) OR (stearoxy dimethicone)) OR (stearyl dimethicone)) OR (stearyl methicone)) OR (vinyl dimethicone))
AND (toxicity)– 20/0; Pubmed alert: 2 hits/ 1 useful
AND (nanoparticles) – 6/0

[*In PubChem,TOXNet, ECETOC, NICNAS, ECHA, Google, Google Scholar, Research Gate*-12/7]
Linear silicones; Linear polysiloxanes; Method of manufacturing; Impurities, Dermal toxicity; Dermal sensitization; Dermal irritation; In vivo toxicity; In vitro toxicity; Toxicity; Eye irritation; Ocular irritation; Vaginal irritation; Cytotoxicity; Genotoxicity; Carcinogenicity; Mutagenicity; Developmental toxicity; Reproductive toxicity; Safety; Epidemiology; Silicone animal studies

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)
- Toxnet (https://toxnet.nlm.nih.gov/); (includes Toxline; HSDB; ChemIDPlus; DART; IRIS; CCRIS; CPDB; GENE-TOX)

appropriate qualifiers are used as necessary
search results are reviewed to identify relevant documents

- Connected Papers - https://www.connectedpapers.com/

Pertinent Websites

- wINCI - http://webdictionary.personalcarecouncil.org

- FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse
- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- EAFUS: http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true
- GRAS listing: http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm
- SCOGS database: http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm
- Indirect Food Additives: http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives
- Drug Approvals and Database: http://www.fda.gov/Drugs/InformatioNRnDrugs/default.htm
- http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf
- FDA Orange Book: https://www.fda.gov/Drugs/InformatioNRnDrugs/ucm129662.htm
- OTC ingredient list: https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm135688.pdf
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/

- HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/

- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
- OECD SIDS (Organisation for EcoNRmic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- NICNAS (Australian National Industrial Chemical NRtification and Assessment Scheme)- https://www.nicnas.gov.au/

- International Programme on Chemical Safety http://www.inchem.org/
- 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) technical reports - http://www.who.int/biologicals/technical_report_series/en/

- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

ORIGINAL ASSESSMENT

JUNE 1999 PANEL MEETING – ORIGINAL ASSESSMENT/DRAFT REPORT

Full Panel – June 14-15, 1999

Dr. Schroeter indicated that his Team determined that an informal data request consisting of the following items should be issued:

(1) Methods of manufacture
(2) UV absorption data
(3) Dermal reproductive and developmental toxicity data

Dr. Belsito noted that after reviewing numerous reproductive toxicity studies, his Team identified minimal effects on the seminal vesicles that were considered insignificant by Dr. Carlton, and, overall, determined that the available data in the report are sufficient for evaluating the safety of this group of ingredients. However, Dr. Belsito said that his Team recommended that the report be tabled due to concern that a body of data from Industrial Bio-Test Laboratories (which, in the past, has come under question) should be removed from the document.

Dr. Bergfeld noted that, on the preceding day, Dr. Schroeter's Team had a lengthy discussion on testicular effects (decreased spermatogenesis and testicular size) that were reported.

Dr. Shank indicated that his Team has not seen these data, from Industrial Bio-Test. He agreed that all of the Industrial Bio-Test data should be removed from the present report, but also indicated that the findings have generated concern over the effects of these chemicals on the testis.

Dr. Bergfeld noted that another question that was raised in Teams relates to the inhalation toxicity of these chemicals. She recalled that the particle size was considered small, giving rise to little or no concern about potential pulmonary effects. She recommended that this concern be included in the report discussion at a future date.

The Panel voted unanimously in favor of tabling the Stearoxy Dimethicone report.

Dr. Bergfeld said that the report is being tabled with the understanding that the data from Industrial Bio-Test Laboratories will be removed, and that there will be a special look at testicular size and spermatogenesis in reproductive toxicity studies and a special note on inhalation toxicity and particle size in various products.

Dr. Andersen said that in the announcement of the results for this meeting, he will indicate that if any interested party has data relative to decreased spermatogenesis or particle size issues, the Panel would appreciate the submission of these data.

SEPTEMBER 1999 PANEL MEETING - ORIGINAL ASSESSMENT/DRAFT TENTATIVE REPORT

Full Panel – September 9-10, 1999

Dr. Belsito recalled that the Draft Report on these ingredients was reviewed at the June 14-15, 1999 Panel meeting, and, at that time, the data needs were related primarily to inhalation exposure. He noted that because information on the particle size of Dimethicones used in the inhalation study was not received, his Team was unable to evaluate the safety of the Dimethicone group in aerosolized products. However, these ingredients were considered safe as used in other cosmetics products. Dr. Belsito also noted that the Panel made the decision to delete all reproductive toxicity studies that were performed at a testing facility whose test results are regarded as suspect.

Dr. Schroeter noted that the ingredients being reviewed are high molecular weight compounds that are not absorbed, and, therefore, are safe. He also said that the issue of inhalation exposure will have to be addressed in the report discussion.

Dr. Bergfeld asked if the Panel is accepting the proposed safe as used conclusion, with a restriction on the use of these ingredients in aerosolized products.

Concerning the aerosol restriction, Dr. McEwen recalled that the Panel recently addressed the question of inhalation toxicity in another safety assessment by considering the particle size and by developing (using the published literature) a kind of algorithm as to what would or would not be considered a safe particle size. Thus, Dr. McEwen recommended that the Panel conclude that these ingredients are unsafe at certain particle sizes, rather than conclude that these ingredients are unsafe for use in aerosolized products.

Dr. Shank recalled that information on the particle size of Hexyl Methicone (mass median aerodynamic diameter [MMAD] = 0.27 μm), not a cosmetic ingredient, is included in the inhalation toxicity study in the report text. He noted that this study indicates that methicone derivatives have the potential for inhalation toxicity.

Dr. Bergfeld confirmed that this is the only inhalation toxicity study in which information on particle size was given.

Dr. Shank commented that if large particles were used in the other inhalation toxicity studies, then there would be no respiration and the results would be negative.

Dr. McEwen said that, usually, the particle size in an aerosol (10, 15, or 20 μm) is much greater than 0.27 μm. He noted that particles 10-20 μm in diameter are not respirable.

Dr. Bailey said that in the absence of data to demonstrate Dr. McEwen's point, the question of inhalation toxicity remains open.

Dr. Shank asked if the Panel could conclude that the ingredients are safe as used as long as there are no respirable particles.

Dr. Belsito said that the Panel could indicate that the ingredients are safe when formulated so as to avoid particle sizes that are less than a certain diameter.

Dr. Andersen noted that, in this case, the particle size that is respirable is known, but the ingredient particle sizes in cosmetic products are not known.

Ms. Fise said that the Panel has the option of saying that the available data are insufficient until sufficient data for evaluating the safety of these ingredients have been received.

Dr. Bergfeld recalled that the Panel has addressed the issue of pesticide contamination in a way that is similar to what was proposed today for the Stearoxy Dimethicone ingredient family. She said that the Panel has indicated in the report discussion for botanical ingredients certain limitations on pesticide impurities, because data on the pesticide content of these ingredients were not provided.

Ms. Fise proposed that the Panel request information on particle size, such that the Panel can determine exactly what the particle size in cosmetics should be.

Dr. McEwen noted that this information has been provided on other ingredients that have been reviewed by the Panel.

Dr. Andersen said that CIR has information on what is respirable, but does not have data on particle size for products containing the Dimethicones.

Dr. David Bower (with RT Vanderbilt now, formerly with ISP) noted that a similar discussion on particle size took place during the Panel's review of PVP (polyvinylpyrollidone), which is no longer used in cosmetics. He recalled that he was the toxicologist at ISP who provided CIR with data on this ingredient, and said that the following information/comments may be helpful in the present review: Anhydrous hair sprays typically have a particle size (MMAD) of 60 to 80 μm. Typically, less than 1% is under 10 μm. Pump hair sprays and aqueous aerosols typically have a particle size of 80 μm or higher (as much as 120 μm), with much less than 1% under 10 μm. So, if the Panel is concerned about the inhalation dynamics of plasticizers used in hair sprays at a level of approximately 1%, or even less, the following calculations can be done: In the hair spray, 8% resin contains 1% Dimethicone. So, the concentration of Dimethicone in the hair spray is 0.08%, of which less than one-half of 1% is respirable. Calculations such as this can be used to get around the problem of what is respirable and how much is actually exposed.

Dr. Belsito noted that the Panel's concern about inhalation exposure should be included in the report summary and discussion. He said that the exposure assessment described by Dr. Bower (including information on the average particle size in a spray versus a pump) will be incorporated. He added that it is the Panel's expectation that this will be the particle size of any Dimethicone-containing spray, and that it is not respirable.

Dr. Schroeter said that the Panel's conclusion will be safe for use, with the understanding that a report discussion containing cautionary elements and information on chemistry, the delivery systems, and use levels of the Dimethicones will be developed.

The Expert Panel unanimously concluded that the ingredients in the Stearoxy Dimethicone ingredient family are safe for use in cosmetics, with the understanding that a report discussion containing cautionary elements and information on chemistry, the delivery systems, and use levels of the Dimethicones will be developed. The issuance of a Tentative Report on this group of ingredients was approved.

FEBRUARY 2000 PANEL MEETING – ORIGINAL ASSESSMENT/DRAFT FINAL REPORT

Full Panel – February 14-15, 2000

Dr. Schroeter recalled that a Tentative Report with a safe as used conclusion on these ingredients was issued at the September 9-10, 1999 Panel meeting, and that the additional data available since then do not warrant any change in this conclusion. Dr. Schroeter also noted a discrepancy between the uses of Dimethicone polymers in cosmetics reported by FDA (7 uses) versus those that were received from the cosmetics industry (10 uses).

Drs. Bergfeld and Belsito agreed that the basis for the difference in reported uses should be clarified.

Dr. Belsito requested deletion of the skin irritation study (rabbits) on a mixture of Dimethicone and mineral spirits from the CIR report. He noted that the necrosis observed was due to the mineral spirits, and not Dimethicone. The Panel voted unanimously in favor of issuing a Final Report with a safe as used conclusion on the Stearoxy Dimethicone ingredient family.

PRESENT ASSESSMENT

DECEMBER 2019 PANEL MEETING / INITIAL REVIEW: REREVIEW

Belsito Team – December 9, 2019

DR. BELSITO: Methicones. Okay. We first published the safety assessment in 2003, considered unlikely for any of the polymers to be absorbed into the skin because of large molecular weight. We concluded that they were safe as used in cosmetic products. We had limited inhalation exposure. There were a few ingredients that were used in aerosols.

It's been 15 years, and so it's time to look to see if we need to re-review. The frequency and concentration of use have generally increased in the ingredients quite significantly. The reported frequency of dimethicone has increased to 12-, almost 13,000 from 1,600.

A report of maximum concentration of dimethicone has also increased from 80 to 85. The rest of the others, really not significant. So, it's really dimethicone we're looking at.

So, I thought that the new and existing data covered dermal, eye, and lip. The major question was inhalation. And the only other thing would be the low molecular weight polymers, and I was wondering if we could use language like as used in foods, in our discussion about low molecular weight polymers of good manufacturing process. But inhalation would be the issue.

Are we happy with that? Particularly, if we have some statement about low molecular weight polymers? So, in 2019 the concentration in powders has gone up from 30 percent, in '98, to 53 percent in powders.

DR. SNYDER: In sprays it's gone from 16 to 85. And there was inhalation data on PDF Page 35 and 36 of the old report. And in the discussion of the old report, on page 44, PDF 44, they discussed the particle size distribution being one percent, less than ten microns.

So, if we just had that and didn't have these significant increased uses, and significant increased percentages, I'd probably say okay. But there's a little bit -- in a little bit of a gray zone there with now going from 16 percent to 85 percent concentration use in a spray.

Are we assured or are we reassured that in a 15-year period, that the particle size distribution is consistent with what it was previously. We have no new data on particle size distribution.

DR. BERGFELD: I put reopen.

DR. LIEBLER: Yeah, I said the same thing. I was originally a little uncertain about whether we should reopen this, but the dramatic increase in concentration of use and the numbers of uses.

I said reopen because of those things. We also have significant new data; some of which should be addressed even though it would appear likely that the conclusion may not change. But I think we can't do the level of diligence we're responsible for by just affirming the original conclusion and not reopening it.

DR. BERGFELD: Plus, we have new --

DR. LIEBLER: Microphone.

DR. BERGFELD: In addition, we have new ways of attacking or approaching inhalation. So, we have to update that.

DR. BELSITO: Okay. I mean, that's what I thought was going to be the issue was inhalation. Okay.

MS. FIUME: So, can I ask -- so this will eventually come back as a draft report; so we can't do any type of data requests right now, but we can give a heads up to industry in our post-meeting announcement.

So besides particle size distribution, is there any other piece of information that you think -- I know this isn't a full review, but just based on the preliminary look, that you might need, that we could just give a heads up, saying this type of information could help the panel come to a decision.

DR. SNYDER: Certainly, any additional inhalation data.

MS. RAJ: Did you have concerns about not having DART data and there's been, I think, a slight increase in -- or some documentation of baby product use?

DR. SNYDER: I would defer to Dan, but I think this is still too large to be absorbed, correct?

DR. LIEBLER: Yeah, I basically would agree.

DR. BELSITO: Yeah, we're going to put language about GMP and low molecular weight polymer, so I think that will --

MR. GREMILLION: Is that essentially saying formulated to be non-respirable, putting language in there? When you say the language about the molecular weight?

DR. LIEBLER: That's -- we've never been able to get away with formulate to be non-respirable.

MR. GREMILLION: Well, yeah. See, I'm trying to get an idea --

DR. BELSITO: No, eliminating the molecular weight polymers is to eliminate the issue of dermal absorption.

DR. LIEBLER: And systemic toxicity. Two different things.

DR. BELSITO: Yeah.

DR. LIEBLER: Yeah, two different issues. Yeah.

MR. GREMILLION: The other question I wanted to ask is a reference to, like, a case study with a premature baby. Does that, you know, point to any particular inhalation data that you might want to see? I mean, it seems like they concluded that it wasn't the dimethicone, but it struck me as interesting.

DR. BELSITO: These were for asthmatic, no?

MR. GREMILLION: This was on page 19.

MS. RAJ: Well, I think the other ingredient in that product, I think, are known to be irritants from what I heard -- especially, the Peruvian balsam oil, I was told.

DR. BELSITO: Yeah.

MR. GREMILLION: Yeah.

DR. BELSITO: I think Tom is talking about the case report for the premature infant --

MR. SNYDER: Yeah.

DR. BELSITO: -- who developed pneumonitis.

MR. SNYDER: Mineral oil, yeah, yeah.

DR. BELSITO: Mineral oil, yeah. And the Peruvian balsam for the eosinophilia, yeah.

DR. BERGFELD: Tt has vitamin E in it, very similar to those inhaled products.

MS. RAJ: And the authors did refer to the panel, if you noticed, to, I guess, be assured that it wasn't caused by the dimethicone.

DR. BELSITO: That's circular argument for us.

Okay. So, we're going to reopen, primarily concentrating on particle size, distribution and any additional inhalation toxicity.

Oh my, read-across. This is our last one?

DR. KLAASSEN: Yes.

Marks Team – December 9, 2019

DR. MARKS: And next is methicones. And I'm going to probably delay this a minute until Tom gets here. Oh, yeah.

So this is a re-review document. There are 20 ingredients, and a safety assessment was first published in 2003. The Panel came to a conclusion based on its large -- these are polymers -- concluded they were safe.

So every 15 years or so, Lisa, we take a look back at the ingredient's conclusion and then see if there's new data, whether the conclusion should be changed or modified. And our decision is whether we should reopen or not now.

So there's been a marked increase in -- we moved on to methicones, Tom.

DR. SLAGA: Okay.

DR. MARKS: And this is a rereview assessment of dimethicone, methicone, and a substantive methicone polymers. 2003, it was safe. Marked number of increased uses, concentration of dermal uses has also increased. In the original report, there was no sensitization at 100 percent dimethicone. I felt we didn't need to reopen, but Ron, Tom?

DR. SHANK: Oh, the other team's going to love this. We may want to reopen --

DR. MARKS: Oh, you may? Okay.

DR. SHANK: -- for extensive impurity data on the ingredients other than dimethicone. Because it was -- new data suggested that the polymers may contain significant levels of low molecular weight impurities. That's on page 14.

We have plenty of toxicity data on dimethicone itself, but not the others. So, the impurity issue may make read across difficult.

MS. RAJ: I think that language that I've taken from the review was more in the context of, during the process of making these polymers, it may not be 100 percent, that specific polymer. Like there may be, I guess, these other -- I don't know what you'd call them -- intermediates. In other words, it may not be 100 percent of what you're trying to create.

That's, I think, more what that's saying.

DR. SHANK: Okay.

DR. MARKS: So, let me make sure. So you're suggesting maybe we should open this for clarification of the impurities of these polymers?

DR. SHANK: Other than dimethicone, yes. But the number of uses of the other ingredients, other than dimethicone, was pretty small.

DR. ANSELL: So, where was this statement?

DR. MARKS: Page 14.

DR. SHANK: Page 14.

MS. RAJ: In impurities.

DR. SHANK: Let me find it. I'm not too fast.

MS. RAJ: It's the second paragraph.

DR. MARKS: "Therefore, it may be worth considering at high molecular weight linear methicones may contain impurities that are not just shorter counterparts with low molecular weights." Is that what you were focusing on, Ron?

DR. SHANK: Yes.

DR. MARKS: "But possibly other siloxane polymers with physicochemical properties, which could affect dermal penetration and/or cellular toxicity." Ohhh. I highlighted that, but I didn't focus on it.

DR. SHANK: I figured that would be a red flag for the B team.

DR. SLAGA: And it would give the opportunity to add this additional data we had to the report, if we reopen. Because we got a lot more, and there was very little before.

DR. ANSELL: Is this new data, that polymerization results in a spectrum of materials including --

MS. RAJ: It was a pretty recent review, yes, that I took that from. At the time -- I'm not sure if I've received it since -- but I think there was a conference paper, or something, talking about dermal penetration of low molecular weight silicone polymers.

DR. ANSELL: Because typically, we would not recommend reopening, unless there were new applications or new information which justified the amount of work that would go into not only the industry side, but the Panel side.

So, I don't know where that would fit in terms of we didn't consider polymerization results in a spectrum -- a distribution of molecular weights. So, if this is suggesting something new, then you guys can decide if it's just -- that's how --

DR. SLAGA: If we have the same conclusion, we don't reopen it. Yeah. I mean, that's what I originally put down.

DR. MARKS: Don't reopen?

DR. SLAGA: Yeah, don't reopen. And then I just put a note that there's a good bit of data in here, though. And sometimes you like to put it in the report.

DR. MARKS: Yeah. I had that at the bottom. A synopsis of new data.

DR. SLAGA: Yeah, but it doesn't change the conclusion, this data.

DR. SHANK: But that can go in the summary.

DR. MARKS: Yes.

DR. SLAGA: Yeah.

DR. SHANK: We don't have to reopen it to add the new data.

MS. RAJ: And I guess you weren't concerned with the increase in mucus membrane exposure for lipstick concentration?

DR. SHANK: I wasn't. That was for dimethicone, wasn't it?

MS. RAJ: Yeah.

DR. SHANK: Yeah.

DR. MARKS: I hear now, Ron -- because we're going to be -- our team is going to be moving. Do we not reopen, and then handle this in the re-review summary?

DR. SLAGA: That's what I would say. Yeah.

DR. MARKS: And then if we say that, what are we going to say? Because you raised the issue of what are these impurities. Do we need clarification?

DR. SLAGA: No.

DR. MARKS: Because in the re-review summary, if we need clarification, then we need to reopen it. I guess the other is --

DR. SHANK: I was anticipating tomorrow's discussion. And if there's consistency, I'm sure the impurity issue will come up. It doesn't bother me that much, and I wouldn't reopen it just for that.

DR. HELDRETH: I'm looking back at the original reference that Preethi used. The impression I'm getting isn't so much that they're talking about impurities, per se; it's just the natural distribution of chain links when you do polymerization.

For instance, for most polymerization reactions, you're not going to get all of the -- exactly what molecular weight. You're going to get a median value where most of the chain links are, and then it's going to be this bell-shaped curve of longer or shorter chain links in that situation.

I think that's what the author was getting at there.

DR. SHANK: Okay. Then what I would recommend is, not to put it under impurities. It's a distribution of molecular weight of the polymers. And I understand that. That's fine. I was thinking of some kind of monomer or other chemical that might be there.

MS. RAJ: Would you put it under method of manufacture then, or where would you put it?

DR. PETERSON: Chemical characteristics.

DR. SHANK: Chemical composition.

DR. PETERSON: Composition.

DR. SHANK: Chemical properties.

MS. RAJ: Okay.

DR. SHANK: And not call it impurities.

DR. HELDRETH: You could have it as a its own statement right before. Under chemical and physical properties right before hexyl methicone. You could have it as a general statement about --

DR. MARKS: Chemical properties.

DR. SHANK: The main chemists may see it differently than I do.

DR. MARKS: What do you think?

DR. PETERSON: I agree. If the issue is really that the polymer lengths are different, and that's the issue and not impurities, then it belongs up in chemical/physical properties.

DR. SHANK: Thank you.

MS. RAJ: Okay. Thank you.

DR. MARKS: Okay. So, with that in mind, it seems like it would be pretty straight forward. We're going to move not reopen. And then we put clarification maybe -- I'm not sure that's the best way, now, to put it. But in the re-review summary, we clarify -- we move the distribution of polymers to the chemical property section, something like that.

DR. HELDRETH: Yeah. If the full panel agrees tomorrow not to reopen this, most of this text just completely disappears. Because we're just going to condense down to a re-review summary, and that paragraph wouldn't really exist in the end product.

DR. SHANK: Okay. Because the way it's worded here, it sounds like they're worried about things other than just smaller polymers.

DR. ANSELL: Right. That we've discovered a new monomer, which -- not potentially affect, but was unknown.

DR. HELDRETH: Yeah. The exact language in the source document says, "Due to the specifics of the polymerization reaction, it results in a product that must be treated as a mixture of polymers, including oligomers with variable chain links and consequently variable molecular weights."

DR. SHANK: Okay. That's different.

DR. ANSELL: Which is true of many of the compounds we've spoke about, including the ethoxylation.

MS. RAJ: So, in the re-review summary, I guess, do you have anything specifically that you would want to mention?

DR. MARKS: I mean, it's interesting because the way it's worded now it caused concern, and in the impurities section.

If we note it in the chemical properties section, that there's a distribution of polymers, it can be as simple as that and don't say anything more. Although, I think most of us would know that any polymer there's going to be a distribution of length. But we could put it in there to be explicit. Does that sound good, Ron?

DR. SHANK: Yes.

MS. RAJ: I guess, would you have any language that, in spite of significant increase of use and in these certain categories, like why the panel feel safe about these ingredients?

DR. MARKS: Oh, because the data supports its safety. So, increased use doesn't create any concerns, unless it was a new use in which we had not considered the safety prior, such as perhaps on babies or on inhalation or something like that.

MS. RAJ: There is currently no DART data, which I'm sure you guys noticed.

DR. MARKS: Yeah. What I interpreted -- there were increased numbers of uses, but the products being used were virtually the same. The concentration on a leave-on was increased. But again, it wasn't like there was a whole new category. Is that how you interpret that?

DR. SHANK: Yes.

DR. MARKS: So, tomorrow I'm going to move not reopen. And then, do we want to bring -- I guess even though it's editorial, should we bring up the issue of the clarification of impurities on page 14, and moving that? Or just put that as a discussion here today, which is public knowledge, and not even bring it up tomorrow, unless the Belsito team has concerns about it?

DR. HELDRETH: That's right. Unless it's really the basis for your decision.

DR. MARKS: And you've heard everything, so I won't mention it tomorrow. Okay?

MS. RAJ: Thank you.

Full Panel – December 10, 2019

DR. MARKS: So, this is a re-review of the safety assessment of dimethicone, methicone, and substituted methicone polymers. There are 20 ingredients which were evaluated in 2003, and the panel concluded these were ingredients that were safe as used in cosmetics. Our team felt that that conclusion could remain the same and we move not to reopen.

DR. BERGFELD: Is there a second?

DR. BELSITO: No.

DR. BERGFELD: Okay.

DR. BELSITO: We felt that the increases in number of uses was so extremely high, including increase concentrations in products that could be aerosolized, that to do due diligence we needed to reopen this report.

DR. MARKS: I guess, if we don't have any tox alerts; just because the uses go up -- and noted, yeah, marked increase in the number of uses and the concentration of dermal uses including.

DR. BELSITO: Yeah, the dermal didn't bother us; it was the marked increases in the potential inhalation.

DR. MARKS: And we had quite a discussion about "impurities." And we felt that actually what was meant in this tentative memo -- or report -- was that it was really a distribution of polymers. And so we would move to the chemical properties section. But, inhalation didn't come up in our discussion so, I guess, clarify, was there an inhalation tox alert?

DR. BELSITO: Paul, you want to comment?

DR. SNYDER: No, there wasn't any specific alert; it was just that the uses went from 1600 to 13,000. And the greatest increase in concentration was the spray use; it went from 16 percent to 85 percent for sprays, 30 percent to 53 percent for powders.

So we thought just we could proceed to relook at it. We could reaffirm the conclusion, but we thought we'd like to see, you know, some additional information -- if there was any additional information regarding particle distribution or anything like that we could gleam from these increased uses and things.

Because obviously there's got to be new data in regard to the monomer content, I think would be an issue also as impurities. And, there was limited acute inhalation data in the old report.

DR. BERGFELD: Ron?

DR. SHANK: Using our usual wordage about particle size and distribution in the respiratory tract is not sufficient? Rather than opening it in a re-review summary, couldn't you just repeat what we say about the respiration of particles?

DR. SNYDER: That's an option. I think that's still on the table. I think just because we reopen doesn't mean that we're going to change anything; it's just that we want to look at the data a little bit more carefully and see where we're at. Because this is a significant change in uses and concentration used, compared to the old report.

DR. LIEBLER: If it had been a modest change in usage, but an increase in concentration, I would be certainly open to reaffirming the original conclusion and not reopening the report. It's just that on top of the concentration increase, the dramatic increase in number of uses, I felt it was due diligence for us -- I think I used that term in our discussion -- for us to open the report, even if we may end up in the same place.

DR. BERGFELD: Marks team?

DR. SHANK: Okay.

DR. MARKS: Sure, because we're deciding on the side of being safe. So, of course we endorse that. So we'll second. I'll withdraw my motion, and I'll second the motion to reopen this safety assessment.

DR. BERGFELD: So, all those in favor of reopening Methicone? Thank you, unanimous.

Okay, moving ahead, and I think the discussion well outlines what is needed. Moving on to Dr. Belsito's ingredient.

JUNE 2020 PANEL MEETING – SECOND REVIEW: DRAFT AMENDED REPORT

Belsito Team – June 8, 2020

DR. BELSITO: At the December meeting we had a re-review of 20 ingredients to determine if safety assessment should be reopened. And we decided because of a significant increase in reported frequency in concentration of use, the multiple formulations, especially ones that could be inhaled -- we decided to reopen the report and look for more data on particle size, distribution and inhalation toxicity. Additional data has not been received. And then it wasn't clear to me. Are we adding simethicone into this report?

MS. RAJ: Yes. Sorry, go ahead.

DR. HELDRETH: We've been asked to.

DR. LIEBLER: Preethi, go ahead, and then I'll follow.

MS. RAJ: Yes, simethicone along with ten other ingredients, I believe, have been proposed by the SSC.

DR. LIEBLER: So this was one of the things I referred to in my initial presentation that was brought to Lisa and I to discuss. If you go to PDF page 71, down near the end of the report, it's the CIR SSC memo where they propose adding several other ingredients, which begin at the bottom of the page and go on to the next page -- so capryl dimethicone, hexyl dimethicone, and several others, including -- and then in the third paragraph from the bottom on that page, "We think simethicone defined as a mixture of dimethicone with an average chain length of 200 to 350 dimethylsiloxane units and Silica to be added to this report."

So Lisa and I agreed that the ingredients at the bottom of this page and the top of the next page -- so let's see. That's five plus five -- so ten additional ingredients are fine to add. They certainly are chemically similar enough. They would belong with the ingredients in the remaining part of the report.

The only hang up is simethicone. And it may not be a problem, but it's a mixture of basically a dimethicone polymer in silica. And so as we are all well aware of the issues surrounding silica, it all depends on what kind of silica is in this. If it's synthetically produced amorphous silica, it's probably no problem. And it also depends on how much is routinely in this. If it's possibly crystalline silica or contaminated with crystalline silica, it would be an issue.

And having said all that, of course, this is a widely used over-the-counter medicinal ingredient, so it's probably okay. But based on the information that we currently have before us, we don't know.

DR. BELSITO: So what would we need, Dan? We would need the cosmetic definition of what simethicone is? Or would we assume that it's the same as the OTC drug?

DR. LIEBLER: So that would be one thing we would need to know. And then the method of manufacture, composition, and impurities should take care of it. As long as it's satisfactorily addressed in our description of that ingredient. I think it would be okay. And I think the ten ingredients other than simethicone are no-brainer additions. They make perfect sense.

Simethicone also may be a nearly no-brainer addition. We just need a little bit better documentation on what this is. Because it's the only ingredient that's a mix of a dimethicone polymer and something else, in this case silica.

DR. BELSITO: Okay. So we're going to go with adding in all and questionably silica -- simethicone, rather.

DR. LIEBLER: Right.

DR. BELSITO: And the information that we need on simethicone is what kind of silica is in it?

DR. LIEBLER: Right. So we'll need physical properties, chemical-physical properties, method of manufacture, and impurities. That should cover us there.

MS. RAJ: Thank you.

DR. BELSITO: So we hand it back in and we sort of give a hint this is what we need. Is that what you're suggesting?

DR. LIEBLER: Correct.

DR. KLAASEN: (Inaudible) being used to (Inaudible).

DR. BELSITO: I'm sorry, Curt. You broke up.

DR. KLAASEN: (Inaudible) if we're adding this chemical with the potential of silica in it, (Inaudible) how it's being used. If it's being used in any inhalation -- if it's likely to be inhaled or not.

DR. BELSITO: Well, we would get that in terms of when we see where it's used, right?

DR. KLAASEN: Oh, for sure. (Inaudible).

DR. LIEBLER: The simethicone says there's 519 uses, two of which are face powders. We have that data already.

MS. RAJ: Yeah. It's in the March to June supplement, I believe.

DR. LIEBLER: I doubt we're going to have a problem here, but Curt put his finger on the right point. This is mainly an inhalation issue, and it's going to depend on what silica is in this.

DR. KLAASEN: Correct.

DR. BELSITO: Well, I mean, we'll find out when we see the data, right?

DR. LIEBLER: Yeah.

MS. RAJ: So just to clarify, is this going to be a parallel IDA, and then would I, as the writer, be trying to pull in new data for these ingredients that we're going to add?

DR. LIEBLER: What do we do when we're sort of adding new ingredients to a report that's just starting? I mean, it's not really an IDA. We haven't presented the available data. We haven't even been able to pull in the available data yet.

DR. HELDRETH: So the stage of the report, last time you saw it, we were bringing it to you to see if you wanted to reopen this as a re-review. And you said thumbs up. In the interim, afterwards we and the Scientific Support Committee suggested some additions. So those are available for you to look at now. And currently this is a draft amended report before you. So two options now are to either go forward with a conclusion and issue a draft report with a conclusion or to put out an insufficient data announcement for whatever data needs you feel there are.

DR. SNYDER: Well, we received the inhalation data that we need to clarify the inhalation issue. But the request to add these additional ingredients has raised a concern for some missing data related to the silica involved. So, I think, Don, we need to -- we got data to clear the inhalation issue. We got data also that these are very large (Inaudible) new ones. But I think Dan is right with the point about the silica. That needs to (Inaudible).

DR. BELSITO: Then that would go with the no-brainer idea. Adding simethicone is not a no-brainer.

DR. LIEBLER: Yeah. One thing we can do, if you want to accelerate this report, is we don't include simethicone. We do that in some other way at some other time. And then I think our data needs are largely met. But if we add simethicone to this, we're literally at square one for a key ingredient.

DR. ANSELL: Yeah. We can't reopen and then conclude insufficient. I mean, if the materials can't be supported by the existing data, then they don't belong in the family. To the extent that the simethicone has a question mark on it, I'd be interested in how to resolve that -- that question mark. But insufficient isn't one of the choices.

DR. BELSITO: All right. Even the OTC use of simethicone is oral. It's not for -- there's no inhalation exposure, right?

DR. LIEBLER: Yeah.

DR. ANSELL: It's not recommended for aerosols.

DR. BELSITO: Okay. I mean, I think that what I'm hearing is we add an "all, except simethicone" and go with a "safe-as-used" conclusion.

DR. LIEBLER: Yeah. That's fine.

MS. RAJ: And I'm guessing in the discussion we wouldn't need to make mention of simethicone then, right?

DR. LIEBLER: Right. Right. Like it never happened.

DR. HELDRETH: It will get reviewed again. Just not here.

DR. LIEBLER: Yeah. That's right.

MS. RAJ: Any particular language you would like to see in the discussion?

DR. BELSITO: "Formulated to be nonirritant." Is that going to be part of our conclusion? Let me see. We just changed to Microsoft 365, so I apologize. But this is not the way I'm used to seeing the document discussion. Obviously, "particle size for potential inhalation." And then I had a question about the ocular issues. It's used up to 37.8 percent in an eye area. Is that problematic?

DR. SNYDER: I didn't ping that, so.

DR. LIEBLER: Let's see. Which table is that? Oh, I'm sorry. I'm thinking of the ocular tox data. I guess it's not summarized in the table.

MS. RAJ: No, it's not in the table. This was in the cosmetic use section you'll see that. It's page 20, I believe.

DR. BELSITO: Page 25 on dimethicone.

MS. RAJ: Under the cosmetic use section for the report, it's page 19 where I see that at the last paragraph.

DR. SNYDER: Yeah. I mean, I think, Don, that would be covered. If there's any issue it would be right in that irritation. So I guess the -- I mean, that was the whole reason we opened this because increase frequency of use and increase concentration of use, along with the inhalation. So I thought we were okay clearing it.

DR. BELSITO: But if you look at page -- under the ocular data --

DR. LIEBLER: Page 25 of the PDF.

DR. BELSITO: Yeah. 25. Ocular irritants -- actually on 26. It says, "Although there appear to be better ocular tolerance for medical-grade dimethicone, it also caused some corneal changes." I mean, I think it at least deserves some discussion. I mean, I'm presuming -- I'm not used to these doses and viscosities that they're giving and how that impacts upon the cosmetic viscosities in a finished formulation.

DR. LIEBLER: Yeah. Preethi, on the beginning of the ocular irritation section, which is PDF 25 at the bottom, in the italics it says, "Most ocular irritation studies using rabbits classified dimethicone as a mild to minimal irritant." Then it says, "The most common finding was a conjunctival reaction. However, a few studies reported severe reactions." And then, "Similar to dimethicone, methicone and vinyldimethicone also produced conjunctival reactions."

That's why I was asking is there a table with data on studies. Because in the rest of the paragraphs, except for that short line on C30-45 alkyl dimethicone, they all report some degree of reaction involving ocular irritation to these compounds. So it seems like fairly commonly observed. But a lot would depend on dose.

And in the case of this one thing Don mentioned, medical grade dimethicone producing somewhat better ocular tolerance. So that's kind of vague. I think we need to better document the data. And then this does need to be addressed in the discussion.

DR. SNYDER: But you have to remember this is part of a re-review. So that italicized is from an old report we think was -- we already said safe as used. And we are aware of this ocular irritation previously.

DR. BELSITO: Yeah. But the eye -- concentration in the eye and eye products has gone up significantly from when we last looked at it. It's now 37.8.

MS. RAJ: Yeah. I'm not seeing a table for ocular data in the original report. But I think there were like a few studies mentioned, which, as Dr. Snyder said, was summarized in italics here.

DR. LIEBLER: I think if the rationale driving this concern in reopening the report is increased frequency of use and increased concentration of use, we need to try and square that with the concentrations that produce the effects in these studies.

MS. RAJ: And I guess you mentioned something about viscosities. So are the viscosities, I guess, presented in this report not something you normally see in clinical use or --

DR. BELSITO: I've just never seen data where they're talking about different viscosities of, you know, the same material. I mean, it's just foreign to me.

DR. HELDRETH: For this particular report, the viscosity is a direct result of the degree of polymerization. So the higher the viscosity that you see, the longer the polymer chains are. So it's an indirect way of telling you how big these molecules are.

MS. RAJ: Yeah. That makes sense.

DR. BELSITO: So it says medical-grade dimethicone, which has a viscosity of 1000 centimeters squared per second, was safer. Do we have information on what cosmetic grade dimethicone is? We don't.

DR. LIEBLER: No.

DR. HELDRETH: The thing is it can vary from manufacturer to manufacturer, from formulation to formulation. I mean, you can attenuate the degree of polymerization for all of these very easily with heat and time, and there's even some additives that can further the propagation or slow it down or completely terminate it when it's smaller.

DR. BELSITO: Now, since we're adding in a whole bunch of other ingredients other than simethicone, there still may be data that we didn't look at and that's not in this report, correct?

DR. HELDRETH: Yes. We will do an extensive double check to make sure that there's no other data on these additions.

DR. BELSITO: Okay. I mean, so then how do we proceed if there could be other data that might change our conclusions?

DR. HELDRETH: As Jay alluded to, you know, these should all be no-brainer additions. The data that's already in the report should support the additions that the panel is making today.

DR. BELSITO: Okay.

DR. HELDRETH: If it doesn't, you know, you can decide not to add those in. But we will make sure that there's no other data on these additions. It may be somewhat unlikely that we'll find additional data on these add-ons since they are very specific to the cosmetic industry.

DR. LIEBLER: Yeah. I want to just clarify that our recommendation -- the recommendation I made and Lisa made to include these ingredients that the SSC recommended was based on chemical similarity and similarity for use. We didn't see any data on these. And Bart's probably right, we may not get much specific data on these -- much additional data. But it wasn't an assessment of the data or the safety. It was simply an assessment of the chemical similarity that these belong together in the same report.

DR. BELSITO: Okay. I mean, I'm fine with that. I'm just trying to clarify where we're going here. So I guess in the discussion we would not need, I think, to talk about certainly the significant increase in use concentration. And I think where we really need to probably stress -- and I'll ask Curt, Dan and Paul -- exactly wording is the inhalation issues.

I think that, basically, in our conclusion I think we would have to say "formulated to be non-irritating both to skin and eye," which is sort of different, because usually we talk just about skin. But here we're getting data that the dimethicone, which is 37.8 in an eye preparation, could potentially have significant irritation potential.

DR. SNYDER: And, Don, I reviewed the old report here quickly, and there was one study with dimethicone that there was no ocular irritation at 10 and 29 percent. But there was at 35 percent. And then in the summary in the old document -- the original report -- they talked about the conjunctival reaction of being mild to minimal but no severe reactions. And then we must have been comfortable that we weren't anywhere near that 35 percent positive reaction. I think we do need to address that in the re-review.

DR. ANSELL: I'd just add that while the data is relevant in assessing its ocular irritation, the intentional addition to an ocular product would not be a cosmetic. So at these high concentrations, the potential for irritation is relevant but not necessarily at the concentrations from a cosmetic application.

DR. SNYDER: Yeah. But I think this is akin to the incidental ingestion -- incidental inhalation because there is -- the one that has the 39 percent is (Inaudible). So there could be an incidental exposure of the eye, even though it's not intended to be used on the eye.

DR. LIEBLER: Yeah. That's it.

MS. RAJ: So would it be sufficient to say that at that concentration that we mentioned, the 39.5 percent, there may be an incidental exposure to the eye? But that, I guess, at that level of concentration is not very, I guess, prevalent for eye use or -- I'm not really sure how to say that.

DR. LIEBLER: No, you can't really put it that way. We know that there is ocular irritation voided from the old report. Paul, you said it was about 35 percent?

DR. SNYDER: Yeah. They tested it at 10 and 29 and 35. 10 and 29 did not cause any irritation, but 35 did.

DR. LIEBLER: Yeah. So if we have an ingredient used at 37 percent in a product that's going to be applied around the eye, there's a potential for ocular exposure and ocular irritation. So we have insufficient data to support the safety -- at this point, we have insufficient data to support ocular safety at that concentration of use.

DR. BELSITO: Well, in the study on PDF page 26, where they are looking at the ocular irritancy of dimethicone, it looks like, from what I can read -- this is the first paragraph at the top -- this was pure dimethicone.

MS. RAJ: Wait. Which page are you on again, Dr. Belsito?

DR. BELSITO: PDF page 26. It says "Ocular irritancy of dimethicone was evaluated in a study group: three mice, three guinea pigs, three rabbits -- five separately-manufactured samples of dimethicone. For the test, a drop of dimethicone was instilled once daily." So it sounds like it's pure dimethicone. And it says, "The authors opined that ocular irritancy and inflammatory effects of silicone fluids may be pH-dependent." So it sounds like it could be formulated to be nonirritant depending upon the pH.

MS. RAJ: Yeah. I remember this particular study. I think their emphasis was more on the pH of these samples than necessarily viscosity or other things.

DR. BELSITO: Yeah. But again, it was 100 centimeters squared per second was the -- and the medical grade. So that means, Bart, this was an even longer chain. Is that right? Or shorter?

DR. HELDRETH: The high viscosity --

DR. BELSITO: Medical grade is supposed to be 1,000 viscosity.

DR. HELDRETH: -- readings are going to be longer chain. Whereas lower viscosity we're talking smaller molecules.

DR. BELSITO: Okay. So this is a smaller molecule of (Inaudible) centimeters squared. Again, we don't know what cosmetic grade methicone is. I'm not an ocular toxicologist. Would one predict that a shorter chain would be more irritant than a longer chain?

DR. SNYDER: According to these authors, it wouldn't matter. It would matter about the pH of the fluid, the (Inaudible). So I think we could go with the caveat that you said -- when formulated not induce ocular irritation -- concentration of use. Yeah.

DR. BELSITO: Right. That's the way I interpreted it, for skin a well.

DR. SNYDER: Yeah.

DR. LIEBLER: Yeah. And I think we still need to note it in the discussion to come back to the original question Preethi posed to us.

DR. SNYDER: I think the discussion -- we'll have to bring in that old data that there was ocular irritation at 35 percent, and the current concentration of use exceed that. We do need to discuss that.

DR. BELSITO: Right. And then bring in the fact that, in this study, it appeared that there was a pH effect on that irritation so that it could be formulated presumably at 37.8 percent to be not irritating to the eye.

MS. RAJ: Okay. Thank you.

DR. KLAASEN: (Inaudible) popular irritancy test before which all guinea pigs on the eight to ten. (Inaudible). What's going on there?

DR. BELSITO: You keep breaking up on me, Curt. I didn't really fully understand your question.

DR. KLAASEN: I guess, in this study, by eight to ten on the screen there, all of the guinea pigs had died. It's more than just a little irritation.

DR. BELSITO: Which study are you on?

DR. KLAASEN: It's on the screen here.

MS. RAJ: It's the same one.

DR. KLAASEN: The one you have been talking about.

DR. BELSITO: Oh yeah, okay.

DR. SNYDER: Yeah. That was 100 percent applied every day for ten days.

DR. KLAASEN: Yeah.

DR. LIEBLER: That's still surprising.

DR. KLAASEN: That's what I was saying. I mean --

DR. BELSITO: That is weird. I've never heard of animals dying from an ocular study.

DR. KLAASEN: Correct. Usually the worst I've ever seen is blindness.

DR. BELSITO: Yeah.

DR. KLAASEN: Not death. But okay.

DR. SNYDER: Well, if you look at the old report, there is an awful, awful lot of ocular irritation data in that old report. Again, I think that this is (Inaudible) we have one that says only three guinea pigs -- three guinea pigs and three rabbits. It appears to be that there is an irritation issue. (Inaudible) it looks like somewhere around the mid -- 30 percent or more. So I think we can alleviate that with the "when formulated to be non-irritating to the eye."

DR. BELSITO: Yeah. And it may be nice to actually create a table on this and to bring in an italicized version as we do when we're quoting data from the old report -- all of the ocular studies were published or that we referenced in the old report and then these new ones.

DR. SNYDER: We're starting to trickle down a little bit into that -- this not being a no-brainer. I guess this is an add-on. This is the main -- never mind.

DR. BELSITO: Yeah. This is not an add-on. This is something we've already ruled on. So I mean --

DR. SNYDER: Which is pretty intuitive that we reopened because of that increased concentration of use.

DR. BELSITO: Right. That's exactly the reason we reopened.

DR. SNYDER: We need to address it.

DR. ANSELL: So I think it's appropriate to talk about the formulated to be non-irritating based on the data. But in the discussion, we shouldn't conclude or imply that 37 percent directly injected to the eye is equivalent to a cosmetic ingredient which contains 37 percent.

DR. BELSITO: No, I think we can put that in the discussion and say that, obviously, the cosmetic is not intended to be applied to the eye. But given our concerns that there could be, you know, incidental exposure -- accidental exposure to the eye, that we would hope that a cosmetic that was meant to be applied to the eye area would be one where they've looked at ocular irritancy and adjusted pH, or whatever, to avoid that.

DR. ANSELL: Right. Right.

DR. LIEBLER: Yeah. I just think that this is an important enough issue, since it is the reason we reopened the report, that we need lay out the data in a table, including the data that was referred in the previous report, just to indicate -- just to allow us to take one more look, when we look at this, I guess, in September again, to make sure that we can calibrate our assessment and our discussion appropriately. Because I think just saying "formulated not to be irritating," I mean, it basically may be okay. But given the high concentration of use, it pushes us into the toxic range in at least one study. This study with the rats and rabbits dying is very unusual and not toxicologically plausible for this kind of a chemical. So there must have been something else going on. I think it's incumbent on us to look at the full body of available data on tox on these for ocular.

MS. RAJ: Yeah. And I will say that this study is a bit unique with providing the pH values of the samples. I don't think other studies would necessarily provide that. But I'll try to make it as comprehensive as possible -- the table.

DR. LIEBLER: If it's 100 percent dimethicone, it doesn't even have a pH.

DR. BELSITO: Yeah.

DR. LIEBLER: It's nonaqueous.

DR. BELSITO: Okay. A few other points in the document. On PDF page 21 for dimethicone, the new data, "dimethicone when used as a condom lubricant was detectible." I presume it was in blood, but that's not mentioned. Do you see what I'm talking about, Preethi?

MS. RAJ: Yes, I don't think it was in blood, Dr. Belsito. I think they had externally swabbed areas that were in contact with the condom that had the dimethicone on it.

DR. BELSITO: Okay. Well, we just need to clarify where that was detectible.

MS. RAJ: Okay.

DR. BELSITO: And I had a question. Okay. I guess that's answered now -- that I understand that centimeters squared per second is viscosity. It was under the product toxicity oral studies.

DR. HELDRETH: Yeah.

MS. RAJ: And I guess the panel was okay with this notation for viscosities because I think we got a comment from council about that.

DR. LIEBLER: Well, the standard units are pascal-seconds, which is a kilogram per meter per second. So you have a mass -- I mean, you get this. It should be in it. It's not represented here. That may be what they're referring to.

MS. RAJ: Okay.

DR. HELDRETH: You know, we just -- Preethi reported them as we found them, but if you would prefer, we could convert them all to the pascal-seconds if that'd be helpful.

DR. LIEBLER: I think that would be standard usage for viscosity.

MS. RAJ: Thank you. Did you have more comments, Dr. Belsito?

DR. BELSITO: I did, but my screen just went blank. Does anyone else have any other comments while I'm trying to get this all back up here?

DR. SNYDER: I did not.

DR. BELSITO: Okay.

DR. KLAASEN: Fine.

DR. BELSITO: Okay. Here we go. On PDF page 23, it says -- just a clarification, this is on the chronic tox study for dimethicone. It says test article increases in ocular opacities in 300 milligrams of the females and 1000 milligrams, you said, of males and females. I presume that's just of males, correct? Because the females it was three. Or, I guess, was it both sexes at 1000? Okay.

MS. RAJ: Yeah.

DR. BELSITO: Yeah. Fine. My misreading. It must have been late. Okay. So --

DR. SNYDER: Yeah. The better wording for that would be at 300 and greater for females and at a 1000 for males. That would make that more clear.

DR. BELSITO: Okay.

MS. RAJ: Okay. Thank you.

DR. BELSITO: So we're going to add in everything except simethicone. We're going to see if there's any additional data out there for the add-ins. In the discussion, we're going to point out that, while we don't expect the eye makeup to be applied to the eye, we are concerned given the concentration that there could be incidental exposure. So it should be formulated to be non-irritating. We're going to talk about particle size and respiration. And our conclusion will be "safe when formulated to be non-irritating to the eye and the skin." Is that correct?

DR. LIEBLER: Yes.

DR. BELSITO: Does anybody have any wording, particularly for inhalation? Paul, Dan, Curt?

DR. KLAASEN: No.

DR. SNYDER: I mean, if the inhalation toxicity profile was minimal, and we received adequate data to suggest that there's no issue.

MS. RAJ: Was the data from -- I think it was the SCHSC citing the micron sizes and, you know, where it would sit in the respiratory system if inhaled? Would that be language that's useful to bring in?

DR. SNYDER: Yes, because that goes with our boilerplate where the particle size percentages (inaudible) and micron.

DR. BELSITO: Okay. Anything else? Okey-doke.

MS. RAJ: Thank you.

DR. BELSITO: Curt, Paul, Dan, we're all happy?

DR. KLAASEN: Yeah. We're happy.

DR. BELSITO: Okay. Okay. So then we're moving on to pomegranate. Oh, the --

MS. RAJ: There's Tris --

DR. BELSITO: Oh, Tris. Yeah, I keep skipping over that one, Bart, for some reason. And I was fine with all the comments that council made on the methicones. You guys as well?

DR. KLAASEN: Yes.

DR. LIEBLER: Yes.

DR. SNYDER: Yup.

Marks Team – June 8, 2020

DR. MARKS: And Lisa, you're going to be really on the hot spot with this one. Let me bring that up here. Look at Preethi's memo from February 21st.

The Panel first published the safety assessment of dimethicone, methicone, and substituted-methicone polymers in 2003 with a conclusion that these ingredients were safe. At the December 2019 Panel meeting, we were presented with a re-review of these 20 ingredients. There was a significant increase of reported uses -- frequency of use and concentration. And we wanted -- the Panel consensus was to get more data on particle size and distribution, inhalation toxicity. To date, additional data have not been received. What else?

And then, we actually in December felt that we didn't want -- our team felt that we didn't need to reopen, but now we have the issue of adding ingredients as well as dealing with the inhalation toxicity. That was the biggest concern in December. The CIR Science Committee, SSC, and the new Grouping/Clustering Working Group -- that's you, Lisa -- I assume you proposed adding 11 ingredients, including simethicone which is a mixture of silica and dimethicone.

DR. PETERSON: Yeah.

DR. MARKS: My feeling is -- even though that said the silica in simethicone is amorphous silica, is this a no-brainer?

DR. PETERSON: Um, so, yeah.

DR. MARKS: Let's see. So I think the key is the goal posts have changed a little since December because we aren't dealing with the issue of reopening for adding ingredients. And there -- besides the simethicone, there are 11 other ingredients. And then Alex's comments -- here there were comments that I thought our team should address -- is she mentions, should there be limits on other substitutes like carbon chain lengths, saturation, other molecules other than carbon. So actually, things have changed a bit since December.

Does the team want to reopen? Or I shouldn't say reopen; we've already reopened it. Do we want to proceed with adding 10 or 11 ingredients? Are these no-brainers, or do we want to go back to not reopen and deal as, I think, Ron Shank suggested the inhalation toxicity in the re-review discussion? So a lot -- sort of a couple different issues. So Lisa, Ron, and Tom, your comments?

DR. PETERSON: So, if I may add first, both Dan and I didn't feel that the simethicone should be added because of the silica, and there would be questions around that. And in terms of a group, it adds some different concerns than the other ones would have. So my recommendation, which would be probably also Dan's recommendation, is that this simethicone doesn't really belong as part of this group, but the other ones do.

DR. SHANK: I agree. The silicon dioxide has not been reviewed by the Panel, and so I don't think it's a no-brainer to add the simethicone silicon dioxide. The others I guess are okay, but not the -- I would not add the simethicone.

DR. MARKS: I'm trying to get my notes as to what the (inaudible), so there'd be ten that would be added, Lisa, to the draft.

DR. PETERSON: Yeah. I believe so.

DR. MARKS: Where do I have that? I know I put that list in here.

DR. EISENMANN: You have reviewed the -- the silica is the synthetic amorphous silica that you just completed review of.

DR. MARKS: I realize that, Carol. I guess, even though it says that it's amorphous silica and we concluded that amorphous silica would stay safe, to me, it reopened the silica issue all over again. As you can tell, I was a little bit -- I was definitely hesitant about it and, Lisa, you and Dan sounds like reinforce that concern. It's not a no-brainer. Where are the --

MS. RAJ: So it's on page 71 of the PDF. You'll see the PCPC memo with the add-on suggestions.

DR. MARKS: Yeah. Okay. Yeah. Capryl Dimethicone, Hexyl Dimethicone, then the C20-24 goes up the different carbon lengths here. So Lisa, you think these -- in the past when we've added ingredients in a rereview, we used the term "no-brainer" -- that you could take all the data you already have in the report and just add these on and either read across or they would tag along and not require a large discussion as we might have to do as you mentioned with the simethicones. So Lisa, you and Dan were fine that these shouldn't be an issue, and I'll ask that same question to Ron Shank and Tom Slaga. From your viewpoint, these add ons are not an issue?

DR. SHANK: Correct, except for the simethicone.

DR. MARKS: Okay.

DR. SHANK: The others are okay.

DR. MARKS: So there's no question in my mind that it's reopening because we're adding ingredients.

DR. PETERSON: And then, if there's data associated with them, that probably should be added too, right?

DR. SHANK: Pardon me?

DR. PETERSON: If there's data associated with these compounds, that should be added to the report as well.

DR. SHANK: Oh, yes. So we need to handle the inhalation toxicology issue -- aerosols containing 85 percent dimethicone.

DR. PETERSON: And we didn't really get any information about particle size.

DR. SHANK: Right.

MS. RAJ: Well, there was the resource document, I think, from SEHSC. I'm trying to remember. That should be, I think, in the data supplement file.

DR. SHANK: Yes?

DR. PETERSON: The March to June supplement?

MS. RAJ: No, data supplement, June 2020. It's on page 6.

DR. SHANK: I don't remember.

DR. MARKS: Are you talking about within the last week?

MS. RAJ: No, not the last week. This was sent --

DR. MARKS: If it's June 2020, we're talking about in the last couple of days. I don't remember seeing that supplement, but maybe I missed it.

MS. RAJ: No, this was sent in March.

MS. FIUME: That supplement came in the original mailing with the other reports, but the name of it was "data supplement" rather than a report name. It would have been on your original flash drive.

DR. MARKS: Okay. And do you know which page that is for Ron?

MS. RAJ: Page 6. Page 6 of 17. Would it help for me to share the screen?

DR. PETERSON: Yeah. That would be awesome.

DR. MARKS: Yeah. That'd be great because I have 72 pages in the document I'm looking at. So 6 of 17 --

MS. RAJ: Okay. Okay. Can everybody see?

MS. FIUME: No.

DR. SHANK: No. Oh.

MS. FIUME: Yeah. Now we can, Preethi. Now it's there.

MS. RAJ: Okay.

DR. SHANK: Yeah. I have it.

MS. RAJ: Yeah. I was thinking you all could possibly use language from here because -- tell me if there's an area where you'd like me stop but -- it has this diagram here I think towards the end and all this language about like how, if particles are between 10 and 100 micrometers, it shouldn't be deposited.

DR. PETERSON: Yeah. But it doesn't say what size the particles are if they are sprayed out.

MS. RAJ: Hmm.

DR. PETERSON: That was my concern. I've seen -- I understand all this but --

MS. RAJ: Okay.

DR. PETERSON: -- there's no information about with the particular chemicals what size are those particles.

MS. RAJ: Okay. As in for the data we have you mean?

DR. PETERSON: Yeah.

MS. RAJ: Okay.

DR. PETERSON: Because you can't assume -- I am uncomfortable with assuming that it's going to be a certain size. But, you know, there are scientists that measure these things.

MS. RAJ: Yeah. I was thinking you might use some language from here.

DR. PETERSON: But we don't know what size they are. So if we knew what size they were, then we could use the language there. That makes sense to me. But we don't know what the size of the particles are.

MS. RAJ: Okay.

DR. MARKS: So would that be an insufficient data announcement?

DR. BERGFELD: Yeah. I think it would be.

DR. EISENMANN: But the difficulty is you're never going to get particle size for every single product because they're highly variable. I mean, this is the issue we go round and round. You need this information, but it's all dependent on the -- it's not just dependent on this ingredient. It's dependent on the formulation. It's dependent on the product, the spray nozzle. There's a whole lot of variables, and it changes from one -- I mean it's very difficult for me to describe, but it changes with each product.

DR. PETERSON: Yeah. I mean I understand that, but for us to say a blanket statement that it's safe because we think this is what's going to happen because we expect the particle size to be X, Y, and Z, we don't really --

DR. EISENMANN: Maybe we need to say the particle size needs to be X, Y, and Z.

MS. KOWCZ: This is Alex, Lisa. Is it possible to -- to maybe have a range, Dr. Marks, where it would be acceptable to the Expert Panel instead of having a specific micron size, have a range of it?

DR. MARKS: Ron and --

DR. BERGFELD: Dr. Marks, if we're confident less than --

DR. MARKS: Ron, I'm going to rely on you in terms of this is -- obviously, if we're really -- that's an important issue. It probably needs to be in the conclusion. And somehow, you know, just as we say, it does not cause -- formulated not to cause sensitivity. Do we put on something to the effect this does not -- formulated with particle size not to cause inhalation toxicity? Other ways we've handled it is have a robust discussion about the inhalation toxicity.

And I think we're ready to go to a tentative report. It doesn't sound like we're going to get any more data, even though, Lisa, you bring up the issue of the particle size. Carol brings up some in terms of that's probably not going to be the whole story. Do we handle it in a conclusion to alert the formulators or the manufactures, or do we handle it all in the discussion?

DR. PETERSON: Well, there is an inhalation study that basically says there wasn't a problem. I mean, so I only raise the particle size because I think that was something that was requested and as a -- you know, I don't want to go down a rabbit hole, but I have trouble with that statement about, if it's this size, then this. But if we don't know what size it is, I'm not sure that we can argue it's safe in the discussion. But if there's been inhalation testing that shows that it's safe -- and there was one study on page -- it's an inhalation study. It's on the bottom of -- I'll have to get to the page.

DR. MARKS: Actually, Ron suggested in December we just use the inhalation resource document and not reopen it. That was, of course, not taking in consideration the suggestion adding ten more ingredients. But Ron, do you still like that?

DR. SHANK: Yes.

DR. MARKS: You said, if there's an inhalation study to support its safety, and then just deal with the inhalation as we've done in the past with the resource document and don't even mention inhalation in the conclusion?

DR. SHANK: Correct.

DR. MARKS: So Ron Shank, you would be in --

DR. SHANK: Rely on the resource document. It explains very well the role of particle size and solubility and chemical reactivity. So if the methicones are formulated such that they are not respired into the deep lung, it should be a no problem from inhalation.

MR. GREMILLION: Can I -- this is Thomas from CFA. This sounds like just to confirm -- we're saying formulated to be non-respirable is --

DR. MARKS: No, that would be a conclusion. That's what I was talking about, Thomas. We would say it's safe, and then in the discussion before that, we would use the resource document to tell the formulators our position as far as inhalation toxicity. That's how I interpret it. Is that correct, Ron?

DR. SHANK: Yes. Yes.

MR. GREMILLION: I mean, I guess it seems like having it in the conclusion would have the advantage of being a clearer flag on potential respiratory risk.

DR. PETERSON: On the bottom of page 22 is the inhalation study. The mice died, but everybody else is fine.

DR. MARKS: Tom, I haven't heard from you. What's your feelings? Just keep it simple with a safe conclusion, add the ten ingredients, and rely on the inhalation toxicity resource document which would appear in the discussion to further elucidate this? And, of course, Preethi, you would include that -- emphasize out that study of safety that Lisa mentioned.

MS. RAJ: Dr. Peterson, where were you looking again?

DR. PETERSON: It's on the bottom of --

DR. SHANK: It's on page 22.

DR. PETERSON: Yeah, 22.

MS. RAJ: Okay.

DR. PETERSON: It's from the previous report.

MS. RAJ: Okay. Is this the, I guess, short-term tox or --

DR. PETERSON: Well, it was a 28-day study. Yeah, short term.

MS. RAJ: Okay. Thank you.

DR. MARKS: Tom, I don't know whether your speaker works or not -- your mic. Are you okay with proceeding in that manner?

DR. SLAGA: (no audible response)

DR. BERGFELD: I couldn't hear you.

DR. SLAGA: (no audible response)

DR. BERGFELD: (Inaudible)

DR. MARKS: I have a feeling, Tom, you don't have your mic on. Monice, does Tom have his mic muted?

DR. BERGFELD: I can't hear her either.

DR. MARKS: It says muted. Well, Tom, raise your hand if you don't like the conclusion. So I'm going to move tomorrow that a tentative report be issued with safe for all the ingredients including adding the ten new ones. And the exception of that, of course, is we aren't going to include simethicone because of the silica issue. And in the discussion, we'll include the inhalation resource document to emphasize the issues with the inhalation toxicity with these -- the lack thereof. Does that sound good, Ron and Lisa?

DR. SHANK: Yes.

DR. PETERSON: Yep.

DR. SHANK: Yes.

DR. MARKS: And then, Tom --

DR. SLAGA: Yeah.

DR. MARKS: I assume you say yes too?

DR. SLAGA: Yes.

DR. MARKS: Okay. Yeah. I can hear you just briefly. Okay. Any other comments before we finish with these? Okay. If not, okay. We'll move onto the next ingredient or ingredients. Let's see. Tris Citrate.

Full Panel – June 9, 2020

DR. MARKS: Okay. Again, I'm working off of two computers and three screens, so I can't exactly -- yeah, I have a lot of comments about this. So, let me see, this is a draft amended report on the safety assessment of Dimethicone, Methicone, and Substituted-Methicone Polymers, from Preethi's February 21st memo. And, in 2003 these ingredients were declared safe by the Panel. And in December 2019, we decided to reopen to review the inhalation toxicity more closely. There was a marked increase in use and concentration since the original report in 2003. And, Paul, if I remember correctly you were particularly concerned about the spray and what the inhalation toxicity might be.

Since that memo, the CIR SCC Committee -- and Lisa and Dan, I don't know if you participate in this new group and clustering working group at that point -- but, it was proposed that 11 ingredients be added including Simethicone. And if you want, I'll read off the other 10 ingredients. Any rate, Simethicone, we had difficulty including as a no-brainer since it's a mix of silica and Dimethicone. And, even though the silica is supposedly amorphous silica, we felt there would be some issues about inhalation toxicity. Even though on Wave 2 there was some clarification about amorphous silica, aerosol formation, particle size, etcetera.

The other ingredients, which were proposed to be added was Capyrl Dimethicone; Hexyl Dimethicone C20-40, 24-28, 26-28, 30-60, and then 32, 20-20 Alkyl Dimethicone, and then Capyrl Methicone, and C20-24 Alkyl Methicone, 26-28 Alkyl Methicone.

Our team felt that we could move forward with an amended tentative report, safe with the added 10 ingredients. And we would rely on the inhalation resource document in the discussion to confirm the safety of these ingredients. So, that's a motion.

DR. BERGFELD: Dr. Belsito, you want to respond?

DR. BELSITO: Yeah, so, we had issues particularly with the ocular toxicity because this is used in products, up to 37.8 percent, around the eye area. And while, of course, they are not meant to be applied to the eye they could accidentally get into the eyes since there are being used around the area. So, we went safe when formulated to be non-irritating -- and this is a new conclusion -- to the skin and the eye.

DR. MARKS: No problem. Do you include the other 10 ingredients?

DR. BELSITO: Yes. And we did not include Simethicone for the same reason that you brought up.

DR. BERGFELD: So, a friendly amendment to Dr. Marks for (audio skips). Dr. Marks?

DR. MARKS: Yeah, that's fine.

DR. BERGFELD: A friendly amendment then.

DR. MARKS: I'll retract my motion, and I will second Don's motion.

DR. BERGFELD: Okay.

DR. MARKS: Concerning formulated to be non-irritating. And you said that --

DR. BELSITO: To skin and eye.

DR. MARKS: Yes.

DR. BERGFELD: That's new.

DR. MARKS: Yes. Well, the new would also be the 10 ingredients too, adding that. So, again, it would be an amended tentative report for both, for those changes in conclusion.

DR. BERGFELD: Amended tentative. Okay? So, we have a motion that's been seconded, amended tentative conclusion. Any other discussion regarding this motion, or this ingredient?

DR. MARKS: I'll let Lisa, Ron and Tom speak if you have any problems with including the irritation.

DR. SHANK: No problems.

DR. PETERSON: No problems.

DR. SLAGA: No problem.

DR. LIEBLER: I'd like to just point out that this is a good example of what our sort of chemist clustering group, with basically Lisa and I, were able to do here. Council has suggested adding ingredients to the report. They came to us first, via Bart. We both discussed them. We came to a pretty quick consensus, and then we were ready to report back to our teams.

I suggest that if we have any future additional ingredients in a certain situation, that this is a good way to handle it. That way the teams can kind of start off on the same footing with respect to our assessment of the chemistry and the suitability including ingredients. Lisa and I can advise our teams. Teams can come to an appropriate conclusion, in this case we were in sync and that's good.

DR. BERGFELD: (Audio skip) favor of this conclusion of an amended tentative report, raise your hand.

DR. MARKS: You were kind of breaking up, Wilma.

DR. BERGFELD: I am breaking up? All right -- now I'm okay?

DR. MARKS: Yeah, now you're better, but I think we all got the message to vote on Don's motion.

DR. BERGFELD: I didn't see Paul vote.

DR. SNYDER: I'm sorry.

DR. BERGFELD: Okay. Any opposed? None? This is then a final report, unanimous.

MS. RAJ: Excuse me?

DR. BERGFELD: Yes.

MS. RAJ: Sorry, Dr. Bergfeld, may I ask a few questions to the Panel?

DR. BERGFELD: Yes, absolutely.

MS. RAJ: So, I know in the Belsito team you had mentioned creating an ocular irritation table, bringing in data from the old report. I just wanted to clarify is that absolutely necessary?

Because I was told, you know, besides making all the data, I guess, available to the Panel in these reports, when it finally goes to the final stage we'll have to remove the old data anyways. So, I just wanted some clarity on that.

DR. SNYDER: I think what we wanted was in the discussion to talk about the new study where there were rabbits, guinea pig and mice, I think, they were treated and there were some pretty profound ocular results. And, in the old report there was also some positive irritation to the eye at 30 percent, and we have a highest concentration of use at 38 percent. That's why we -- but I think we can capture that in the discussion. I don't think we need to (audio skip).

MS. RAJ: Thank you, Dr. Snyder. And, also, specific language that can be added from the inhalation resource document in the discussion?

DR. SNYDER: Yes, around particle size.

MS. RAJ: Particle size? So, is this referring to particle size distribution in different types of products?

DR. BERGFELD: Paul, did you hear that question?

DR. SNYDER: Yeah, I mean, I guess we normally discuss that in the discussion (audio skip) the particle size, minimize the less than 10 microns, you know, according to the boilerplate.

MS. RAJ: Okay. I just wanted to see if there was anything in particular that is, I guess, different from standard boilerplate that should be added.

DR. SNYDER: I didn't have any thoughts.

DR. BERGFELD: Any other questions or comments then? Have we satisfied you, then, with what you need to do for us?

MS. RAJ: I think so.

DR. BERGFELD: Okay. Thank you.

MS. RAJ: Thank you.

DR. BERGFELD: Thank you for your question. All right, Dr. Belsito, the Sulfites.

DECEMBER 2020 PANEL MEETING – THIRD REVIEW: DRAFT FINAL AMENDED REPORT

Belsito Team – December 7, 2020

DR. BELSITO: Okay. So then we're going to methicones. And again, this is one where we got comments ahead of time, from Women's Voices of the Earth, about the spray makeups. It's a little disconcerting. I tried to get the old paper, but for whatever reason Columbia Library stopped carrying that journal 18 months ago. So I couldn't get it.

Was anyone able to look at that paper that she referenced? Because when I looked at it, it didn't really have -- I mean, when I looked just at the abstract, it doesn't really say anything about methicones per se. And I couldn't really figure out what they were saying.

DR. LIEBLER: It was about airbrush particle sizes.

DR. BELSITO: Well, it didn't specifically -- the abstract didn't specifically say airbrushed. It said aerosolization of common nano-enabled consumer products, such as cosmetics, has significantly increased engineered nanoparticle inhalation risks. But do we know that airbrushed cosmetics have nanoparticles?

I couldn't get the full report. I just have the abstract which says that these aerosolized nanoparticle consumer products, even when aggregated -- it says mean total particle concentration pods at five and ten. I mean, it's not my area of specialty, so I don't have the full article.

DR. LIEBLER: Don, I did go to the Vanderbilt site and they do subscribe to Inhalation Toxicology. But when I tried to pull this up, it wouldn't open the issue. And I don't know why.

DR. BELSITO: Well, did you check? Because Columbia stopped subscribing it 18 months ago. So this was like in August of 2019. So that's why I couldn't pull it up, I could just pull up the abstract.

DR. LIEBLER: Yeah. I don't know why. I've got the abstract in front of me. And they use common nano-enabled -- well, I'm sorry, they -- we develop fully automated aerosol generation systems to examine aerosol properties. Where did they say airbrush?

DR. BELSITO: They don't in the abstract.

DR. LIEBLER: Yeah.

DR. BELSITO: It just says nano-enabled consumer products such as cosmetics. And it doesn't say what kind of cosmetic.

DR. LIEBLER: So Alexandra's text to us has additional text that's not in the abstract. So evidently, she was able to access the paper. But it says, the system mimicked consumer application and potential exposure, by spraying a liquid powder cosmetic by a commercial airbrush nebulizer that consumer uses.

And I looked those up, and those are good old fashioned airbrush tools. They produce a very, very fine particle distribution. I know they've been used by hobbyists to spray paint plastic aircraft models. For example, they product a very thin, very even coating of paint. But they can be used for, obviously, all kinds of different things. And I would not be in the least bit surprised if they produced a different particle distribution.

So anyway, the study appears to use techniques that are appropriate to gauging particle size distributions. And these distributions do include a much smaller particle size than we normally associate with sprays and certainly with pump sprays.

So, I think that this has to be -- we really do have to take this into consideration. I don't know how widely used these airbrushes are in application of cosmetic products. But it was easy to me to look on the web and find multiple products in both airbrushes for sale and products that go with them.

So I don't know if we're capturing this in our assessment of products use concentrations. And I just don't know if the industry surveys are capturing this type of application. Because if they're not, it's something, it's a gap in our knowledge that's potentially very important.

DR. BELSITO: And she points out several cosmetics that contain methicone and dimethicone. MAC Pro Performance HD Airbrush Makeup, and dimethicone is the fourth highest concentration, and then it also contains methicone.

MS. RAJ: Good morning, everyone. This is Preethi. I had a question. So Dr. Liebler, you just said something about the particle sizes in the paper being much smaller than sprays in pump sprays. So would then -- I mean even if it is in, I guess, airbrush makeup, I don't know if in our report we have reported concentration of use for airbrush makeup sprays?

DR. LIEBLER: Right. That's my concern. See, I just don't know that industry is capturing this information or that -- I mean, the council's capturing this information. I don't know if Carol is on, she'd be ideal to respond to this.

DR. EISENMANN: Yes. I'm on.

DR. LIEBLER: Oh, Carol, what's up with these things? Have they hit your radar?

DR. EISENMANN: I will have to discuss in more detail with CIR SSC. But I'm not sure our members are the ones that are making these products, that's the problem. But again, you're reviewing these ingredients in the context of the use information that's been told to you. So you could write something, in the discussion, that you're not considering that use at this time because you don't know any information about it.

DR. BELSITO: Well, I mean --

DR. EISENMANN: But I just do the survey based on the FDA Cosmetic Product categories.

DR. BELSITO: I understand. But we do know that they are being used in airbrush makeups that are sold by a major manufacturer such as MAC. And we have some data, although I think it would be nice if when people submit information to us, if they include that they get the right to provide us with a copy of the full report.

But we don't have the inhalation toxicity, that data that would allow us to clear a respirable methicone. So I think that would be insufficient. I think our conclusion should be insufficient for products with the potential for inhalation. We can't say that we're not aware that it's being used in an airbrush makeup that potentially has respirable particles.

DR. LIEBLER: Yeah. I agree with that, Don.

DR. BELSITO: You know? And simply go out in our conclusion and say that the data are insufficient to support use in airbrush makeups or other makeup applications where the particle size could be respirable.

MS. FIUME: And Don, I think didn't Jinqiu is on the line, and I think he's reviewed these papers as well. So if you have any questions specific to him, he could also respond.

DR. KLAASSEN: And Monice just sent us that paper.

DR. LIEBLER: Yeah.

DR. KLAASSEN: We all have a copy of it now.

DR. BELSITO: Okay.

DR. SNYDER: So the point of departure here would be from the 2003 paper where we said that the incidental inhalation was not an issue because of the particle size. We now have data of a different aerosolization method, which we don't know the particle size. Is that the summation of what we're saying?

DR. LIEBLER: No, we actually do know the particle size and it's small.

DR. SNYDER: Okay.

DR. LIEBLER: Yeah, it's submicron. So that's the issue there literally in our face.

DR. KLAASSEN: One to ten microns, I think.

DR. BELSITO: Yeah.

DR. ZHU: Hi. This is Jinqiu Zhu. May I make a comment on this study?

DR. KLAASSEN: Please.

DR. BELSITO: Yes, please.

DR. ZHU: Yeah. I read this paper. So in this study, they assume the spray model, the airbrush system, is very special, you know, it's not a model. The products were sprayed at the whole body or sprayed into the air. In fact, the products are sprayed directly at the nose. So as the author said, this is a nose-only inhalation exposure system. And the spray duration is 20 minutes. So, that is a very long application period. So basically, these studies provide a model in which products that directly spray the nose for 20 minutes, you know.

So because the airbrush system isn't new, it's not like the classical inhalation model previously used. So we're expecting a better inhalation model for airbrush existing reviewing. Because, basically, most inhalation models are using three to five minutes as the spray duration input.

DR. LIEBLER: Jinqiu, I think your point is well taken. But my concern is not really about the toxicology model here that's used, nose only sort of inhalation. But it's the fact that we now know that these airbrushes can generate particles that are much smaller than the other sprayed formats that we've considered on the panel so far.

And if these are being used, then there is a potential for respirable particles. And regardless of the toxicology per se, this clashes directly with one of our sort of underlying assumptions for sprayed particles. Because we've always had some ambiguity as to the extent that are respirable. But here there's a very substantial distribution as shown in figure two of the paper, the Pearce paper, that shows that these particles are in a respirable size range. That's the issue I think that we need to think about.

DR. ZHU: Yeah. I agree. So this study just to showing that there is like the arrow. So generation system is developed. And then we can use this system to generate robust animal data. And then based on the animal data, we can apply the tiered approach as we summarized in our inhalation document. And then to apply some kind of model to extrapolate animal data to human exposure. So for the human health risk assessment, our goal is to determine the actual dose of fine particles that are deposited in the deep lung tissue, right?

DR. LIEBLER: Well, if we use this tiered model to address aerosols produced by airbrushes, I think we'd need some further analysis, wouldn't we?

DR. ZHU: Yeah. Yeah. But we don't have that data.

DR. LIEBLER: Right. We don't have that. We either can say that they're insufficient for products that are delivered by airbrushes, or we would need more data to be able to assess the risk.

DR. BELSITO: Yeah. I think the data are insufficient. We can't say that it's unsafe, simply that the data are insufficient. And what we would need would be a chronic respiratory tox study.

DR. LIEBLER: Right. And it just applies to products that are delivered by airbrush nebulizers.

DR. BELSITO: Right. Well, I think that maybe, Dan, can we be even more generic that sprays, such as airbrushes, that can deliver particle sizes that are respirable?

DR. LIEBLER: Yeah.

DR. BELSITO: And use airbrush as an example?

And looking through this paper it sounds to me like what they were looking at, because they're talking about darker shades, are these spray on tans. And in fact, you're in those machines for 10 to 15 minutes. You're supposed to be covering your eyes and have nasal plugs. But if they're sold directly to consumers, I don't know what the package labeling says about that.

Then I guess the only other comment that I had was -- why isn't this popping up as to where the page was? So anyway, Bart had a comment about our conclusion, where we specifically said about ocular irritation, and we've never done that before. We specify skin and ocular. And I sort of agreed with him. So the conclusion that we had was that yada, yada, yada when

formulated to be non-irritating to the skin and the eye. And that's a departure from naming specific organ toxicities. Should we just say formulated to be non-irritating?

DR. LIEBLER: Right. And then we handle the skin and the eye in the discussion.

DR. BELSITO: Right. And then the other part of our conclusion now is that the data are insufficient for use in spray products that would generate particles that would be respirable, such as airbrush makeups, right?

DR. LIEBLER: Yep.

MS. RAJ: Thank you, Dr. Belsito and team. So would you say maybe a sentence or two added to the second paragraph of the discussion would be sufficient for the insufficient for inhalation part?

MS. FIUME: Actually, can I take us back a step first?

MS. RAJ: Sure. Sure, Monice.

MS. FIUME: Procedurally, Preethi, correct me if I'm wrong, but we have not issued an insufficient data announcement for this report. Is that correct?

MS. RAJ: Not yet, no.

MS. FIUME: So procedurally, I don't think we would normally go ahead with an insufficient conclusion without first requesting data in an IDA. So we would probably need to go back a step to an IDA if it's going to be in the conclusion. Don, do you agree?

DR. BELSITO: Yeah. I think that here's been a substantive change to the conclusion, and we need to give people the 60-day comment period.

MS. RAJ: Okay.

MS. FIUME: And so, then besides requesting the inhalation data, I guess this goes back similar to our conversation earlier today. So we really don't have verified information -- to use Paul's word -- of use of these in airbrush products. So should that be part of the IDA, would be asking for information and concentration of use on these in airbrush products? And possibly particle size information specific to those cosmetics?

DR. KLAASSEN: That's a good idea, yeah.

MS. FIUME: Because if we're going to include that in the discussion about airbrush products, but there's nothing in the body of the report, I would imagine a discussion could be crafted. But there is nothing in the body of the report supporting that discussion item currently.

DR. BELSITO: Okay. So we're going to ask for information regarding concentration of methicones and particle size in airbrush makeups. Is that what we're saying?

MS. FIUME: I think that would support your reason for your insufficiency. But, again, that's up to the panel members.

DR. BELSITO: I think we can certainly bring in the Pearce paper into the report. And then offer that at this point it's insufficient, based upon information regarding concentration and particle size in these airbrush makeups. And if that information suggests that they're respirable, then it would be insufficient for chronic respiratory tox.

DR. LIEBLER: It's an interesting problem because we've got these producers of products, that are apparently outside the usual orbit of the trade association, that are producing what are clearly cosmetic products, and delivery mechanisms that are sort of different than what's covered. So we're not getting data on these. We're not getting reported use concentrations on these. They exist in reality out there, but they're not part of the regular data stream. So they don't go into our reports.

And then they come out of left field when somebody like Alexandra, or Women's Voices for the Earth, you know, or somebody else like that reports them to us. And then we have to kind of come in and try and wedge them into our discussions. So I don't know how we -- this is not a problem that the expert panel can really deal with, except to the extent that we point out that the data are insufficient to support the safety.

And a sufficient amount of these conclusions will eventually build up that it might provide pressure on the airbrush cosmetic industry, if you will, to begin to submit information and play ball. Maybe they will. Maybe they won't. But I think we're kind of stuck with a conundrum here. We basically can say we're aware of this, there are no data, and we can't support the safety.

MS. RAJ: Thank you, Dr. Liebler. I had a question also about council's comment of whether we should have that statement about viscosity in the discussion. I know we had discussed that at the last meeting about how manufacturers don't necessarily say what the viscosity of these ingredients are. But then we don't really know what the viscosity in the formulated product, like the product that's actually used. So I guess council was wondering is that really necessary to have that in the discussion?

DR. LIEBLER: Where did that come from? I don't remember.

MS. RAJ: Well, I think the reason, Dr. Liebler, is because so much of our data when we presented the data, viscosity was mentioned as, I guess, one of the information points or kind of relative viscosities if you will. But of course, in cosmetic manufacturing we have no idea about these. And also there was a discussion, I think, about the difference between what would be used in cosmetics and what would be medical grade. I think dimethicone in one of the studies, that's in the report.

DR. LIEBLER: Because the viscosity of the ingredients probably doesn't control too much what they would be in the actual formulated products.

MS. RAJ: Right.

DR. LIEBLER: I don't remember -- I hope that wasn't something I brought up. I have no recollection of where that came from and why that's in our discussion at all.

MS. RAJ: Oh, okay. Well, I mean we definitely talked about it, but maybe it doesn't warrant being in the discussion. I don't know.

DR. LIEBLER: That's my opinion.

MS. RAJ: Okay. So we can remove that?

DR. BELSITO: Right.

DR. KLAASSEN: I agree. I agree.

MS. RAJ: Okay.

DR. BELSITO: But yeah, in response to your comment about us not getting this data, one of the manufacturers of airbrush cosmetic is MAC. And MAC is a subsidiary of Estee Lauder, which is a member of PCPC.

DR. LIEBLER: Oh. So we should be getting it.

DR. BELSITO: And we're obviously not.

DR. LIEBLER: So phone calls need to be made.

DR. BELSITO: Yeah. I think someone from council should contact the people at MAC. And, you know what I mean, because this is really embarrassing quite honestly, to me. To have this brought up by someone who is not even -- I mean, fortunately, who is monitoring the situation, and we didn't know about it.

DR. LIEBLER: Right. I think we appreciate the efforts of Alexandra and Women's Voices because they brought this to our attention.

DR. BELSITO: Yeah.

DR. LIEBLER: But it shouldn't happen that way.

DR. BELSITO: But it's embarrassing that they had to do that. Just a statement I have to make. And it's upsetting to me because it's my reputation and all of our reputations that go in these reports.

Okay. So basically insufficient for products that have aerosol delivery systems that could deliver respirable particles such as airbrush makeups. And we would need particle size, concentration, depending upon particle size and concentration, and chronic respiratory tox. But just looking at the ingredient list on that MAC, you know, with dimethicone or methicone, dimethicone being the fourth ingredient listed, the concentration's going to be fairly high.

DR. LIEBLER: Yeah. One other point that comes from this is that we may need to think about updating the respiratory boilerplate to consider airbrush delivery devices. This was on the chat, the meeting chat suggestion again from Alexandra Scranton. So, I think it's a good idea for us to put on our to do list.

DR. BELSITO: Yes. I agree. I think probably at the spring meeting we should take a deep dive into that respiratory boilerplate.

MS. FIUME: Noted for that agenda.

DR. KLAASSEN: After we know more about the airbrush.

DR. LIEBLER: Right.

DR. KLAASSEN: I mean, we have to learn about the airbrush before we kind of --

DR. BELSITO: So should we have --

DR. KLAASSEN: -- before we modify the boilerplate. I mean, both need to be done, but I think first of all we need to learn about this whole airbrush phenomenon and what's going on there. Because that might do more than anything to alter our boilerplate.

DR. BELSITO: Well, I mean that's my point, Curt. We should get that information -- a report should be the inhalation boilerplate. And all the information we can get out about airbrush makeups, we should be able to review before that meeting.

DR. KLAASSEN: Okay. I agree.

DR. BELSITO: And this would be like a separate ingredient almost. And it may be helpful if we could get an expert, maybe even two experts, one for, one against, if there's anyone who's saying that airbrush makeups deliver non-respirable particles. I don't know.

DR. LIEBLER: These devices have been around for a long, long time. I used an airbrush when I was about 13 years old when I was painting plastic airplane models.

DR. BELSITO: I figured you did, but you weren't painting your face.

DR. LIEBLER: I don't know when they were -- I don't know when -- right, exactly. No. I didn't paint my face. But I don't know --

DR. KLAASSEN: Unless Don's trying to paint the mustache.

DR. LIEBLER: I don't know when these started to be applied for makeup, but these devices have been around for a long, long time.

DR. BELSITO: I think they became popular with the tanning industry.

MS. FIUME: So Carol, is that something industry thinks they could provide some speakers for the panel?

DR. EISENMANN: I won't know until I ask them.

MS. FIUME: Okay.

DR. BELSITO: Yeah. I would start with Estee Lauder, Carol, and the people in MAC.

DR. EISENMANN: I will.

MS. RAJ: Would the panel want some background information as to when, I guess, airbrush makeup application started, to be in the report?

DR. LIEBLER: No. Not necessarily.

MS. RAJ: Okay.

DR. BELSITO: I mean, we don't really care when they came into existence, the fact is they exist, and we have to be (audio skip) them.

MS. RAJ: Right. Right.

DR. BELSITO: Okay. Anything else on the methicone? So this was to be a tentative final and it's now going back to where, Monice, exactly?

MS. FIUME: It will go back to an IDA status since we have an insufficiency. And that hasn't been asked for previously.

DR. BELSITO: Okay. Okay. So it goes back to IDA. Anything else? Okay.

MS. RAJ: Thank you.

DR. BELSITO: Let me select this. Yes. I want to save the changes. Okay.

Cohen Team – December 7, 2020

DR. COHEN: This is a draft final amended report. This is Preethi's. Safety was assessed in 2003 and then reopened in 2020. At the June meeting, the Panel decided it was appropriate to add ten additional ingredients for a total of 30, and simethicone was excluded, I think, because of the silica.

Caprylyl Methicone had the highest use concentration of all the newly added chemicals, at 16 percent in an eye lotion. And dimethicone is now reported to be used at 85 percent in a moisturizing formulation. There was a fair amount of new information included in this report.

Before we talk about some issues of how we sort of sign this out, I'll just to ask the team for their comments and thoughts. Tom, you want to start?

DR. SLAGA: I wouldn't have any toxicological concerns. Isn't this the one that we have the Women's Voices?

DR. COHEN: Yes, right.

MS. RAJ: Yes, Dr. Slaga.

DR. COHEN: Yeah, we'll talk -- yes, I wanted to bring that up afterwards.

DR. SLAGA: I have no problems with it.

DR. SHANK: I think the report is okay.

DR. COHEN: What about you, Ron?

DR. SHANK: Yeah, Ron Shank. I think the conclusion is okay as is. I would leave in the eye because there are several formulations used around the eye, so that doesn't bother me that that's a part of the conclusion.

The issues raised by the Women's Voices of the Earth is about inhalation of small particles, this is airbrushed makeup products, and that's not listed by the PCPC, so I don't know what these products are. So, if PCPC can tell us are these airbrushed makeup products to be considered in this report. And if they are, and these are all nano-sized particles, then we have to discuss this because that would be a potential for inhalation toxicity. That's all I have to say.

DR. COHEN: So were you able -- so you reviewed the letter, and they discussed these very small particles, and it's not clear to you --

DR. SHANK: Yes.

DR. COHEN: -- whether the airbrushed devices are similar to the atomizers we have in our boilerplate language?

DR. SHANK: Correct. They aren't. They are apparently producing very, very small particle sizes. And we haven't had that brought to our attention, by PCPC, that this is a cosmetic product. So I think that needs to be clarified.

MR. GREMILLION: Can I also -- sorry, this is Thomas Gremillion from CFA.

DR. COHEN: Go ahead, Tom.

MR. GREMILLION: I just wanted to --

MS. KOWCZ: Are we using raise the hand or not? Sorry. Are we using raise the hand here or not? Or are we just speaking? I just wanted to bring that up.

DR. COHEN: Well, we can use the raise the hand only on the nine people on this screen, so if you'd like, you want to start and then -- go ahead. I do see your hand there.

MS. KOWCZ: Okay. Thanks, Dave. I just wanted -- this is Alex from PCPC. So we don't have any information on the companies that make the airbrush. But I don't think we have any members that are involved in that at all. I just wanted to make sure that that was clear.

DR. BERGFELD: What does the FDA say about devices of such? They regulate devices.

DR. SADRIEH: Yeah, the FDA regulates devices for medical use. I don't know about, you know, these devices.

DR. COHEN: Okay.

MR. GREMILLION: I wanted to ask --

DR. COHEN: Is this the situation -- sorry, go ahead, Tom.

DR. SADRIEH: But, even if the device were regulated, it's the product that is in nano -- you know, the particles come from the product. They're not coming from -- you know, the device is sort of like the delivery system for it, but it's the product itself that is capable of becoming sort of -- that turns into a nano particle, and that is made available that way.

DR. COHEN: But, if it's a liquid that normally could be applied with a finger, we'd never have the conversation about this. It's the way it's delivered that's creating the particles. So I think you're right, you might not be able to have certain particle sizes with certain of these devices, but I suspect that this combination is very much device dependent. But I would need more information. I'm sorry, Tom, go ahead. You had your hand raised.

MR. GREMILLION: Yeah, not to get this off track, but I also just wanted to ask about what it means to "formulate as non-irritating to the eye?" The report starts out just pointing out this is unprecedented, and the reasons why it's kind of a new issue. I looked back at the transcripts, and there's something about one of the studies having different pH levels. And I just wondered if there was an alternative way of addressing this eye irritation potential without just saying, "formulated to be non-irritating." It seems like that's a bit of a (inaudible).

DR. BERGFELD: It can go --

DR. COHEN: Tom, that's the next thing on my agenda.

MR. GREMILLION: Okay. Sorry.

DR. COHEN: That's the next thing on my agenda. For the particle size, is this a circumstance -- since FDA isn't sort of regulating this, and PC doesn't have information on it either, do we need an outside source to help us adjudicate the issue of the device and the particle size? Bart, do you have any advice in this?

DR. HELDRETH: Sure. So, if what I think you're getting at is that we really don't understand the safety of these ingredients if used in these airbrushed makeup devices.

DR. COHEN: Mm-hmm.

DR. HELDRETH: If that's the case, and we feel like we have insufficient data for that use --

DR. COHEN: Ah. Yeah.

DR. HELDRETH: -- the Panel can conclude insufficient data for this type of use. So the Panel could say, safe for this use or that use, maybe depending on the use type. Here in airbrushed makeup, maybe we don't have the right information for that. So that's one possibility to go down that road.

We previously had issues with particle size and inhalation issues, and often it's very difficult to figure out what the right answer is, even when the experts come in and talk to us about it, because it seems to vary from not only ingredient to ingredient, but airbrush device to airbrush device, what kind of particle size are you going to get out of it.

DR. COHEN: Ah. Yeah.

DR. HELDRETH: If you feel like you don't have the information in front of you, to make the call on that, you can say that I don't have enough information.

DR. SHANK: I like that. I think that's a good way to go.

DR. COHEN: Well, I --

DR. BERGFELD: I do too.

DR. COHEN: I do too.

DR. PETERSON: I like it as well.

DR. SLAGA: I do too.

DR. HELDRETH: And then, if that becomes the conclusion of the Panel, and the report goes final, two years from now the conclusion for use in airbrushed makeups of these ingredients will go to a use not supported category.

DR. SHANK: Okay.

DR. PETERSON: That's great.

DR. COHEN: I like that. Now, I just want some help from the Panel and the other experts as this is my first meeting. But this issue which is, formulated to be non-irritating for the skin and the eye. And Preethi, in her report, called that out and made some specific issues that I thought we might go through and you can help me get through.

One is that the eye is incidental. We have other products coming up later in our agenda that have considerable eye toxicity. And I'm sure there's been many like this. So how do we deal with that? This is an incidental exposure.

Second issue was that most of the reported uses of the ingredient are not categories for use in the eye area. I don't know if I agreed with that because, when I looked in the use tables, there were hundreds or thousands of hits for eyeliner, eyeshadow, eye lotion, eye makeup remover.

DR. SHANK: Correct.

DR. COHEN: So, I just need a little help there. And, third, with the issue of historically utilized conclusions, based on concentration of use rather than organ systems, and formaldehyde was used as an example, but there's a lot of products in this assessment, and it's not the same as giving a single concentration. And how does one formulate to be non-irritating in the eye? Does that mean that it goes in eyes? So, can you guys help me through this? I don't know if I could support it.

DR. PETERSON: So, when you put on makeup -- I mean, yeah, I think it would be helpful to talk to somebody that actually uses these products. They do get in your eye sometimes by accident or -- I think numerous eye makeups can be irritating to the eye.

So, I guess, my -- so it's a fact that eye makeup can be irritating to the eye. And it would be nice if they'd formulate it so it wasn't. But I'm guessing, you know -- so my question is, this has not got to be the first product that has had some eye irritation issue, and I think we should be consistent. So, if in the past, they just were formulated to be non-irritating. Otherwise, I could be supportive of starting and going forward, saying not being irritating to the eye. Because it certainly would be nice for eye makeup not to be irritating to the eye.

DR. COHEN: So what kind of tests would you expect?

DR. SLAGA : I agree with that. I think we should deal with the eye in the discussion and have just, formulated to be non-irritating to the skin. And do not add the eye but discuss that in the discussion, emphasizing that care should be taken when it's around the eye.

DR. COHEN: I agree.

DR. SLAGA: We have never used that before.

DR. BERGFELD: Yep.

DR. PETERSON: So is the exact statement, "to formulate not to be irritating to the skin" or just "not to be irritating," and then we put --

DR. SLAGA: Not to be irritating, with the skin being understood.

DR. PETERSON: Right. But if we put both, it's potential irritating to the skin and eye in the discussion, then we can go with the historical phrase, which is "to be formulated not to be irritating".

DR. SLAGA: Okay.

DR. PETERSON: But the discussion --

DR. SLAGA: That could be discussed.

DR. BERGFELD: I agree.

DR. COHEN: I guess my concern was when we signal that, what information are we looking to get back that would allay our concerns? I mean, we have ocular tox. We have ocular tox on a lot of products, and some of them can be very irritating to the eye, and we've never used this.

DR. SLAGA: Mm-hmm.

DR. COHEN: We can't specify a specific concentration because there's so many on here. I like Tom's point about just calling a little further out in the discussion about that. Ron, what do you think?

DR. SHANK: Yeah, you can handle it in the discussion. I don't mind it being in the conclusion, but, if the rest of the Panel would like to see us stick to what we've been seeing in the past, "when formulated to be non-irritating," and then discuss ocular irritation in the discussion section, that's fine with me, either way. I don't think it's a big deal.

DR. COHEN: Yeah, Wilma?

DR. BERGFELD: I think that you have to consider if you do it for this, you're going to have to do it for all that come up under eye preparations in the future and maybe going back.

DR. SHANK: Yeah.

DR. BERGFELD: That is a strong consideration here. So, I would approve of it. If you want to mention it in the discussion, that's fine, but I don't think we should make it a big callout.

DR. SLAGA: Right.

DR. COHEN: Yeah, I had a hard time understanding it this past week as I was reviewing it. Okay. So, we would proceed as -- what would be the verbiage? Is it safe as used in present practice and concentration and formulate to be non-irritating?

DR. BERGFELD: Yes.

DR. SHANK: Yes.

DR. SLAGA: Perfect. Yeah.

DR. COHEN: And everybody was in favor of that?

DR. PETERSON: Yes.

DR. SHANK: Yep.

DR. SLAGA: Yep.

DR. COHEN: And we'll put insufficient data for airbrushed use.

DR. BERGFELD: In the discussion.

DR. SLAGA: Yes.

DR. BERGFELD: In the discussion.

DR. COHEN: In the discussion. In the discussion. Okay. Let me mark that down.

MS. RAJ: Thank you, Dr. Cohen. I had a few things to ask. So, does the Panel think that there needs to be any more changes to the Ocular section in the discussion, based on what you were just talking about?

DR. PETERSON: Yes.

DR. COHEN: Well, I think in the discussion, in that second to last paragraph, where it says, "However, the Panel stated that manufacturers should be cognizant of incidental and accidental exposure to the eye and specified that products containing the ingredients included in this report must be formulated to be non-irritating to the eye." I think the last part of that sentence needs to be edited to be non-irritating, because you can call out the importance of the incidental and accidental exposure in the eye, and we talk in that paragraph about the ocular irritation.

MS. RAJ: Okay.

DR. COHEN: Does anyone want to add anything further from the Panel? Any thoughts on more of this -- more in the discussion on the ocular toxicity?

DR. BERGFELD: I think at the bottom of that, in the next paragraph, in the last sentence, "must be formulated to be non-irritating," it should be "should."

MS. RAJ: Okay.

DR. BERGFELD: I don't think it should say "must."

MS. RAJ: Okay. Thank you, Dr. Bergfeld.

DR. COHEN: Yeah.

MS. RAJ: So, the Council had brought up a question about whether we need to have that statement on viscosity. Because in a prior meeting, Dr. Cohen, we had discussed the difference between medical-grade dimethicone and what could possibly be the version in cosmetic products. Because a lot of, I guess, the data in this report, if you noticed, they mention the viscosity of the ingredients. Of course, we wouldn't know what the viscosity would be in a formulated finished product, but the Council felt that maybe that short one sentence in the discussion wasn't necessary.

DR. SHANK: I agree, definitely.

MS. RAJ: Okay. Okay. Thank you.

DR. SLAGA: I do too.

MS. RAJ: Okay.

DR. COHEN: So it gets struck?

DR. SHANK: Yes, that one sentence.

MS. RAJ: Thank you.

DR. COHEN: Okay. Any other comments? Okay. Next is the Glycerin Ethoxylates.

Full Panel – December 8, 2020

DR. BELSITO: Okay, so, this was another interesting material. Of course, I just lost it here. So, at the last moment we got, again, a letter from Women's Voices for the Earth, pointing out that this was being used in spray makeups, or airbrush makeups I should say; accompanied by an article by Pearce et al., indicating that the aerodynamic diameters of particles delivered by these aerodynamic sprays are within the respirable range. Which sort of throws a monkey wrench into our safe as used conclusion (audio skip) respiratory boilerplate.

And, so, we thought that we would like a little bit more information on particle size. We would like the ability to review the Pearce paper. And, so, we would like to move this back to an insufficient data announcement to further look at these sprays, these makeup spays, and to further look at the -- more time to look at the data that was presented in the Peirce paper that we really didn't have time to fully evaluate because neither Dan or I could access the complete manuscript. Monice did send us a copy, but it was in the middle of the meeting. Dan, I don't know if you had a chance to review it any further last night or if you have any additional comments?

DR. LIEBLER: No, I don't have anything to add right now. I mean, the key point of that paper I thought was that the particle size distribution is definitely in the respirable range.

DR. BELSITO: Right, and if it is then we would need chronic respiratory toxicity to cover these -- whatever they call these -- airbrush makeup applications.

And we also sort of discussed a little displeasure with the fact that one of the companies that was quoted by Dr. Scranton as making this, is a MAC preparation, which is a subsidiary of Estee Lauder which is a PCPC company as far as I'm aware. And, we were just not made aware of these product types.

So, again, sort of caught blinded here. So, if in fact these particles are respirable, then we'd have to change our conclusion regarding airbrush makeups. And they would be insufficient pending a chronic respiratory toxicity.

DR. BERGFELD: So, your motion is to go out with another IDA. And I just have to ask Bart about -- this is a final, so what is the protocol for this? Does it go out -- in what manner?

DR. HELDRETH: Yes, anytime there's a new data need that's separate from a previous data request, yes, the Panel may issue an additional IDA.

DR. BERGFELD: Okay.

DR. HELDRETH: Alternatively, the Panel could form a conclusion, although the report could not go final; it can come back as a tentative that has an insufficient conclusion for the airbrush use.

DR. BERGFELD: All right.

DR. HELDRETH: So, either option is available to the Panel.

DR. BERGFELD: And Don is proposing IDA. Is there a second to Don's motion? Dr. Cohen, is your team seconding, or agreeing?

DR. COHEN: We had some other comments so maybe we should wait for a second.

DR. BERGFELD: Please -- any other one -- anyone seconding?

DR. COHEN: Okay, I --

DR. BERGFELD: Well go ahead, since there isn't. Go ahead. We're still going to discuss.

DR. LIEBLER: I'll second Don's motion so we can have discussion.

DR. BERGFELD: All right, go ahead.

DR. COHEN: So, Don, we sort of came up -- it's not a split, but a safe in the present practices of use and concentration, and insufficient data for use with an airbrush device. We thought the other uses seemed reasonable. We also have formulated --

DR. BELSITO: We can't say safe as used in the present practices of use since we know presently it's being used in airbrush makeups.

DR. COHEN: Wait, so we can't have safe except airbrushes?

DR. BELSITO: Well, we could --

DR. COHEN: Or can't (inaudible) insufficient?

DR. BELSITO: We could say safe as used in cosmetic products that are not applied by airbrush technology, and insufficient in products that are applied by airbrush technology, pending chronic respiratory toxicity. Or just insufficient for airbrush use, and the insufficient data would be (audio skip) respiratory toxicity. We certainly could do that.

DR. COHEN: I like that.

DR. SHANK: I favor that.

DR. HELDRETH: Yeah, this would be very similar to what we did when we looked at Formaldehyde and Methylene Glycol. We said safe as used for nail use. Then we had a percentage for skin topical use. And then we said unsafe for the hair straightening treatments. So, we divvied it out by application.

DR. BELSITO: I mean, I'm happy with that.

DR. BERGFELD: Okay. We have one more comment or a question, Preethi?

MS. RAJ: Yes, Dr. Bergfeld, good morning. I just wanted to confirm with the Panel, I believe both teams said yesterday that we are changing the conclusion to, safe when formulated to be non-irritating not specifically to the skin and eye as it was presented. Correct?

DR. BELSITO: That's correct Preethi.

DR. COHEN: Yes.

DR. BELSITO: Just safe when formulated to be non-irritating.

MS. RAJ: Okay.

DR. BERGFELD: I think both teams agreed to that, yes.

MS. RAJ: Thank you, yes. And also, I appreciate you mentioning the Pearce paper. It sounds like the Panel just wanted time to review this paper. But since we technically don't have data to support the kind of data that's in that paper, it sounds like you just need to review the paper, but it won't necessarily need to be brought into our report, correct?

DR. BERGFELD: Don?

DR. BELSITO: Well, I think the paper needs to be brought into the report to show that the aerodynamic size of particles generated by these airbrush makeups are respirable as demonstrated by the Pearce paper. Which is what causes us to say that the data are insufficient to support the safety of the use of methicones by airbrush technology.

MS. RAJ: So, would that be brought into the discussion, Dr. Belsito?

DR. BELSITO: It would be, I think -- I'm not sure where you'd bring the Pearce paper; you can't bring it into the discussion until you bring it into the report. So perhaps, as part of our usual respiratory boilerplate and use section, you can put that, the Panel is aware of the use of methicones in airbrush technology, and that the data would indicate that aerodynamic particle size generated by these airbrush sprays are potentially respirable. Just something to that extent.

MS. RAJ: Okay.

DR. BELSITO: And then at the discussion you could point out that we don't have chronic respiratory toxicity on these, and therefore the data would be insufficient for use in a product that would deliver respirable particles such as airbrush makeup applications.

MS. RAJ: Okay. Thank you, that's helpful.

DR. BERGFELD: Any other questions?

DR. SHANK: Well, I don't think you want chronic inhalation.

DR. BELSITO: You don't think we want to --

DR. SHANK: This is Ron Shank. I don't think you want a chronic, because even with the airbrush you wouldn't apply it for days on end. Chronic would be like several months exposure.

DR. BELSITO: But, I mean --

DR. SHANK: So, just say inhalation.

DR. BELSITO: I don't know how women use this. Wouldn't you spray on makeup every day?

DR. BERGFELD: Yes.

DR. SHANK: But not all day. The duration of exposure is very important in inhalation toxicology.

DR. BELSITO: Then I think what we probably would need, in addition, is how these products are used. I mean, I have no clue as to how they're used.

DR. SHANK: Right.

DR. BELSITO: Are they simply used for tanning? Because there was this whole thing about darker pigment in the Pearce paper, making me suspect that they could be used for the spray tans that people get. In which case they may be getting them only every two to three weeks. I don't know in what type of product they're used. But if it's used in a women's foundation base, that's something that could be used every day.

DR. BERGFELD: Well, I think that Don -- Ron didn't you say you just would say inhalation studies rather than chronic? Just make it generic?

DR. SHANK: Yes.

DR. BELSITO: All right. I mean, I'm fine with inhalation studies.

DR. SHANK: Okay.

DR. BERGFELD: Okay. Well, we have a motion that has been seconded that talks about going out as an IDA. And, Don, are you going to rescind that and go with Dr. Cohen's motion?

DR. BELSITO: Yeah. So, I'll rescind that and go safe as used in products where the particle would not be respirable, and insufficient in delivery systems such as air-spray makeup technologies, which would deliver respirable particles, or something to that effect. It needs to be wordsmith.

DR. BERGFELD: That's a conclusion, that long piece? That should be in the discussion don't you think?

DR. BELSITO: Well, no, we need to tell what kind of products it's insufficient in.

DR. BERGFELD: Well, insufficient in sprays, I guess. I mean, something shorter.

DR. COHEN: How about --

DR. BELSITO: I mean, you can't say sprays, Wilma, because it's sufficient in pumps and the other types of sprays we look at.

DR. BERGFELD: Okay.

DR. BELSITO: It's only insufficient in airbrush sprays that deliver respirable particles.

DR. BERGFELD: Well then airbrush sprays. David, you have something, Dr. Cohen?

DR. COHEN: No, no, I think Don just clarified it.

DR. BERGFELD: Okay. So, the conclusion will be split, a split conclusion here.

DR. BELSITO: Yes.

DR. LIEBLER: Wilma, Tom Gremillion has a comment.

DR. BERGFELD: Okay, thank you. I didn't see his hand.

DR. GREMILLION: Yeah, a question. So, it sounds like the boilerplate -- in aerosol products 95 to 99 percent of droplets and particles would not be respirable to any appreciable amount. Is that boilerplate being abandoned now, or is it some special about this?

DR. BELSITO: Thomas, we actually discussed that in our team yesterday, and felt that that should be something that we address specifically at a future meeting, that boilerplate, with more information about these airbrush sprays and the use of nanoparticles in sprays.

So, yes, I think the answer to your question is at least my team felt that we need to relook at that boilerplate.

DR. GREMILLION: Okay.

DR. BERGFELD: Okay? So, we have a new motion. And we have a seconded, I believe. And, any other comment before I call the question on the new motion of the split conclusion? All those opposed indicate by stating your name. I hear nothing so unanimously approved a split conclusion on this ingredient. Thank you all, and if there's any problem with the discussion, I'm sure that Dr. Belsito and Cohen can assist. Okay, moving on to Wheat, Dr. Cohen presenting.

DR. HELDRETH: Dr. Bergfeld?

DR. BERGFELD: Yes, go ahead.

DR. HELDRETH: Before we move on, could I suggest a historically more common type of conclusion to the effect of, safe as used when formulated to be non-irritating except that the data are insufficient in airbrush cosmetics?

DR. BERGFELD: Is that acceptable, Don and David?

DR. BELSITO: That's perfect. Thank you, Bart.

DR. COHEN: Yeah.

DR. HELDRETH: Okay, Thank you.

DR. BERGFELD: Thank you. Thank you for cutting down all those words. Thank you. Dr. Cohen, Wheat?

SEPTEMBER 2021 PANEL MEETING – FOURTH REVIEW: DRAFT FINAL AMENDED REPORT

Belsito Team – September 13, 2021

DR. BELSITO: Okey-doke, so now we're moving on to methicones. So, at the December 2020 meeting, we had a draft final amended report on 30 ingredients in the absence of needed data on particle distribution, size, type, and duration of exposure. We issued a revised tentative amended with a split conclusion, safe in cosmetics in the present practices of concentrations of use when formulated to be non-irritating, but insufficient to make a determination of safety for the utilization of these ingredients with airbrush use.

But now we go back to the discussion that we had with the silicates and the hair sprays and deodorant sprays, which I did not address because I missed the Women's Voices of the Earth comments.

So, I had just okay, safe as used just as airbrush, but do we need to go back and what are the aerosol uses here?

MS. RAJ: Well, Dr. Belsito, I can tell you that there is an 18.6 percent use of dimethicone in spray deodorants, which might have been what WVE was referring to.

DR. BELSITO: Yeah. It looks like for amino bispropyl dimethicone, incidental inhalation spray, 9 -- 8.4, 9. It's pretty high.

DR. SNYDER: So what drove it? Do we have any indication what drove the dramatic increase in frequency of use to almost 8,000 and 0 for methicone to 579? What drove that?

DR. BELSITO: Probably because it believed to be calming to the skin. It's like bisabolol. It's thought that these methicones are used in a lot of barrier repair creams and things like that. So I think that's probably what's driven the increase, but that's just a guess.

So we have spray uses, so I think we need to, at this point, do what? Amend our conclusion?

DR. LIEBLER: So we addressed this with the silicates because of the issue of crystalline silica.

DR. BELSITO: Right.

DR. LIEBLER: And, I mean, that's not an issue with these molecules, so I'm not sure. Aside from the airbrush, I'm not sure why we would display a concern about incidental inhalation.

DR. BELSITO: Well, because the only data that we have on inhalation is five rats, four hours, nose only, 25 percent dimethicone. We have no long-term studies.

DR. SNYDER: You get that new data that you just stated, 18.6 percent in spray deodorants. That's quite a bit higher.

DR. BELSITO: Yeah, I know. That's what I'm saying.

DR. SNYDER: Yeah. Okay.

DR. BELSITO: It's not just airbrush. I mean, we know from what Alexandra sent us that the particle sizes in these sprays, both deodorant and hair, can be respirable. We don't have any data to support inhalation of methicones.

MS. FIUME: So, Don, did you see the information from the old report on PDF page 50 where it was 29-day studies of dimethicone? Is that information at all helpful in determining safety in products?

DR. BELSITO: I didn't think 29 days was helpful either, but again, inhalation is not something that is my forte. Dan, Paul, your thoughts on a 29-day inhalation study?

DR. LIEBLER: I couldn't tell you that myself.

DR. SNYDER: Well, what specific study are you talk -- there were ones that were cats, rabbits, and guinea pigs, and rats.

DR. BELSITO: That's the one.

MS. FIUME: Yeah, so that was summary data from the old report.

DR. SNYDER: That's actually negative because all four mice died in the 20th exposure. Three others died during the post-dosing. The link between treatment and death was uncertain. I mean, that's not a very powerful study, but there is pause there I think.

DR. BELSITO: Yeah. I mean, dark and mottled lungs, fluid in the trachea. It began, at least one of them fairly high concentrations of use in these sprays.

DR. SNYDER: What about the method of manufacture and the impurities, Dan?

DR. LIEBLER: Oh, I had no problems.

DR. SNYDER: With regards to incidental inhalation? Nothing?

DR. LIEBLER: Nothing, no.

DR. SNYDER: Okay.

DR. LIEBLER: It doesn't shed any light on incidental inhalation, I mean I think that other than this issue I thought the report looks fine. I didn't have any edits.

DR. BELSITO: I didn't either, but --

DR. SNYDER: I didn't either until she said 18.6 percent of the spray deodorant because then it was only the airbrush issue, which I assume we're going to deal with.

MS. FIUME: The actual spray is up to 85 percent dimethicone.

MS. RAJ: I'd only mention that particular one because I know, for silicates, I think there was no deodorant spray use for those ingredients, but, since that memo was for both methicones and silicates, I figured maybe they brought up the deodorant spray because we have this percentage here in this report.

DR. LIEBLER: So, in conclusion, if we put in that data are insufficient to support use in products with incidental inhalation, that's the nuclear options for those. The other possibility is that we can put something in the discussion.

DR. BELSITO: But, if we truly believe it's insufficient to support it, how can we discuss our way out of that?

DR. LIEBLER: Yeah.

DR. BELSITO: I mean, I think, again, we need to go back and address the respiratory boilerplate given the new information that we have on potential particle size in these sprays and the lack of inhalation tox data on the methicones, we have to go insufficient.

DR. LIEBLER: Mm-hmm. Okay, well, I don't see an alternative to it that I think we can live with, do you?

DR. BELSITO: I don't.

DR. LIEBLER: Then I think our path is pretty clear. So, after the first sentence of the conclusion, we need to insert that the data were insufficient to support the safety of these ingredients in cosmetic products where incidental inhalation may occur.

DR. BELSITO: Yeah, so we need to finesse even the first sentence because we're saying in the present practice for use and they're used in sprays. Are safe in non-aerosolized cosmetics?

MS. FIUME: That would be new language.

DR. BELSITO: Well, how do we usually say it when there's both non-inhalation and inhalation exposure and we're going to go insufficient for inhalation?

MS. FIUME: I think we've done either products that can be inhaled or when incidental inhalation may be expected. I think it's been in both ways.

DR. BELSITO: Okay, so what are we going to say here? "The Expert Panel for Cosmetic Ingredient Safety concluded that the following 30," yadda, yadda, yadda, "are safe in cosmetics." We can't say in the present practices of use; that sentence is now incorrect.

I mean to me the simplest way to say is, safe in non-aerosolized cosmetics in the present practices of use as described are non-formulating. However, the Panel also concluded the available data are insufficient to make a determination of safety for the utilization of these ingredients in products with the potential for inhalation exposure. Would that be okay?

DR. SNYDER: Have we asked for inhalation data to support safety then?

DR. BELSITO: Well, we've got to offer data because --

DR. SNYDER: Did we go out IDA on this and ask for inhalation data?

MS. FIUME: So I'm trying to look back to the minutes to see what has been discussed about it. So in December 2020 --

DR. SNYDER: We had ten ingredients. That's all I have in my notes. I don't have anything about an IDA.

MS. FIUME: So, Preethi, these are correct that, after the June meeting when they would have originally seen the draft amended report, did we go a tentative amended report?

MS. RAJ: Yes.

MS. FIUME: What was it?

MS. RAJ: I recall in December, even though we went from the draft final amended to a revised tentative amended report, we did put those data needs out there. I don't know if it was called a formal IDA, but the Panel did say that they needed additional information to confirm safety for airbrush use.

DR. SNYDER: Yeah, that's what we're kind of stuck on because we now have this new information, if we verify it regarding these deodorant sprays which is a different issue to me than what we were dealing with before.

DR. BELSITO: Right.

DR. SNYDER: Because that's --

DR. BELSITO: Well, I mean, then I think your point is valid. It looks like we never -- I mean we just went ahead with our understanding of the respiratory boilerplate and went with a safe as used without specifically asking for the additional data on inhalation, so I think we need to -- I don't know -- bring this back as an insufficient data and ask for chronic inhalation or additional inhalation studies?

MS. FIUME: We have asked for particle size and inhalation studies at the last go around. So that has been asked for as part of the tentative amendment report.

DR. BELSITO: Okay.

MS. FIUME: So Paul and all of you, can you help me understand the language that is on PDF page 46 regarding deodorant sprays, is it that you no longer accept what is said in that boilerplate language?

DR. SNYDER: I guess we got that data that says that up to 50 percent of the particles are in respirable range. We didn't have that before, did we?

DR. BELSITO: No. Well, the data was there; we didn't have it. Alexandra provided it. I think, as Monice said, we need to get back and look where these -- vetted articles. I mean, we just have not looked at the articles that are quoted there. So I think we need, again, to relook at the respiratory boilerplate. We need to look at those articles. We need to search to see if they're -- I think she's probably been very complete if there were additional articles. She may or may not have brought them to our attention, but I think we need to revise the literature search and see what else we can find on these particle sizes.

As Dan pointed out we have four references that really are one reference, and we need to clear that up. But, until we do that, in the absence of inhalation toxicity or information that these sprays where it's up to 86 percent do not contain respirable particles, that's not the information that Women's Voices of the Earth is telling us. I don't think we can assess safety for aerosolized products.

MS. FIUME: So I'm trying to look at the resource document that does exist and we do in it, it says, "Propellant, deodorant, antiperspirant sprays have consistently small or medium particle and droplet sizes than propellant hair sprays. The mean values for volume size under 90, 50, and 10 nanometers released from the antiperspirant sprays are 4.1, 23, and 35.3 micrometers, respectively." So I don't think we've ignored that information in the past. That's why I was wondering if -- and I know it's been a long time since it's been looked at so I think Jinqiu's point was she may have been combining some thoughts in what she sent to us.

But I don't, not being a trained toxicologist, I can't say that one way or the other based on what I'm looking at. But, in the past, we have looked at the fact that deodorant sprays do have different particle sizes than the regular hair sprays.

DR. LIEBLER: Tracy Guerrero's got her hand up.

DR. BELSITO: Yeah.

MS. GUERRERO: Hi, yes, this is Tracy from the silicones and --

DR. BELSITO: We can't hear you, Tracy.

MS. GUERRERO: Okay, I'm off mute. Can you hear me now?

DR. BELSITO: Just faintly.

DR. LIEBLER: You're very faint.

MS. GUERRERO: Okay, I'm going to try this. Can you hear me now?

DR. LIEBLER: Much better. Thank you.

MS. GUERRERO: Okay, great. I just got earbuds off. I apologize for that. So just a reminder, I'm with the Silicones Environmental Health and Safety Center. Back in early 2020, we did conduct a data call in on the ingredients in this group specifically to look for inhalation data, and we did not have any. So I just wanted to close that loop because you all had indicated you were looking for particle size and inhalation data. We did not have any particle size, that hopefully, PCPC or someone else can address that.

But as far as inhalation data, we do not have any available, and that we ran that data call in from the last time you did an assessment on these substances up through 2020.

DR. LIEBLER: Okay. Thank you.

DR. SNYDER: I can't find the resource document for inhalation, but did we reference this 2004 Tuinman in our document?

DR. BELSITO: Monice, you're muted.

DR. SNYDER: Where they provide us in that letter with those graphs showing that particle size distribution for deodorant sprays, is that referenced in our document?

MS. FIUME: What was the first author's name?

DR. SNYDER: Well, his last name is T-U-I-N-M-A-N-I-L, 2004. The TNO report.

MS. FIUME: I am not seeing that author.

DR. SNYDER: Don, it almost seems like what we need for any of these that have this respiratory question, we almost need to table them until we rereview our resource document and bring that up to the current issues that we're dealing with here, airbrush included.

DR. BELSITO: The silicates, I think we got around that, but I agree with you the methicones. Maybe the best approach is just to table it. Dan, your thoughts?

DR. LIEBLER: I agree with that. I mean, it's staring us in the face with this high reported use in deodorant spray. I mean, we can't get around that.

DR. BELSITO: Right, and now we've got verification that even from Ms. Guerrero that there is no respiratory tox studies out there. We're not going to get any information that's going to help us.

MS. FIUME: So is, just as a point of discussion, is tabling the only way that you can see it go. The only reason I'm asking is because of the high number of reported uses and not knowing how long it will take to bring the new respiratory document back to you. It may go back in December; it may be next year.

DR. BELSITO: Okay, maybe we can go insufficient for cosmetic products where incidental inhalation is -- there's a potential for incidental inhalation.

DR. ANSELL: I think the issue is looking back at the inhalation guidance. I'm not sure our conclusion now is that it is insufficient based on the guidance. I believe that the guidance -- it's been a while since I read it -- but we liked it the last time through. That it was explicit and provided guidance on how to assess these materials. But to conclude that it's insufficient because none of us remember what the guidance actually says, I think, could be inappropriate.

DR. BELSITO: Then would you go for tabling, Jay?

DR. ANSELL: Yeah, yeah. I think there's significant number of questions that came up. They may or may not be answered to the Panel's satisfaction within the guidance, but I think we need to look at that as opposed to concluding that it's not there and that it's insufficient. So that would be --

DR. SNYDER: Sorry, Jay. If you go to page 70, Don, PDF page 70, the abstract there -- it says here that, "Although adverse effects were noted in one inhalation study, small aerosolized particles, the expected particle size for cosmetic products will be primarily in the 60 to 80 micron. Less than one percent would be under ten microns." So that was the basis for that conclusion, but now we have data that suggests that up to 50 percent may be respirable.

DR. BELSITO: Right. I mean, that's the whole point.

DR. SNYDER: I mean, we don't know. We've got to verify this and --

DR. BELSITO: Exactly. We need to go and look at the papers that were presented to us. We need to analyze that. We need to potentially rework our respiratory boilerplate because, in the absence of doing that, we're going to have to go insufficient for inhalation uses of the methicones.

DR. SNYDER: To Jay's earlier point, we should also deal with the airbrush. Saying that, that technology either is or isn't under the purview of cosmetics based upon a discussion with the FDA.

DR. BELSITO: Right, we can do that and the respiratory boilerplate. But I mean, I think that the question before us now is, do we table it, or do we say safe for non-aerosolized uses and insufficient for products with the potential for inhalation?

MS. FIUME: I do just want to further my response to pause question earlier about the Tuinmanil paper. So that information is not a published document, but it is included in one of the references. That information came from a paper that is referenced in our inhalation boilerplate document. So it, itself, is not referenced, but it is included in a paper that is referenced.

DR. SNYDER: Yeah, that's part of the whole iteration about referencing, using one resource with not its primary references. And that's a very dangerous thing to do because, if somebody propagates something incorrectly, all of a sudden it becomes scientific fact, in fact, when it's not. So I'm not comfortable until we verify the primary references to suggest that we have the right interpretation in our resource document. I just want to make sure that we're spot on, and, if we're spot on, it may end up clearing all this stuff.

I'd rather just have some comfort level going forward. I know I hate to delay these things when they get this late in this stage, but I just don't think we have any other way around it. And I think the airbrush thing is something we just can't leave out there either. We've just got to get this buttoned up.

DR. BELSITO: Yeah, I agree, Paul.

DR. LIEBLER: We may not need to fully revise the guidance document before we can deal with this because I can imagine that the guidelines document was more of an ongoing project, and it's going to need revision. I don't think that needs to be completed before we deal with this, but we do need to iron out the citable data on particle sizes and respirability to include in our report on the methicones and maybe any other ingredients where this would apply so that we can craft our discussion and justify whatever conclusion we do. We're tabling it to get those ducks lined up, essentially. That's what we need to do.

DR. BELSITO: Okay. Paul, are you comfortable with the table suggestion?

DR. SNYDER: Yeah, I was the one who suggested it. But I also think, like, what about when we do the surveys? Is there anything better we can do with regards to us applying the aerosolized uses. I mean, are we capturing all the airbrush uses now, or are there other technologies that are aerosolizing that we're not aware of? Or, I guess, I'd like to have some assurance from Council that what they're going out and looking for is capturing things that are important for our assessments.

DR. BELSITO: Monice, Preethi, any comments to Paul's?

MS. FIUME: So, from the CIR side, our information that comes from VCRP does not point out whether or not something is an airbrush use, and then anything we have that points out spray use comes to us from the Council in their survey. So, that's the information that we can gather, so I don't know if Jay has any other input. Because I don't know, Jay, you may have said Carol may be changing how she does the survey.

DR. ANSELL: Yeah, I don't know. I'll ask her or we can address that tomorrow. I think one of the solutions is perhaps to be more explicit in what we are assessing. I know that after our last discussions on airbrushing, we went out and were unable to convince ourselves that airbrushing should be included within the broader category of the considerations for deodorants and hairsprays. So I think that needs to be highlighted and perhaps amended within the guidance. But I'm just looking at the guidance now, and, at the lower tiers, we do not argue particle size anymore. We assume 90 percent respirable.

So, I think I've just now had an opportunity while we're talking here to reread it, but I think a number of our concerns are going to be addressed within the boilerplate. But I agree with the tabling. Let's reread it and consider it within the context of stuff that we only saw this morning. But, yeah, look at it. I'm just reading these things that --

DR. BELSITO: I don't think we can ignore this to claim with an 80 plus percent in a spray product.

DR. ANSELL: Yeah, no, no, I just think that we should not also ignore our guidelines. I think we just need to reread them and decide again.

DR. BELSITO: Right.

MS. FIUME: I know Jinqiu couldn't jump over now because they're discussion silicates, but I will also relay to him what the concerns were. He is intimately more familiar with that document than I am since he's worked on it so much. And I will point out which reference and sub citation was called to question so he could look at it even a little more. And then he may be able to give you more insight tomorrow in the full Panel meeting --

DR. BELSITO: Okay.

MS. FIUME: -- that I can provide.

DR. BELSITO: Okay, but at this point, it sounds like we're pretty unanimous in my team with a table motion. Any other comments on this?

DR. LIEBLER: Don are you reporting on this tomorrow?

DR. BELSITO: I don't know, Dan.

MS. FIUME: No, Cohen team is. That's a Cohen.

DR. BELSITO: Okey-doke. So we're moving --

MS. RAJ: Sorry, if it hasn't been mentioned already, part of the issue with the airbrush use is because we don't know much about the regulation of the devices with which these cosmetics that have these ingredients are being applied. So, yeah, that's also something I guess maybe the Panel would like more info on.

DR. BELSITO: Right.

DR. ANSELL: Yeah, the delivery device is not part of the safety assessment no more than we look at, say, a big brush or a small brush. It's all about exposure, so how the applicator is regulated I'm not sure is going to be particularly relevant in our assessment of the safety. It's all about the exposure.

DR. BELSITO: Right. But I think airbrushing is something that, at least if I'm understanding from the comments from Dan and Paul, that we all want more specifically discussed in a new boilerplate.

DR. ANSELL: Right, and we do too. We agree with that, that this probably needs its own bucket for discussion.

DR. BELSITO: Right. Okay, anything else on the methicones?

Cohen Team – September 13, 2021

DR. COHEN: Hi, Preethi. Okay, so why don't we get started. Our first item on the list is methicones, dimethicone, methicone, and substituted-methicone polymers. This is a draft, revised final amended report. Preethi has this.

We issued a draft final report, which had public comments for 60 days. We have VCRP from 2021, and we had a correspondence regarding ingredients used in airbrush technology. Our last issuance was a split conclusion of safe in cosmetics and the present practice and concentration of use and concentration when formulated to be non-irritating, but insufficient determination for safety in airbrush use.

There wasn't much new on this, and I'd open it to the Panel for any further comments that then wanted to just -- as Wilma said in the introduction, to discuss the airbrush issue going forward, so thoughts? Tom?

DR. SLAGA: I thought it was a nice report. I really didn't have any problems. As you mentioned, Women's Voice should be discussed, and that's it.

DR. BERGFELD: If I could add, I thought that the Women's Voice brought up a real issue for all aerosols.

DR. COHEN: I think it's exactly the point I was going to make, which is our boilerplate about aerosols being largely non-respirable because of the pumps that are used. I think that, when that boilerplate was made, this wasn't much of an issue, but we're seeing it more and more. And should our boilerplate change to indicate that we can't adjudicate that issue of any of these chemicals used in airbrushes unless we have specific information about airbrushes.

DR. BERGFELD: Well, they particularly pull out that trigger spray, which I guess delivers greater and smaller particles.

DR. PETERSON: Yeah, I have always been a bit uncomfortable with the boilerplate statement because it's -- yeah, and I think that the science presented suggests that that needs to be rethought.

DR. COHEN: Ron, anything further?

DR. SHANK: No. I think as far as the methicones, our report, it's okay, and I would leave the insufficiency for the airbrush.

DR. BERGFELD: Did you want to change that to aerosol, or no?

DR. SHANK: No, because we have quite a bit of ventilation toxicology data on dimethicone within the respirable range. The particle diameters were less than one micrometer, so for this report, I think we're okay.

We don't know enough about airbrushes, how they're used. We appreciate the input from the Women's Voices of the Earth. The citations presented in her letter don't necessarily address airbrushes, so I think the insufficiency for airbrush remains, and we have the inhalation toxicology, so we don't need the boilerplate for this report.

DR. PETERSON: Okay.

DR. COHEN: So are you suggesting we pull the boilerplate out and just leave our conclusion as is, not including pumps or sprays of any sort that might contain this?

DR. SHANK: Yeah, let me find the discussion again.

DR. BERGFELD: It's on the third paragraph of the discussion.

DR. SHANK: Yeah, that's about airbrushes. Okay. Yeah, in that second paragraph of discussion.

DR. COHEN: I would expect these to wind up in hairsprays and other areas where you're going to create a mist, but I thought the boilerplate covered that part of it. It's just the airbrush and maybe some other technology that I'm not that familiar with could fall outside of this boilerplate. I hadn't contemplated removing the boilerplate for this.

DR. HELDRETH: Yes, I believe that the biggest difference between pump and pressurized aerosol sprays versus airbrush technology is that we don't have uses and practices data on airbrush apparatuses.

DR. SHANK: That's right.

DR. HELDRETH: We don't know how they're used, and we don't even have any survey of what these airbrush devices are like to be able to come up with some sort of a risk assessment. And even the categories that we get on the use and concentration don't include airbrush. They include certain types of sprays and powders that may be inhaled, but we really have almost no information on the aerosols, I'm sorry, on the airbrush uses.

So, I think it would be completely worthwhile to update our boilerplate, our inhalation document to say, when it comes to airbrush, we just don't have any information. We just don't have enough to make a conclusion. I think at this point we don't have the inhalation document in front of us to review, so that can be something we bring back in the future, but, at this point for this document, certainly I think that the Panel already has a conclusion that says we don't have that data. We don't have that information and can't conclude on it.

DR. SHANK: Right. Many years ago, the Panel was given the particle size distribution for various kinds of cosmetic products that were pumps, aerosols, a variety of them, and the boilerplate that we have now is based on that.

The material sent by the Women's Voices of the Earth are not -- I haven't read them because we just got it on Friday -- but it sounds like those are not studies on cosmetic formulations, whereas the material we have in our boilerplate was based on cosmetic formulations. I think that makes a difference. I would leave the boilerplate alone for now until we have a chance to review it and add the consideration of airbrushes. I would not remove it from this document. I think this document is okay.

DR. COHEN: So, Ron, you're suggesting sort of a case-by-case addition of the airbrush comment.

DR. SHANK: Yes. Yes.

DR. COHEN: So we're okay leaving our conclusion from last time and proceeding to final?

DR. SHANK: I think so, yes.

DR. COHEN: And is that the right terminology we're going to maintain what we --

DR. BERGFELD: That we confirm our conclusion.

DR. COHEN: Confirm it.

DR. BERGFELD: I think that we could suggest to Bart and Monice that we go back to PCP and ask them to supply some more information regarding these delivery systems.

DR. HELDRETH: Yes, and we certainly can do that. We did do it -- I don't remember what committee it was -- but it was at least a few meetings ago, asked for uses and practices information, and I believe the response was it's just not available for these devices, at least not at this time.

MS. KOWCSZ: Bart, this is Alex from PCPC, and you're absolutely right, we did reach out to our members that do use the application of airbrush technology, and we did not get any further information. Just wanted to confirm just what you said. Thanks.

DR. BERGFELD: Well, I think we keep asking because we've done that before with the late submissions, et cetera. Keep asking, finally, it will happen.

DR. COHEN: Okay.

DR. HELDRETH: I believe that Thomas Gremillion has a question or comment to make.

MR. GREMILLION: Good. Thanks. I just wanted to, I mean, I wanted to confirm my understanding of this. The boilerplate now says, "In practice, the particles released from cosmetic sprays have these small diameters," but that really should read, "In practice, the particles released from cosmetic sprays other than airbrushes have these diameters" -- sorry, "they're sufficient or large, not to be hazardous." The Women's Voices of the Earth letter is suggesting that it's not just airbrushes; it's other types of cosmetic sprays for which that statement is inaccurate. Is that -- I mean, am I understanding that, the gist of this?

DR. SHANK: It's not inaccurate; it just doesn't cover airbrushes.

MR. GREMILLION: But this most recent letter doesn't -- it isn't alleging that other products also have released particles that are smaller than those ten microns.

DR. SHANK: But it's not clear if those -- that information is based on aerosolizing formulas.

MR. GREMILLION: So that would --

DR. SHANK: Many of those, I think, were done on model systems. So you're not (inaudible)?

MR. GREMILLION: Does that get back to the formulate to be non-respirable? The discussion that --

DR. SHANK: Well, we'll review, apparently, the boilerplate in the near future. As far as the methicone report is concerned, we have inhalation toxicology data on respirable particles. So the question about particle size is not relevant or is not a problem with this methicone report. And we'll deal with particle size distribution again when we review the boilerplate.

DR. COHEN: Yeah, I think we have to look. The boilerplate could give the vague impression of various types of aerosols that are made and it too -- sort of, anyone just casually reading it, it may not be so obvious what type of device is creating that type of spray or aerosol, so I think we should look at that boilerplate again and be careful how we deploy it because we could neutralize material from the rest of the report just with the boilerplate.

We have good inhalational tox, and then we put a boilerplate in. That kind of papers over all the detail that we might have had before. Okay.

DR. PETERSON: Yeah, I agree with that, and I just want to say that they do talk about different kinds of sprays in this memo and that deodorant sprays, for example, give smaller particles. So I do think -- I wasn't around when the boilerplate was generated, but it seems like perhaps the technology, the types of uses of the different formulations, might be different, and I just agree with the boilerplate being revisited. And I also support what's been said about this particular report, that we have the inhalation data that supports its safety.

DR. COHEN: So I'll proceed with our prior conclusion. Bart and Wilma, is there a boilerplate task force of some sort for these things? No, okay.

DR. HELDRETH: No, there's not (audio gap) going. It was just a consensus to the Panel. I'll ask our in-house toxicologist, Dr. Jinquiu Zhu, to get to work on this right away, and the Panel will have a revised version to go over at the December meeting.

Full Panel – September 15, 2021

DR. COHEN: This is a draft revised final amended report. In December 2020, the panel issued a revised tentative amended report with a split conclusion of safe in cosmetics in the present practices and concentrations of use and concentration when formulated to be nonirritating. But, we had an insufficient finding to make a determination of safety for the utilization of these ingredients with airbrush use. Our team affirms this conclusion and would make that motion, and after the second we can discuss the aerosol boilerplate and other comments.

DR. BERGFELD: Is there a second, or a comment?

DR. BELSITO: We had a quite different approach.

DR. BERGFELD: Okay, if you would proceed with a comment.

DR. BELSITO: We thought that this really needed to be tabled because there are spray uses, and per the articles that were sent in by Ms. Scranton from Women's Voices for the Earth apparently both deodorant and hairsprays can have respirable particles. We have no chronic inhalations toxicity on Methicones, and we're recommending tabling it pending a review of the article she sent, a search for other articles, and a rework of our respiratory boilerplate. It's not just airbrush now; I think it's all spray applications.

DR. SHANK: May I comment.

DR. COHEN: Please do.

DR. SHANK: We do have inhalation toxicology data, acute.

DR. BELSITO: Acute, but not choric, Ron. People are going to be putting their (audio skip).

DR. SHANK: You don't need the chronic inhalation study; people aren't chronically exposed. The exposures are very short-term, maybe frequent, but the exposure is short. And, the inhalation studies on Page 49 were definitely respirable particles. So, I think we can keep the conclusion that we have. We can change in the discussion the boilerplate, but we do have inhalation toxicology data.

DR. BELSITO: Okay, well, inhalation toxicology is not my forte so I'll pass this on to Dan and Paul.

DR. SHANK: Okay.

DR. BERGFELD: Dan?

DR. LIEBLER: I'm going to look to Paul; sorry Paul, but I've got to.

DR. SNYDER: This wasn't so much tabling it for the absence of inhalation data. It's just that we have new data suggesting that the particle size distribution for these hairsprays and deodorant are vastly different that what's in our boilerplate. And, the boilerplate does not address the airbrush uses, and now we have particle size information on airbrush uses. So, we thought that it would be just cleaner, rather than having the split conclusion, to go back and revisit our inhalation boilerplate and then maybe we would affirm the split conclusion or, most likely, we would then have just a single conclusion depending upon how we looked at the data regarding those particle size distribution exposures.

I'm not necessarily in 100 percent agreement that short-term frequent use over lifetime is justified in an acute study with a very small numbers of animals. So, I was in agreement with our group in tabling it to have a relook at that boilerplate.

DR. SHANK: Why can't we just take the boilerplate out of the report? We use boilerplates when we don't have data, and we have data.

DR. COHEN: I suppose if we take the boilerplate out we would have to change the conclusion to include aerosols, as opposed to airbrush. And, my concern -- I'm not sure how much of a concern it is, but, there are a lot of non-aerosol products that use these Methicones. And if we're holding them up for that specific issue, if we issue this statement with safe as used and take out the boilerplate and put insufficient for aerosols, we can at least move a lot of these forward and come back to aerosols when we adjudicate the boilerplate.

DR. SHANK: That's good.

DR. BELSITO: We discussed that option as well, so I'll pass it on to Dan and Paul, but that was another option we had for doing this.

DR. BERGFELD: Dan, Paul?

DR. LIEBLER: I don't have any objection to doing that.

DR. BERGFELD: Paul?

DR. SNYDER: I don't have any objection; I would think that Bart would prefer that we put it to rest the best that we can and not let it linger. I guess how would that fall in the priorities then as far as what we look at? How many uses do we have for aerosol use?

DR. BELSITO: Quite a few.

DR. SNYDER: Yeah. So, I just don't think that's the best approach. And, we'll talk about this on other reports; I think that it would be better just to put these to rest cleanly. Most likely we'll be able to do that if we have a relook at that new data and that particle size distribution and things. So, I just felt that rather than leave a bunch of these kind of half-hanging out there, if we just take a pause here and get our bearing straight back to what we're thinking about our boilerplate.

I mean, there were some findings in those dogs, Ron. There was some hemorrhaging and some fluid in those inhalation studies, so it wasn't like it was totally clean.

DR. SHANK: Very high dosages.

DR. HELDRETH: To your comments Dr. --

DR. SHANK: Very high dosages.

DR. HELDRETH: I'm sorry, to your comment, Dr. Snyder.

DR. SNYDER: Yes.

DR. HELDRETH: If we change the conclusion as proposed to basically exclude aerosols of all types from the safe conclusion, that would be a more restrictive change to the conclusion and the report would have to come back anyway. So then you could have this report back again in December, along with the inhalation boilerplate to take a second look at.

DR. SNYDER: That works.

DR. HELDRETH: So, that would still move it along, but it would still give everybody an opportunity to contribute further.

DR. COHEN: And it opens up the use of, you know, at least give some guidance on non-aerosol use; we've done that. And, just taking it a little bit further, if there are particle sizes that are inhalable, then what are the chances we're going to have a safe as used as a final conclusion without really going into this very deeply?

DR. BERGFELD: David, do you want to rescind your motion and restate it?

DR. COHEN: Yes. We would propose a split conclusion of safe as used in cosmetics in the present practices and concentration of use at concentration when formulated to be nonirritating, but insufficient to make a determination of safety for the utilization of these ingredients in aerosols.

DR. BELSITO: I can second that.

DR. BERGFELD: Second that. And, the comment would be what, in the discussion?

DR. BELSITO: The comment in the discussion I think would be --

DR. BERGFELD: I thought there was some question about removing the boilerplate.

DR. BELSITO: No, I think the comment for the discussion would be the data needed for aerosol is a reexamination of inhalation data and particle sizes.

DR. BERGFELD: Okay, so you're going to leave the discussion point about the boilerplate in?

DR. BELSITO: Well, I mean, we don't know if we're going to have a boilerplate by then.

DR. BERGFELD: No, I don't mean that. I believe that's in there.

DR. BELSITO: Well, when we asked yesterday it was my impression from Monice and Jay that it would be very difficult to get the boilerplate up and changed by December. That was just my impression. Bart, I may be wrong.

DR. BERGFELD: Don, that's not what I meant. I meant the fact that we had put it in there. (Audio skip) suggestion of taking it out.

DR. BELSITO: Right, if we have a new boilerplate that covers the issues of Methicones then we'd leave it in.

DR. COHEN: But, Don, if we're split concluding with insufficient data for aerosols, do we not take the boilerplate out?

DR. BELSITO: We take it out for now, sure.

DR. BERGFELD: Yes, that's what I'm talking about.

DR. BELSITO: Okay.

DR. BERGFELD: Okay?

DR. COHEN: Wilma, I think Thomas has his hand up.

DR. BERGFELD: Thank you. Thomas?

DR. GREMILLION: I want to follow up on Dr. Shank's comment about the chronic exposure, and I guess, well, just ask what's meant by kind of chronic exposure for the inhalation studies.

DR. SHANK: It would be a study where the animals are exposed usually four hours a day, five days a week for more than six months. That's far greater than aerosol use in the cosmetic.

DR. GREMILLION: Yeah, I guess, it kind of harken back for me to discussions we've had before about what is consumer use of these products, and would it in formal beauty shop, or somewhere where someone's using a lot of this with friends or something, would that automatically be classified as kind of professional use or workplace exposure. And I just want to call attention to the fact that the line is a little blurry there between your kind of -- there is no like typical consumer of these products, and, yeah, there might be some high using consumers.

And, needless to say, I have concerns about the boilerplate and what the Women's Voices for the Earth letter brought up. It seems like that shouldn't be in the report because it doesn't seem accurate if that what is in the letter that was submitted is accurate. So, glad to hear that you're taking this approach.

DR. BERGFELD: Anyone else wants to make a comment?

DR. BELSITO: Well, just to follow up on Ron's comment. If we're saying the inhalation toxicity is sufficient for sprays, and we have information strongly suggesting that deodorant and hairsprays can have respirable particles, then why would we exclude airbrush? You know, airbrush is not continuous four hour; it's brief, discontinuous exposure. So, that would really make no sense in our conclusion if we say inhalation toxicity covers respirable particles. But anyways, I'm very happy to exclude products that could be respirable, at this point, and we'll readdress it when we look at all the information that we haven't really had a chance to see, because quite honestly I miss the WVE memo because it came as "Annotated Agenda', which I never opened, and not as "Wave 2".

DR. COHEN: Don, I might suggest that cosmetic airbrush use is not equivalent to, say, an underarm deodorant spray as far as timing and aim, right, you know.

DR. BELSITO: But if we're saying the particles aren't respirable and it's not an issue, then --

DR. COHEN: Yeah, nah, your point's well taken.

DR. BERGFELD: Any other discussion? This discussion overlaps several other ingredients that we'll be looking at. So we'll need to reaffirm what we're going to do with those as well in the near future here. Hearing no other discussion, I'm going to call all those against this motion, please indicate by giving your name. Abstaining? Hearing none, it is approved. So moving then on to Red Algae, Dr. Belsito.

MS. RAJ: Dr. Bergfeld?

DR. BERGFELD: Yup.

MS. RAJ: May I please ask the panel, on PDF Page 57 and 58, I think that second and third paragraph of the discussion, how exactly would the panel want that modified for the next time they see it, beside the boilerplate possibly being changed?

DR. BELSITO: What page is it, Preethi?

MS. RAJ: PDF Page 57 and 58. This is the second and third paragraph of the discussion.

DR. BERGFELD: David, do you want to respond, and then Don?

DR. COHEN: I'm trying to find it. Are we talking about -- now, we're not talking about the airbrush. We're talking about the discussion paragraph --

DR. BELSITO: No, it starts, David, with "the panel noted Dimethicone is now reported to be used at 85 percent."

DR. COHEN: Yeah.

DR. BELSITO: That was the other problem, Ron, the high concentration of use.

DR. COHEN: I'd probably leave the first part of it in and then get rid of "also the panel noted that in traditional aerosol cosmetic products 95 to 99 percent"; I would just get rid of that sentence.

MS. RAJ: Okay.

DR. COHEN: We could probably leave "droplets/particles deposited in the nasopharyngeal and bronchial regions are not toxicological concerns." But I think the particle size and non-respirable size we should get rid of, because our conclusion excludes this for now and we're going to certainly come back and retool this section.

MS. RAJ: Okay.

DR. BERGFELD: And that includes the second paragraph that was referred to by "the panel was made aware"?

DR. COHEN: I don't know if we need to get rid of that, because as part of our aerosol exclusion this sort of corroborates some of that information. I think we could leave that in.

DR. BERGFELD: Okay. Don, are you agreeable?

DR. BELSITO: Yeah, but, Paul, correct me if I'm wrong. You had a chance to read the Women's Voices for the Earth a little bit better than Dan and I. Didn't it point out that there is data on particle size distribution for airbrush products? Is that not correct?

DR. SNYDER: Yes, that is correct. If you look at the next to the last page of that memo they give the particle size distribution for cosmetic airbrushes from Pierce (phonetic) 2019. And they say all of the particles measured in a cosmetic airbrush were less than 10 microns.

DR. BELSITO: Yeah, so there are mistakes in that paragraph if in fact that report is correct. And, again, that needs to be checked. So, Preethi, if that is correct then all of this stuff about "in the absence of data on particle size distribution," et cetera, needs to go away.

MS. RAJ: Okay, are you referring to the Pearce paper, Dr. Belsito?

DR. BELSITO: The one Paul just quoted, yes.

MS. RAJ: Okay. Thank you.

DR. SNYDER: And then we also wanted to clean the document up in regard to using only primary references.

DR. BELSITO: Yeah, one of our four references came from the same reference.

MS. RAJ: Okay. Thank you.

DR. BERGFELD: Any other comments before we move on?

DR. SNYDER: But, I just want to go back to this inhalation thing, because on Page 49 three of the guinea pigs died, Ron, during that acute study, with hemorrhage in the lungs. And then on Page 50, the longer term study where they followed them six week post, all of the mice died within the post-observation period. So, I'm not as certain that that is as clean as maybe I'd like to see it. So like your comments on those animals that died, I mean, in both studies, a short-term study and an acute study, two of the guinea pigs died had hemorrhage in the lungs, even though it was high levels, but then also in the longer term study all four mice that were treated died during the post-observation period -- on Page 50.

DR. BERGFELD: Is Ron still with us?

DR. SHANK: Yes, I'm here. On Page 49, there are two studies where the animals did not die or show toxic effects at high-dosages respirable particles.

DR. SNYDER: No, it says three guinea pigs died during the study, all necropsied animals had hyperemic lungs with hemorrhagic.

DR. SHANK: That is --

DR. SNYDER: Aerosol Dimethicone at a concentration of 2.1 mg/l. And then you scroll down to Page 50, an inhalation study with cat, rabbit, guinea pigs and four mice. During the dosing period all four mice died.

DR. SHANK: Yeah, with that, well --

DR. COHEN: Well, perhaps our split decision has taken care of this issue right now so we don't need to adjudicate it at this particular meeting. For a number of reasons we're going to be looking at the aerosols for the Methicones again.

DR. BERGFELD: Is that agreeable, Paul?

DR. SNYDER: Yes, totally agree.

DR. BERGFELD: Yeah. So, we're going to pull this out to make sure we look at it. And, maybe highlight it, Bart?

DR. HELDRETH: Yes, I believe Jinqiu has a question or comment to contribute.

DR. BERGFELD: Okay.

MR. ZHU: Yes, I want to make a clarification on the references in the inhalation guidance document. For particle size distribution of deodorant sprays, additional measurements have been performed other than the Truman (phonetic) 2004 study, have (inaudible). So, all deodorants of which particle size distributions were measured are grouped together. This particular distribution is chosen as a default distribution representing all deodorant sprays. And, all these original data are covered by citation 23 in the guidance document. This reference is a 70-page government report, which includes all necessary data as default exposure parameters for simulating deodorant sprays.

As you know, in a spray model the particle size distribution needs to be corrected with a (inaudible) factor which (inaudible) the mass fraction of the total sprayed products. So, we cited this report instead of individual original study. But, if the panel asks, we can cite all relevant references in the next iteration of the guidance document.

DR. BERGFELD: Paul, can you respond to that? What do you want?

DR. SNYDER: Again, we need to review this to get our heads around references and what's in those references, because there were significant new data that was provided to us. And I want to see where that stacks up, and due diligence. I want to trust but verify that the Women's Voices for the Earth is correct or that we're correct, and get it right, get it straight. And I think there probably needs some better language in there with this better understanding now of particle size distribution for these different sprays. Because I think this is a big issue going forward.

This airbrush technology is not going to go away. It's going to get more prevalent. And it's totally not regulated, and Jay has some comments regarding that in regard to its application technology and it's not under purview. And we need to get the FDA's take on that. I think there's a lot of discussion that we need to have regarding that technology.

DR. BERGFELD: Jay?

DR. ANSELL: Yeah, let me add, just to be clear the insufficient is not suggesting that the data isn't there. The insufficient is to give us an opportunity to review a new letter that we received essentially the morning, and to review the new guidance documents. So, I actually believe when we review the new inhalation guidance we will find it sufficient, but we just didn't have an opportunity to do that yesterday so we supported tabling to review, or in this case insufficient. But not suggesting the data isn't there, but to give us an opportunity to thoughtfully go back and look at the new papers and the revised inhalation documents.

DR. LIEBLER: And, Jinqiu, it would be really helpful if, as you've done in the past, if you're able to take that memo that we got from WVE and perhaps annotate it with some clarifications with respect to the cited literature, what we've already cited in our guidance document, what is not covered. Because your explanation about the report covering aggregate literature is helpful, but if I knew that at one point it has definitely slipped from my conscientiousness. And I think it would be good to have that in front of us to look at next time.

MR. ZHU: Sure, will do.

DR. BERGFELD: Dan, are you also supporting the fact that Jinqiu should put in all of the references, the primary references, as well as the aggregate reference that was in, for now?

DR. SNYDER: I think we need to look at it.

DR. BERGFELD: Okay.

DR. SNYDER: It depends on how they're cited in the report that we're citing. If we're citing something like a review -- or if we're citing several other papers that all cite one paper, that's just sloppy. But, I'm not sure that's all of what we did, so I'd like to look at how we handled the literature for this in its entirety.

DR. BERGFELD: Okay. All right, I think that we have the marching orders for this particular ingredient.

DR. BELSITO: There's one other point, Wilma, sorry to interrupt you, that we discussed --

DR. BERGFELD: No, that's all right.

DR. BELSITO: -- that hasn't been raised yet. Is there a representative from the FDA? Because we were wondering whether this airbrush technology -- now if it was used in medicine it would be considered a device, right?

DR. BERGFELD: Right.

DR. BELSITO: And it would have to, I presume, have a device approval. It's used in cosmetics. Does it require some type of device approval by the FDA?

DR. BERGFELD: Bart, is there anybody here from the FDA?

DR. HELDRETH: I believe Mr. Wyatt is here from the FDA.

MR. WYATT: Yes, I'm here.

DR. BERGFELD: Would you mind responding?

MR. WYATT: Sure, as for the airbrush it is not regulated by the cosmetics if the product doesn't say it in the directions of use that it requires airbrushing. You know, we're not as an office is going to regulate the airbrushing methods, per se. That would come under CDRH where they do regulate devices. We can certainly take it under advisement, but for now if a cosmetic contains an instruction to use an airbrush on the label, then it comes under CDRH's purview.

DR. BELSITO: I'm sorry; I'm not familiar with the acronym. What is CDRH?

MR. WYATT: Center for Radiologic Health.

DR. BELSITO: Okay, because my concern is there are a lot -- a lot, I don't know the number, but there are ingredients that we have approved for safety based upon lack of respirable particles. And, if those materials are being put into airbrush technology, our findings may no longer be valid. So, I mean, I would hope that some governmental agency would be looking at this new technology.

MR. WYATT: Yeah, just to correct, it's the Center for Devices and Radiologic Health. It would certainly come under their purview to look at that and to evaluate the size of the particles to ensure that they were larger than 10 microns and, based on your boilerplate language, assure safety. If CDRH did look at it and found that a majority consistent with Pearce et al. were lower than 10 microns, then that they may reach the alveoli, then there could be a concern.

DR. BELSITO: Bart, is there some way of bumping this up, or sending a letter to CDRH asking them to look at this?

DR. HELDRETH: I can certainly send them a letter of that sort. I will say that in our searching to review the airbrush uses I did find certain FDA documentation when it comes to using these airbrush devices for spray tan. And, also in that realm there was not a regulation that limited particle size or anything of the sort. It simply left recommendations to the users to protect respiratory exposure.

MR. WYATT: Right, so that was the DHA's recommendations that OCAC (phonetic) has on its website, to hold your breath or plug your nose or keep your mouth shut during these procedures. You know, that doesn't constitute a regulation or anything of that sort. If it's a device, and it's referenced in a cosmetic label to use airbrush, then it would come under CDRH, which is as I said the Center for Devices and Radiologic Health. Does that help?

DR. BELSITO: Yes, we --

DR. BERGFELD: It sort of helps that we need to send a memo over to them and ask them.

DR. SLAGA: Yeah.

DR. COHEN: Agreed.

DR. SNYDER: While we're on this topic of inhalation documents, would it be appropriate, Bart, to have the discussion now about the information that's gathered by the VCRP? And, are we getting the data that we know what are used in airbrush technologies?

DR. HELDRETH: My understand --

DR. SNYDER: Because right now we're concern that we're not getting that data and we may have airbrush technology uses that we're not accurately capturing.

DR. HELDRETH: Yeah, my understanding of the VCRP program is that it doesn't currently have a classification for airbrush use.

MR. WYATT: We have not looked at that specifically. We can certainly inquire with the manager of the VCRP program. Again, it is voluntary but we can certainly look into it.

DR. BERGFELD: Well, I personally thought that when I read through this that it wasn't just the airbrush; it was the trigger sprays and a few others --

DR. COHEN: And the propellants.

DR. BERGFELD: -- and propellants. I mean, it's quite complexed what they can do to force this material onto the skin. So, maybe the whole -- it's a bag of worms. We need to know how their delivery system works, what it delivers, and what the particle sizes are. Okay, well, I guess we can send a letter, also, to the VCRP leader as well as have our FDA representative translate that information.

MR. WYATT: Please feel free to send a letter to our office and we can go back and look through VCRP again to get a better understanding of what information about frequency of use is being provided by the industry for cosmetics that are being delivered by airbrush. I think you all had indicated at one point it was MAC-T or MAC-I that was manufacturing these? That was indicated in the first letter from Women's Voices for the Earth, so Alexandra Scranton did provide information on that. You know, who was making it and what the ingredient statement said. That was in the original letter. I don't know if it was March 2021 or not, but it was a MAC-I and people on the panel were familiar with that.

DR. BERGFELD: Well, I think we have a course of action here and we'll pursue it. And we're going to move on to the next ingredient I think. Bart, did you want to say something.

DR. HELDRETH: Yeah, I'm happy to send memos to each of these organizations. I just want to remind the panel that, you know, we have received presentations and information on consumer common uses and practices for things like pump sprays and propellant sprays. But we previously asked for that type of information and data to do a risk assessment for airbrush technologies and the response that we have received is that will not be forthcoming.

DR. BELSITO: It doesn't hurt to ask again.

DR. HELDRETH: Yeah, no, I'm happy to ask again. I just wanted you to be aware that it's very likely that information will not be received.

DR. ANSELL: These are all good questions but let me remind people that the conclusions of the reports specifically states they're under the concentration and applications that are described in the reports, so perhaps we need to clarify that airbrush was not consistent or in the same category as current deodorants, and aerosols and pumps. But we've never said or made a statement that it's safe under any conditions or any concentrations.

DR. BERGFELD: Well, you could do that if you knew that for sure.

MR. WYATT: And just for the record it's called MAC PRO Performance HD Airbrush Makeup. And the other one that Alexandra Scranton cited it was AIRBASE Ultra Foundation. But I don't know if those have been registered in VCRP. We can certainly double check that though.

DR. BERGFELD: Thank you.

MR. WYATT: Sure.

DR. BERGFELD: Any other discussant points, or comments that need to be made?

DR. BELSITO: Well, I mean, I guess the only other thing is, I believe, I'm not certain, but, is not the manufacturer of Max Cosmetics a member of PCPC?

MS. KOWCSZ: Yes they are, and we have asked them, Don, specifically.

DR. BELSITO: Okay.

MS. KOWCSZ: But not everybody is a member. Not everyone that has airbrush technologies is a member.

DR. BELSITO: No, I agree, but I think, and perhaps she's doing it, when Carol goes out and does the survey she should ask if any of their aerosolize products are being applied by an airbrush technology, just again to do due diligence.

MS. KOWCSZ: Thank you.

MS. EISENMANN: I have added it to that survey, but nobody has responded that they have a product yet.

DR. BELSITO: Well, at least we're trying.

MS. KOWCSZ: Thanks Don.

DR. BERGFELD: Thank you both.

MR. WYATT: And I will (audio skip) VCRP during the balance of the meeting and see if I can get some clarification on what's there.

DR. BELSITO: Well, we'll come back to you then, all right?

DR. SNYDER: I mean not to beat a dead horse, but we do say under the present practices of use in this report. It's just a matter of so if we don't have airbrush uses captured it's okay, but I'm not certain we're capturing airbrush uses. So that's the only last comment so.

DR. BELSITO: Um-hmm.

DR. BERGFELD: All right, are you suggesting we change something else, Paul?

DR. BELSITO: No.

DR. SNYDER: No, I just want us to be aware that this is so convoluted, and so --

DR. BERGFELD: Yeah.

DR. SNYDER: And, that's just, you know, there're different things to think about. It's like you said, this is quite the bag of worms here that we've got to make sure we get all our t's crossed and all our i's dotted, I think, with regard to the boilerplate and the terminology we use, and how we're looking at the data.

DR. BERGFELD: Okay, are we ready to move on?

DR. BELSITO: Well, just one other comment. If we really want to cover it all, perhaps we should consider doing an airbrush technology document and pointing out that this is a relatively new technology that we've become aware of. And pointing out to everyone that our safety assessments were based upon conditions of use as defined in that report. Many of which did not even consider the potential for use in airbrush technology -- something to that effect.

DR. BERGFELD: I'm going to ask a question of you, Don. Do you think that that's the only new propellant development, is the airbrush? There must be others.

DR. BELSITO: Well, I mean --

DR. BERGFELD: I mean, we're pointing to that one, but I'm sure delivery systems are more refined and more refined each year.

DR. BELSITO: I agree, but, again, I think that the greatest concentration of respirable particles is going to come from airbrush technology. And --

DR. COHEN: The letter suggested some other points.

DR. BELSITO: Right, I agree. Well, we'll have to see, and maybe that can be our quote, airbrush technology can be brought into the respiratory boilerplate.

DR. BERGFELD: Yeah, I think that we have to look at all of the aerosol delivery systems.

DR. BELSITO: Okay.

DR. BERGFELD: Okay, let's move on, Red Algae. Dr. Belsito, are you ready?

Amended Safety Assessment of Dimethicone, Methicone, and Substituted-Methicone Polymers as Used in Cosmetics

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The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Lisa A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. Previous Panel member involved in this assessment: James G. Marks, Jr., M.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Preethi S. Raj, Senior Scientific Analyst/Writer, CIR.

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ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 30 dimethicone, methicone, and substituted-methicone polymers; 20 of these ingredients were previously reviewed by the Panel. Most of these ingredients are reported to function as skin and hair conditioning agents. The Panel reviewed relevant new data, including frequency and concentration of use, as well as exposure type, and considered data from the previous report. The Panel concluded that these ingredients are safe in cosmetics in the present practices of use and concentration described in this 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.

INTRODUCTION

In 2003, the Expert Panel for Cosmetic Ingredient Safety (Panel) published a final report on the safety assessment of 20 dimethicone, methicone, and substituted-methicone polymers.[1] Based on the available data, the Panel concluded that the ingredients named in that report are safe as used in cosmetic products. In accordance with the Cosmetic Ingredient Review (CIR) Procedures, the Panel evaluates the conclusions of previously-issued reports approximately every 15 years. In December 2019, the Panel determined that this safety assessment should be re-opened due to an increase in the overall frequency of use for ingredients in this group. The Panel also determined that it is appropriate to include an additional 10 alkyl dimethicone and methicone ingredients (denoted in red below); the complete family of 30 ingredients comprises:

Amino Bispropyl Dimethicone
Aminopropyl Dimethicone
Amodimethicone
Amodimethicone Hydroxystearate
Behenoxy Dimethicone
C20-24 Alkyl Dimethicone
C20-24 Alkyl Methicone
C24-28 Alkyl Dimethicone
C24-28 Alkyl Methicone
C26-28 Alkyl Dimethicone
C26-28 Alkyl Methicone
C30-45 Alkyl Dimethicone
C30-45 Alkyl Methicone
C30-60 Alkyl Dimethicone
C32 Alkyl Dimethicone
Capryl Dimethicone
Caprylyl Methicone
Cetearyl Methicone
Cetyl Dimethicone
Dimethicone
Dimethoxysilyl Ethylenediaminopropyl Dimethicone
Hexyl Dimethicone
Hexyl Methicone
Hydroxypropyldimethicone
Methicone
Stearamidopropyl Dimethicone
Stearoxy Dimethicone
Stearyl Dimethicone
Stearyl Methicone
Vinyl 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 as skin and/or hair conditioning agents.[2] Additional functions are also reported for some ingredients (Table 1).

Excerpts from the summary of the 2003 report are included throughout the text of this re-review document, as appropriate, and are *identified by italicized text.* (This information is not included in the Summary section.) For complete and detailed information, please refer to the original report on the methicone polymer ingredients, which can be accessed on the CIR website (https://www.cir-safety.org/ingredients).

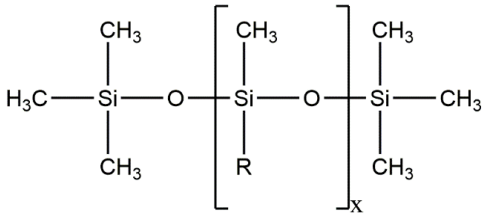
This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that 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 in an European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) report, on the European Chemicals Agency (ECHA) website, and in Australian Industrial Chemicals Introduction Scheme (AICIS) assessments.[3-7] Please note that the toxicological studies described in these documents were summaries and it is, therefore, these summary data that are reported when cited in this safety assessment.

CHEMISTRY

Definition and Structure

The ingredients in this report are all siloxane polymers. Each silicone atom is further substituted with hydrogen, methyl, or other substituents (Figure 1). For Methicone (CAS No. 9004-73-3), most of the silicone atoms in the polymer

backbone each have 1 methyl group and 1 hydrogen atom, while for Dimethicone (CAS No. 9006-65-9), most silicone atoms in the polymer back bone have 2 methyl substituents. The remaining ingredients in this report have 1 or 2 of the substituents on the silicone atoms replaced with an alternative functional group (e.g., Hexyl Methicone (CAS No. 1873-90-1) is substituted with hexyl (C6) chains, and Amodimethicone (CAS No. 68554-54-1) has a nitrogen substituent). The definitions and idealized structures of all the ingredients included in this report are provided in Table 1.



The polymerization of linear methicones, however, often results in a mixture of polymers (chains of variable lengths and molecular weights, including oligomers) and cyclic compounds.[8] Dimethicone is a mixture of fully methylated linear siloxane polymers end-blocked with trimethylsiloxy units.[2] Methicone is a linear monomethyl polysiloxane. The other ingredients included in this review are siloxane polymers of Dimethicone and Methicone.

Viscosity is expressed in both dynamic and kinematic measurements, and is directly correlated with molecular weight and the degree of polymerization of a molecule, i.e., the longer the polymer chains, the more viscous the liquid polymer.[3] Most of the viscosities reported in previous and current data have been described in kinematic centistokes (cSt; cm^2/s), and are converted to the standard, dynamic, Pascal*second (Pa·s; kg/m·s), where specific gravity, or relative density, values were available. To do this, the product of centistoke and specific gravity, or relative density, values, was divided by 1000, to attain Pa·s values. Specifically, a median reported relative density value of 950 has been used for the conversion of Dimethicone samples described in the ECETOC report.[3]

Chemical Properties

Dimethicone is a white, almost odorless fluid polymer.[1] Specifications for Dimethicone stated that the color and odor are specified by the buyer. Also specified by the buyer are the refractive index at 25℃ (within the range of 1.4000 to 1.4035), and the kinematic viscosity (provided that the specified mean viscosity at 25℃ is not less than 20 centistokes [cs] and not greater than ± 5% of the specified mean). It contains 98.5% to 101.1% Dimethicone and the total acid number is 0.01 maximum. One supplier of Dimethicone noted that 100 and 350 cs fluids are generally used for cosmetics.

C30-45 Alkyl Dimethicone

C30-45 Alkyl Dimethicone is a an off-white solid, which occurs in small pellets, at standard temperature and pressure.[4] This ingredient has a melting point of 63 - 74 °C and is considered insoluble in water.

Caprylyl Methicone

At atmospheric pressure, Caprylyl Methicone is a liquid at 20 °C, has a melting/freezing point at -20 °C, a boiling point at 263 °C, and a calculated partition coefficient (log P_{ow}) of 9 at 20 °C.[6] This ingredient also has a molecular weight of 335 g/mol, a relative density of 0.84 at 20 °C, a viscosity of 0.0027 kg/m·s at 20 °C, a vapor pressure of 0.64 Pa at 25 °C, and a water solubility of 2.8 x 10^{-5} mg/l.

Hexyl Methicone

At atmospheric pressure, Hexyl Methicone is a liquid at 20 °C, has a melting/freezing point at < -20 °C, a boiling point at 232 °C, and a log P_{ow} > 6.2 at 40 °C.[7] Additionally, Hexyl Methicone has a relative density of 0.83 at 20 °C and a water solubility of 0.011 mg/l at 20 °C.

Method of Manufacture

Stearoxy Dimethicone is produced by the reaction of dichloropolydimethylsiloxane with stearyl alcohol.[1] Dimethicone is produced by polymerization/equilibration. Cetyl Dimethicone is produced by hydrosilylation of C_{16} alpha-olefins. Stearyl Dimethicone is produced by hydrosilylation of C_{18} alpha-olefins.

No additional methods of manufacture data were found in the published literature, and unpublished data were not submitted.

Impurities

One supplier of these ingredients noted that Stearoxy Dimethicone, Dimethicone, Cetyl Dimethicone, and Stearyl Dimethicone contain no antioxidants or preservatives.[1] Heavy metals are at 5 ppm maximum, and D4/D5 cyclomethicone is at less than 1%.

C30-45 Alkyl Dimethicone

The Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS) noted that C30-45 Alkyl Dimethicone can potentially contain residual monomers which are classified as hazardous according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS)*.[4] As per Australian chemical manufacturing guidelines, however, these are not present above the cut off concentrations for classification.

No additional impurities data were found in the published literature, and unpublished data were not submitted.

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. Use frequencies of individual ingredients in cosmetics is collected from manufacturers and reported by cosmetic product category in the FDA Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetic industry in response to a survey, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

Frequency and concentration of use has generally increased for these ingredients since they were originally reviewed, with some of the increases being quite significant. According to VCRP survey data, the frequency of use of Dimethicone has increased from 1659 reported uses in 1998 to 7656 reported uses in 2021, and the number of uses reported for Methicone increased from 0 reported uses in 1998 to 579 uses reported in 2021 (Table 2).[1,9] Of the ingredients not previously reviewed, Caprylyl Methicone has the highest overall frequency of use (183).[9]

Although the overall increase in the reported maximum concentration of use of Dimethicone is not substantial (from 80% to 85%), increases in concentration according to exposure type are notable.[1,10,11] For example, increases in maximum use concentrations of Dimethicone for products resulting in dermal contact increased from 30% in 1999 to 85% in 2019, application to the eye area increased from 13% (in eyebrow pencils) in 1999 to 37.8% (in eyeliners) in 2019, incidental ingestion via lipstick formulations increased from 20% in 1999 to 71.3% in 2019, and incidental inhalation increased from 16% (in perfume sprays) in 1999 to 85% (in moisturizing sprays) in 2019, and from 30% in 1999 to 53% in 2019 for face powders. Caprylyl Methicone has the highest reported maximum concentration of use for the newly added ingredients; it is reported to be used at up to 16% in eye lotions.[12] The 9 ingredients which are not reported to be in use, according to VCRP and survey data, are listed in Table 3.

As mentioned above, some of the ingredients named in this report are used in cosmetic sprays and powders, and could be incidentally inhaled. Furthermore, it has come to the attention of the Panel that Dimethicone and Methicone are listed as ingredients being used in consumer products which are applied via airbrush devices.[13] However, information regarding this type of use was not reported to the Panel in response to the industry survey, and would not be evident in the VCRP; therefore, details of this type of use (e.g., classification as a cosmetic, drug, device, etc.) are unknown.

The ingredients named in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[14]

Non-Cosmetic

Dimethicone

The allowable concentration of use of Dimethicone as an active ingredient in the formulation of skin protectant drug products for over-the-counter human use is 1 - 30%. [21 CFR § 347.10] Dimethicone has been used as a physical barrier method of eradicating head lice and eggs.[15,16] Dimethicone use is also prevalent in condom lubricants.[3,17] Dimethicone is also used industrially, in various construction sealants, rubber, and paints.[3]

In 2008, at the Joint Expert Committee on Food Additives (JECFA) of the World Health Organization (WHO), the established acceptable daily intake (ADI) level for Dimethicone of 0 - 1.5 mg/kg was withdrawn due to variability in safety data, and was temporarily replaced with 0 - 0.8 mg/kg, while concerns about ocular toxicity resulting from molecular weight and viscosity-dependent absorption and toxicity were evaluated.[18] As of 2011, the original ADI of 0 - 1.5 mg/kg was reinstated.[18]

TOXICOKINETIC STUDIES

Penetration

Caprylyl Methicone

The dermal penetration of Caprylyl Methicone is deemed unlikely due to a low water solubility and an estimated log P_{ow} of 9.[6]

Dimethicone

Penetration of Dimethicone (9.5 kg/m·s and 332.5 kg/m·s) was examined in female human abdominal skin and vaginal tissue.[3] Both viscosities were applied in infinite doses for 96 h to the donor side of split-thickness human abdominal skin sections (reference standard) and full-thickness human vaginal tissue mounted in Franz in vitro diffusion cells. (The identification of the vehicle and receptor fluid was not provided.) The dermal flux rate for Dimethicone (332.5 kg/m·s) in abdominal skin was 0.3 ng/cm^2/h, compared to 2 ng/cm^2/h for vaginal tissue; while the flux rates for Dimethicone (9.5 kg/m·s) in abdominal skin were 0.2 ng/cm^2/h and 6 ng/cm^2/h for vaginal tissue. The authors concluded that there was a low penetration rate, which occurred more rapidly in vaginal tissue, for both viscosities.

In a dermal penetration study, the authors sought to determine if Dimethicone interacts with and alters the stratum corneum lipid microstructure.[19] Excised human stratum corneum tissue samples were obtained from the inner thigh of a healthy 50 yr-old woman and the abdomen of a healthy 26 yr-old man. An in vitro model lipid system containing stratum corneum fatty acids was also used to mimic the skin barrier. These tissue samples were rinsed with 0.001% m/m trypsin inhibitor and stored for 48 h in 76% humidity, at ambient temperature, to achieve an approximately 20% hydration level. The hydrated samples were then treated for 20 min in various viscosities of excess Dimethicone (332.5, 475, 950, or 19,000 kg/m·s) at 37 ºC, removed with a cellulose tissue, and analyzed for change using thermal profile, x-ray diffraction, polarized light microscopy, and transmission electron microscopy. All results indicated that Dimethicone did not disturb or interact with the liquid crystalline structure of the upper layer of the epidermis, and hence is not likely to penetrate the skin barrier.

Absorption, Distribution, Metabolism, and Excretion (ADME)

Several acute pharmacokinetic studies in dogs, rats, and a monkey reported minimal gastrointestinal absorption of Dimethicone and up to 99.99% recovery of the administered dose via excretion.[1] In a repeated dose study, beagle dogs were fed 91% Dimethicone at a dose of 300 mg/kg/d for 120 d in the diet. Although one female showed atrophy of the spleen, and another female had slightly reddened rugae near the stomach and mucus in the intestine, Dimethicone was not detected in any organs or considered absorbed.

Animal

Dimethicone

In a study examining dermal absorption and distribution, an occlusive patch containing [^{14}C]Dimethicone (332.5 kg/m·s) was applied to male CD rats (number not provided) for 24 h.[3] After the initial 24-h exposure period, animals were removed from the metabolism cages, the occlusive patch was removed, and the exposure site was washed. The animals were re-wrapped with a non-occlusive bandage and returned to metabolism caging for continued monitoring and collection of biologic samples. The animals were killed 72 h after their initial exposure and the exposure sites were carefully excised. Radioactivity tracing demonstrated that 70% of the administered dose was found on the patch materials, 11.4% was present at the site of application, and none was found in the blood. Minimal amounts were found in the feces (0.01%) and carbon dioxide traps (0.001%).

Human

In human studies, absorption was seen in humans following ingestion of a Dimethicone sample containing low-molecular-weight polymers.[1] Dermal upper back exposure to Dimethicone for 10 d did not increase blood or urine silicone concentrations in men.

Caprylyl Methicone

According to an estimated blood: air partition coefficient of 1.7 x 10^{-4}:1 for human inhalation, systemic circulation of Caprylyl Methicone is not likely.[6,20] Based on an algorithm,[21] the soluble fraction of Caprylyl Methicone in the blood is << 1%, suggesting the minimal likelihood of this ingredient being excreted in urine as water-soluble metabolites.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

The dermal LD_{50} for Dimethicone was > 2000 mg/kg in rats and rabbits.[1] The dermal LD_{50} for Methicone was > 20 ml/kg in rabbits. The dermal LD_{50} for Vinyl Dimethicone was > 16 ml/kg in rabbits.

C30-45 Alkyl Dimethicone

An acute dermal exposure study with C30-45 Alkyl Dimethicone was performed, in rats, according to the US Toxic Substances Control Act (US TSCA) [40 CFR § 798.1100] Test Guideline (TG).[4] The LD_{50} in rats was reported to be > 2000 mg/kg bw.[4] No further details were provided.

Caprylyl Methicone

In an acute dermal exposure study, performed in accordance with Organization for Economic Cooperation and Development (OECD) TG 402, undiluted Caprylyl Methicone was tested on 5 male and 5 female Wistar rats at a dose of 2000 mg/kg bw.[6] The test substance was spread over approximately 10% of the back area, and covered with an occlusive dressing for 24 h. Test sites were rinsed with water at the end of the application period; animals were examined daily for 14 d, before necropsy. No mortality or signs of systemic toxicity were observed. The dermal LD_{50} of Caprylyl Methicone was determined to be > 2000 mg/kg bw in rats.

Dimethicone

A single, 2008 mg/kg bw dermal application of Dimethicone (332.5 kg/m·s) was made on 5 male and 5 female Sprague Dawley (SD) rats, in accordance with the OECD TG 402.[3] The test substance was spread over approximately 10% of the total body surface and was held in place with a bandage for 24 h. Test sites were rinsed with lukewarm water at the end of the application period; animals were monitored for mortality and clinical signs for 14 d, before necropsy. No mortality or noticeable abnormalities were observed. The dermal LD_{50} in this study was determined to be > 2008 mg/kg bw.

Undiluted Dimethicone (54,150 kg/m·s) was applied to the shaved backs of 5 male and 5 female adult New Zealand White rabbits at a dose of 2000 mg/kg bw.[3] The test site was occluded and Dimethicone was in contact with the skin for 24 h. After exposure, the residual test material was removed with Dimethicone (332.5 kg/m·s)-moistened gauze. The rabbits were frequently observed on the day of treatment, and at least once a day during a 14-d observation period. No signs of systemic toxicity were observed during the study, and no rabbits died during this study. Under the conditions of this study, the acute LD_{50} of Dimethicone in adult male and female rabbits was considered to be > 2000 mg/kg bw.

Oral

Dimethicone, Methicone, and Vinyl Dimethicone were not acutely toxic following oral exposure.[1] Methicone had an oral LD_{50} of > 64 ml/kg in male albino rats. Vinyl Dimethicone had an oral LD_{50} of > 16.0 ml/kg in Sprague Dawley rats. Greasy-textured fur was noted in the rats, while one rat had pneumonia and pleuritis observed at necropsy.

Caprylyl Methicone

In accordance with OECD TG 423, 3 female Wistar rats were administered a single dose of 2000 mg/kg bw Caprylyl Methicone, via gavage.[6] No signs of systemic toxicity were observed over the course of a 14-d post-dose observation period. An expected increase in body weight was observed in all animals, none died prior to necropsy, and no gross pathological changes were observed. The acute oral LD_{50} of Caprylyl Methicone was determined as > 2000 mg/kg bw in female rats.

Dimethicone

Five male and 5 female Sprague-Dawley rats were administered a single dose of 2000 mg/kg bw Dimethicone (57,000 kg/m·s) in corn oil by gavage.[3] No overt signs of systemic toxicity were observed over the course of a 14-d post-dose observation period. All of the rats gained weights, no animals died during the study, and no gross necropsy lesions were observed. The acute oral LD_{50} of Dimethicone in male and female rats was determined as > 2000 mg/kg bw.

Inhalation

Two dogs, 7 guinea pigs, and 7 rats were exposed to a "200 fluid" aerosol of Dimethicone at a concentration of 2.12 mg/l for 6 h.[1] Three guinea pigs died during the study, and all necropsied animals had hyperemic lungs with hemorrhagic areas. Vapor exposure to Methicone, at a concentration of 0.78 mg/l for 8h, and Vinyl Dimethicone, at a near-saturation concentration (no further details provided) for 6 h, did not cause mortality or lesions in rats. Aerosolized Hexyl Methicone was administered by whole-body inhalation exposure to Fischer F344/N rats for 4 h, at varied target concentrations ranging from 1.0 mg/l - 5.0 mg/l with particles having a mass median aerodynamic diameter (MMAD) of 0.27µm - 0.29µm. All rats exposed to the 5.0 mg/l concentration (0.27 µm MMAD) died, while a portion died at the other concentrations. Lesions at

necropsy of the rats who died included dark red or mottled lungs and/or fluid filled trachea. The calculated LC_{50} for both sexes was 1.8 mg/l.

Dimethicone

An acute aerosol inhalation study of Dimethicone (95,000 kg/m·s) was performed in a similar fashion to OECD TG 403.[3] Groups of 5 Wistar rats were exposed for 4 h, nose-only, to solutions of 25% Dimethicone dissolved in petroleum ether, or to two other solvents in separate control groups (control solvents not named). Rats were exposed to mean Dimethicone concentrations of 4315 mg/m^3 (MMAD of 1.55 µm), or 11,582 mg/m^3 (MMAD of 1.52 µm). During, and after, the 14-d observation period, no mortality or clinical symptoms were attributed to Dimethicone exposure. The LC_{50} was determined to be > 11,582 mg/m^3.

Dimethicone (9500 kg/m·s) dissolved in dichloromethane was used to perform an acute aerosol inhalation toxicity study, in accordance with OECD TG 403.[3] Groups of 5 Wistar rats were tested with concentrations of either 153.3, 322.0, 445.6, or 694.8 mg/m^3 Dimethicone (MMAD up to 1.8 µm). Duration of exposure was not provided; however, according to OECD TG 403, exposure can be up to 6 h (nose-only) in rats. No mortality or toxic effects were observed during the 14-d observation period or at necropsy. The LC_{50} was determined to be > 695 mg/m^3.

Short Term Toxicity Studies

Dermal

No adverse reactions were found in rabbits following short-term dermal dosing with 6% to 25% Dimethicone.[1] Rats were dermally dosed with either 0.04% Dimethicone (18.92 kg/m·s), or a solution containing 5% each of four linear/cyclic dimethylpolysiloxanes for 4 wk. No macroscopic changes were noted. Changes were seen in serum total cholesterol concentrations, and dermal dosing resulted in less silicon accumulation in the fat when compared to oral administration.

Dimethicone

Three groups of 10 New Zealand white rabbits (number per sex not specified) were dermally administered Dimethicone (332.5 kg/m·s) via an occlusive patch for 4 wk (28 d) at doses of 0, 100, 300, or 1000 mg/kg/d.[3] On a daily basis, rabbits were examined for dermal irritation prior to application, and were exposed to the test material for 6 h prior to patch removal. Body weight was measured twice a week, and blood samples were taken for hematology and blood chemistry evaluations on day 29 for males and day 30 for females. No deaths or adverse events related to the treatment occurred. Body weight, hematology, blood chemistry, and gross and microscopic evaluation of selected organs showed no changes that were considered of toxicological significance. The no-observable-adverse-effect-level (NOAEL) for dermal application of Dimethicone in rabbits in this study was therefore considered to be 1000 mg/kg/d.

Oral

Mongrel dogs were fed with up to 3.0 g/kg/d of 83% Dimethicone for 12 wk.[1] The liver of dosed dogs had bile pigment deposits in Kupfer and hepatic cells, which were proportional to the daily dose received.

Caprylyl Methicone

Four groups of 10 male and 10 female Crl: WI (Han) rats were dosed with 0, 100, 300, or 1000 mg/kg bw/d Caprylyl Methicone, in corn oil, by gavage, for 28 d.[6] Recovery groups of 5 male and 5 female rats were selected from the control and 1000 mg/kg bw/d group, to be observed for 14 d after exposure. No mortality or clinical abnormalities occurred during observation. An elongated mean activated partial thromboplastin time in the 1000 mg/kg bw/d males became similar to controls at the end of the recovery period. A statistically significant lower red blood cell count in the 300 mg/kg females, an absent pupillary reflex and white stain on the eye of a 100 mg/kg male, slight vacuolation in the adrenal glands of 1 male each from the 100 mg/kg and 1000 mg/kg groups, and 2 males from the 1000 mg/kg/d recovery group, and a statistically significant minimal increase in the liver weights of 300 and 1000 mg/kg females, were all considered unrelated to treatment or toxicologically irrelevant. The reported NOAEL of Caprylyl Methicone was determined to be > 1000 mg/kg bw/d.

Four groups of 10 male and 10 female Sprague-Dawley rats were dosed with 0, 500, 1000, or 5000 mg/kg bw/d Caprylyl Methicone, via gavage, for 28 d.[5] Two females treated with 500 mg/kg bw, 1 male and 2 females treated with 1000 mg/ kg bw, and 3 males and 1 female treated with 5000 mg/kg bw died prior to sacrifice. The unscheduled animal deaths were attributed to aspiration of the test substance, and not the test substance itself. Besides dark, mottled, and congested lungs, enlarged livers, and sores, alopecia, and rough, stained fur in the posterior regions of animals in the 5000 mg/kg bw group, no statistically significant differences were observed in the laboratory and clinical findings. Statistically significant lower mean organ and body weights were only observed in 5000 mg/kg bw males and females; organ to brain weight ratios of the treated groups were not significantly different from controls. The NOAEL was determined to be 1000 mg/kg bw/d and the no-observed-effect-level (NOEL) was deemed to be 500 mg/kg bw/d.

Dimethicone

In a 28-d oral toxicity study, Dimethicone (9.5 kg/m·s and 332.5 kg/m·s) was administered to groups of 10 CDF-(F344)-CrlBr rats in the diet, at concentrations of 10,000 to 100,000 ppm (1 - 10%).[3] No mortality or adverse clinical signs of toxicity were noted during observation or upon necropsy. Test article related symptoms consisted of dose-related increase in matting of male and female rat fur, increased incidence of corneal opacity and inflammation, and significantly decreased mean triglycerides and low-density-lipoprotein levels (LDL) at higher doses (≥ 2.5%). These symptoms were not regarded as adverse effects and the NOAEL of Dimethicone in the rat diet was determined to be > 100,000 ppm.

Inhalation

A cat, rabbit, guinea pig, 2 rats, and 4 mice were sprayed for 4 h with an atomizer containing 10 ml/kg of a sample of Dimethicone (140 cm^2/s; dynamic viscosity or specific gravity values were not available) for 29 d.[1] During the 6-wk post-dosing observation period, no exposure-related adverse effects were seen in the cat, rabbit, guinea pig, and rats. All 4 mice died – one after the 20th exposure, and the 3 others during the post-dosing period. The link between treatment and death was uncertain and the authors concluded that Dimethicone inhalation is harmless.

Subchronic Toxicity Studies

Oral

Mice and rats were dosed for 90 d with up to 10% Dimethicone, via diet.[1] No signs of systemic toxicity were seen during the study or during post-study pathologic examination. Anal leakage of Dimethicone was detected in the high dose groups and in those rats that were fed more viscous Dimethicone. Observations of slight chronic corneal inflammation, opacity, and neovascularization was observed in the eyes of the rats, regardless of dosage, and was regarded as a local ocular effect resulting from contact with the feed. In another rat study, in which animals were fed an antifoam compound containing 0.1%, 0.3%, or 1.0% Dimethicone for 120 d, changes in body weight or spleen weight were observed in the 1.0% Dimethicone dose group.

Chronic Toxicity Studies

Oral

No significant differences were observed in the organ weights of Wistar rats that were fed 0.3% Dimethicone in the diet for 2 yr, compared to controls.[1] Upon pathologic examination, pulmonary lesions, changes in the ovaries and uterus, and mild fatty changes in the liver and tubular epithelium of the kidneys was observed in all treated rats. Rats and rabbits which were fed 1% Dimethicone in the diet (50 or 350 cm^2/s; dynamic viscosity or specific gravity values were not available) for up to 1 yr did not exhibit signs of systemic toxicity.

Dimethicone

Four groups of 30 male and 30 female Fischer 344 were administered Dimethicone (9.5 kg/m·s) in the diet at doses of 0 (control), 100, 300, or 1000 mg/kg bw/d for 12 mo.[3,22] Four groups of 10 males and 10 females from each treatment group were necropsied after 12 mo of Dimethicone administration. The remaining animals (20 male and 20 female rats from each group) were observed for chronic recovery for 12 mo after the 12-mo treatment period. Test article-related toxicological effects in necropsied rats were limited to increased incidence of ocular opacities in ≥ 300 mg/kg bw/d females and 1000 mg/kg bw/d males. Similarly, in the chronic recovery group, there was an increase in eye opacity for all treated male groups, without dose correlation. This result was further supported by microscopic findings of keratitis and corneal dystrophy. The NOEL for systemic toxicity of Dimethicone was determined to be equal to the highest tested dose, 1000 mg/kg bw/d.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Dimethicone was tested in numerous oral-dose (using rats) and dermal-dose (using rats, rabbits, monkeys) reproductive and developmental toxicity studies.[1] In an oral study with rats, 3.3 ml/kg/d Dimethicone was administered directly to the stomach for 6 d. Males treated with 1 of 3 Dimethicone samples (no further details provided) had significantly decreased body weight and/or decreased testes or seminal vesicles weights. No treatment-related adverse findings were noted in pregnant females or fetuses, dosed orally, via diet, and dermally. In an intergenerational study, a motor oil containing an unspecified amount of Dimethicone was applied undiluted in doses of 0.1, 0.4, and 1.5 ml/kg, to the shaved backs of the parental (P_1) and first generation (F_1) of Sprague-Dawley rats, daily for an 8-wk premating period, 3-wk mating period, and throughout gestation and lactation. Mortality was significantly increased on day 0 in the 0.4 ml/kg group, and absolute testes weight was significantly reduced in the adult F_1 male rats of the 1.5 ml/kg group, beginning wk 7, but the relative testes to body weight ratio was not significantly different from controls.

Caprylyl Methicone

Four groups of 10 male and 10 female Crl: WI (Han) rats were dosed with 0, 100, 300, or 1000 mg/kg bw/d Caprylyl Methicone, in corn oil, by gavage, for 28 d; 5 male and 5 female rats from the both the control and 1000 mg/kg bw/d groups

served as recovery animals.[6] The animals were cohoused to facilitate impregnation, after a minimum of 14 d of exposure, for a maximum time period of 14 d. Fertility and conception parameters were not affected, and no maternal abnormalities were observed; no changes or differences in fetal or pup body weights, number of live offspring, sex ratios, litter size, and skeletal, visceral, or external malformations were observed. The NOAEL for Caprylyl Methicone maternal toxicity and developmental effects was determined to be > 1000 mg/kg bw/d.

GENOTOXICITY STUDIES

Dimethicone tested negative for genotoxic effects in multiple Ames tests, at up to 5000 µg/plate, bacterial reverse mutation assays, at up to 79% in formulation, micronucleus tests, at up to 5 g/kg, and in mouse cell and Chinese hamster ovary (CHO) assays, at up to 10,000 µg/ml, both with and without metabolic activation.[1]

In Vitro

C30-45 Alkyl Dimethicone

A bacterial reverse mutation assay was performed with C30-45 Alkyl Dimethicone in accordance with OECD TG 471.[4] The test substance was found to be non-mutagenic. (No further details were provided.)

Caprylyl Methicone

In accordance with OECD TG 471, *Salmonella typhimurium* strains TA97s, TA98, TA100, TA102, and TA 1535 were tested with up to 5 mg/plate Caprylyl Methicone (in ethanol), in a bacterial reverse mutation assay, in the presence and absence of metabolic activation.[6] No precipitates or cytotoxicity were observed and the test substance was determined to be non-mutagenic to bacteria, under these study conditions.

Dimethicone

S. typhimurium strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strains WP2 uvrA and WP2 uvrA (pKM 101) were tested with Dimethicone (57,000 kg/m·s) in a bacterial reverse mutation assay, in the presence and absence of metabolic activation.[3] The assay was performed in two stages, in which a range-finding study, and consequent initial and independent repeat assays were used to evaluate the mutagenic potential of Dimethicone. Based on the toxicity assay, the maximum dose tested was 5000 µg per plate. Although precipitate was observed at ≥ 500 or at ≥ 1500 µg/plate, no appreciable toxicity was observed; Dimethicone was considered non-mutagenic under these study conditions.

In Vivo

Caprylyl Methicone

Groups of 5 ICR mice were intraperitoneally dosed with 0, 1253, 2505, or 5010 mg/kg bw Caprylyl Methicone, or given 80 mg/kg bw of cyclophosphamide (positive control) via gavage, in a mammalian erythrocyte micronucleus test.[5,6] Bone marrow cells were harvested 24, 48, and 72 h after dose exposure. No significant increase in the micronucleated polychromatic erythrocytes (PCEs) was observed in any of the test animals at all harvest times. Caprylyl Methicone was deemed non- genotoxic under the conditions of this study.

CARCINOGENICITY STUDIES

Dimethicone was negative for carcinogenicity in both an oral (up to 2.5% Dimethicone in diet for 76 wk) and a dermal carcinogenicity study (lifetime application; 50 µl of the test article (motor oil) that contained an unspecified amount of Dimethicone) using mice.[1] One treated mouse in the dermal study had a palpable skin mass at the application site during wk 65, which regressed by wk 67; no application site dermal neoplasms were microscopically confirmed in either treated or control mice.

Dimethicone

The carcinogenic potential of a silicone resin containing 92% Dimethicone and 8% silica (300-1050 cm^2/s; dynamic viscosity or specific gravity values were not provided; similar to "Simethicone," a cosmetic ingredient, which is sold over-the-counter as an anti-flatulence medication, without significant adverse effects[23]) was evaluated using groups of 50 male and 50 female F344/DuCrj rats.[24] The rats were given diets containing 0, 1.25, or 5.0% of the test article for 104 wk. Animals were monitored twice daily for signs of toxicity, and body weight was measured alternate weeks. During the study, there were no significant differences in appearance or behavior between the control and treatment groups. Survival rates were also not significantly different between both groups. The relative organ weight percentage for livers in male rats that received 5.0% test article in the diet were significantly lower than those of the livers in male control rats. Lower relative kidney, brain, and heart organ weight percentages were also considered to be statistically significant in treated female rats compared to female control rats. There was a statistically significant, 2 - 18%, increase in the incidence of parafollicular cell (C-cell) adenomas in female rats within the highest dose group (5.0%); however, according to previous carcinogenic assays done by the National Toxicology Program, the naturally occurring incidence of C-cell adenomas ranges from 0 - 34%, as seen in

control rats. The males of the 5.0% dose group experienced a decreased incidence of prostate cancer (8% vs. 22% in controls); however, values for prostatic intraepithelial neoplasias (PINs) were similar across groups. The prostate cancer incidence of the control group was relatively high (compared to historical results elsewhere); thus, the difference between treatment and control groups were considered incidental.

In a long-term toxicity study, 3 groups of 20 male and 20 female F344 rats were observed for oncogenic effects associated with oral administration of Dimethicone (9.5 kg/m·s) at doses of 100, 300, or 1000 mg/kg bw/d for up to 24 mo.[22] Slightly increased incidence of corneal opacity was observed in male rats dosed at 1000 mg/kg bw/d and in female rats dosed at 100 and 1000 mg/kg bw/day, as well as an overall increase in minimal to mild keratitis in all male and female rats (statistical significance not mentioned). A statistically significant increase in the incidence of islet cell adenomas was observed in the 100 mg/kg bw male dose group; however, the lack of an effect in female groups, and high incidence of islet cell adenomas in controls (even when assigned to recover for 12 mo), suggested that that these effects were independent of Dimethicone exposure. No neoplastic changes were observed and the NOEL for oncogenicity of Dimethicone was determined to be 1000 mg/kg bw/d.

OTHER RELEVANT STUDIES

Immunotoxicity

Dimethicone

Four groups of 20 female A.SW (*H-2^s-T18^b-/SnJ*) mice received a single 0.5-ml intraperitoneal (i.p.) injection of one of the following: phosphate-buffered saline (PBS) as the negative control, pristane (2,6,10,14-tetramethylpentadecane) as the positive control, silicone gel (taken from a mammary implant), or Dimethicone (970 kg/m·s).[25] A pretest bleed was taken via orbital puncture prior to injection, after which blood samples were obtained post-injection once a month for 6 mo. The mice were killed after 6 mo of observation, and peritoneal macrophages were collected by lavage. Additionally, immuno-precipitation, fluorescent antinuclear antibody (FANA) microscopy, macrophage culture, kidney pathology, and enzyme-linked immunosorbent assay (ELISA) immunoglobin analyses were performed. Although Dimethicone-treated mice did not produce lupus-associated antinuclear antibodies (observed only in positive controls) various antibody isotopes were observed within 2 mo of injection. Immunoglobulin M (IgM) levels remained elevated compared to controls, and IgG1 and IgE serum levels were significantly elevated at 4 mo in comparison to 5 - 6 mo for the controls. Macrophages from negative control mice secreted little interleukin-6 (IL-6), a pro-inflammatory cytokine, while pristane-, silicone gel-, and Dimethicone-treated mice spontaneously secreted IL-6 and also produced greater, dose-dependent amounts of IL-6 when cultured with lipopolysaccharide. Suspected silicone droplets and expanded vacuoles within the glomeruli of treated mice kidneys also indicated capacity for systemic accumulation.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

Most dermal irritation studies using rabbits classified Dimethicone as a minimal irritant.[1] Studies that scored reactions according to the Draize scale reported primary irritation indices of ≤ 2.8(with test samples containing 5% to 100% Dimethicone). Vinyl Dimethicone was not irritating to rabbits following a 4-h exposure.

Animal

C30-45 Alkyl Dimethicone

A skin irritation test using C30-45 Alkyl Dimethicone was performed in rabbits, in accordance with US TSCA [40 CFR § 798.4470].[4] The test substance was determined to be non-irritating. (No further details were provided).

Caprylyl Methicone

In a skin irritation test, performed in accordance with OECD TG 404, 0.5 ml Caprylyl Methicone was applied neat for 4 h under semi-occlusion to a 25 cm^2 patch of closely shaven skin of 3 female New Zealand white rabbits.[6] After patch removal, the exposure sites were washed with water and scored using the Draize scale for up to 72 h. No signs of irritation were observed in any of the animals, and the test substance was deemed non-irritating.

In a dermal toxicity study, also performed in accordance with OECD TG 404, 3 male and 3 female New Zealand white rabbits were exposed to an occlusive application of 97%, undiluted Caprylyl Methicone (dose not specified).[5] No deaths or clinical signs were noted during the study period. Minor erythema was observed in 4 rabbits within 1 h following the contact period, but had subsided within 24 h in 3 of the 4 animals and 48 h for the last animal. Minor edema was apparent in 1 animal within 1 h, but subsided by 24 h. Desquamation developed in 1 rabbit after 7 d of testing; no other signs of irritation were observed, and the test substance was deemed slightly irritating to the skin.

Dimethicone

Three rabbits and 3 guinea pigs were exposed to non-occlusive, daily applications of 0.5 ml of Dimethicone (100 cm^2/s; dynamic viscosity or specific gravity values were not provided) to a 2.5 cm^2 patch of closely shaven skin for 10 d.[26] No erythema or signs of skin irritation or inflammation were noted in the animals.

In an acute dermal toxicity study, undiluted, Dimethicone (57,000 kg/m·s) was applied to the shaved backs of 5 male and 5 female adult New Zealand White rabbits, under occlusion, for 24 h, at a dose of 2000 mg/kg bw.[3] Erythema was observed at the application site in all 10 rabbits, but resolved by the 7th day of observation.

Sensitization

Dimethicone (tested undiluted and at 79%) was not a sensitizer in 4 assays using mice and guinea pigs.[1] It was not a sensitizer at 5.0% in a clinical HRIPT using 83 subjects.

Animal

Caprylyl Methicone

The sensitization potential of Caprylyl Methicone was evaluated with a Buehler test, according to OECD TG 406.[6] During induction, 20 male guinea pigs were patched with 100% Caprylyl Methicone (in acetone) once a week, via 6-h occlusive patches, for 3 wk. After a 2-wk rest period, a one-time, challenge application of 0.75% Caprylyl Methicone (in acetone) held in place by an occlusive dressing for a 6-h exposure period was made. Two groups of 10 guinea pigs served as the negative and positive control groups. The test article was not a sensitizer.

In a guinea pig maximization test (number of animals not specified), intradermal injections of Freund's Complete Adjuvant/saline (1:1), with and without 5% Caprylyl Methicone, did not cause ulceration of the injection sites and was well-tolerated.[5] During topical induction, administration sites treated only with 5% Caprylyl Methicone (vehicle not provided) showed minor dermal irritation; however, sites treated with 5% Caprylyl Methicone in mineral oil did not show signs of irritation. Challenge applications were made with 5% Caprylyl Methicone in mineral oil, and were observed at 24 and 48 h after patch removal (occlusion not specified). No dermal reactions were seen in either the test or control groups at 48 h, and the test substance was deemed a non-sensitizer.

Dimethicone

Five groups of 8 female B6C3F1 mice were tested for contact hypersensitivity to Dimethicone.[27] Dimethicone was determined to be a non-irritant during a primary dermal irritancy study, and was applied undiluted during both the induction and challenge phases. Eight, 20 µl induction applications, of either saline (challenged with saline), saline (challenged with Dimethicone), or Dimethicone (challenged with Dimethicone) were made for 8 consecutive days, while 5 applications of acetone/olive oil (challenged with 0.5% 1-fluoro-2,4-dinitrobenzene (DNFB)), or 0.5% DNFB in acetone + olive oil (4+1) (challenged with 0.5% DNFB), were made to a 0.5 cm^2 shaved and debrided region of the upper back. After a 6-d rest period, mice were injected with 20 µl of 125-iododeoxyuridine to measure the potential for Dimethicone to elicit a response via radioisotopic methods. Challenge applications were made 7 d after the rest period to the left ear using a cotton swab, and mice were examined for contact hypersensitivity via the mouse ear swelling test (MEST) for 2 d. All mice, except for 8 treated with Dimethicone, were killed after the first MEST; the untreated and challenged ears were biopsied and counted in a gamma counter. After 7 d, the surviving mice, and an additional 8 mice were tested in a second MEST. No statistically significant hypersensitivity was observed in the mice sensitized with Dimethicone, from the radioisotopic or MEST measurements. Subsequent challenge of previously sensitized mice also did not produce any change in the occurrence of ear swelling, and the test substance was determined a non-sensitizer.

Human

Dimethicone

In a human repeat insult patch test (HRIPT), Dimethicone (11,875 kg/m·s) was tested neat as a negative control, and was used as a vehicle for a 5% (v/v) solution of an unspecified test substance.[3] Sodium lauryl sulfate (0.1% aqueous solution) was used as a positive control. Of the 115 subjects enrolled, 106 completed the study; no subjects withdrew due to adverse reactions to the test substance. Induction consisted of 9 consecutive applications, where 0.2 ml of Dimethicone was applied under a semi-occlusive dressing for 24 h. The test sites were evaluated in the following 48 - 72 h. After the 9th application, there was a 10 to 15-d non-treatment period. Challenge occurred in the sixth week of the study; the substance was applied to an unexposed site for 24 h, and graded after 24 - 48 h. No evidence of sensitization to Dimethicone, as a control or vehicle, was observed.

OCULAR IRRITATION STUDIES

Most ocular irritation studies using rabbits classified Dimethicone, ranging in concentration from 10% to 35%, as a mild to minimal irritant.[1] The most common finding was a conjunctival reaction. However, instillation of 0.005 ml 15%

Dimethicone produced minor to moderate conjunctival irritation in all 6 rabbits; the irritation cleared in 5 of the 6 rabbits within 72 h. Additionally, a few studies reported conjunctival reactions, chemosis, and persisting redness, especially when the eyes were unrinsed. Similar to Dimethicone, Methicone and Vinyl Dimethicone also produced conjunctival reactions.

C30-45 Alkyl Dimethicone

The ocular irritancy potential of C30-45 Alkyl Dimethicone was tested in rabbits, in accordance to US TSCA [40 CFR § 798.4500].[4] Slight conjunctival effects were observed, but resolved within 24 h of exposure. The test substance was determined to be non-irritating. (No further details were provided).

Caprylyl Methicone

In an ocular irritation study, performed in accordance with OECD TG 405, 3 female New Zealand white rabbits were treated with 0.1 ml Caprylyl Methicone in one eye for 24 h (the second eye serving as control).[6] The treated eyes were thoroughly washed with saline after 24 h, and were examined at 1, 24, 48, and 72 h post-application. A 0.01% fluorescein-sodium solution was used to examine the treated eyes for corneal lesions at 24 and 72 h. Dilated blood vessels were observed in 2 of the 3 animals, as well as colorless eye discharge with moistening of the lids 1 h after instillation. All signs of irritation disappeared within 24 h of treatment, and the test substance was deemed not irritating to the eye.

In a similar study, also performed in accordance with OECD TG 405 (dose not specified), 3 male and 3 female New Zealand white rabbits did not exhibit corneal injury or iritis.[5] Minor conjunctival redness and minor (in 5 animals) to moderate (in 1 animal) ocular discharge occurred in all rabbits. Ocular irritation subsided within 24 h in 5 animals, and 48 h in the last animal. The test substance was deemed slightly irritating to the eye.

Dimethicone

Sixteen adult pigmented rabbits were tested for corneal tolerance of Dimethicone.[28] One eye of each animal was treated (the other eye served as a control) by forming a hanging suture in the lid which allowed 0.7 - 1.0 ml of generically produced, as well as medical-grade, Dimethicone at varying viscosities (485 - 12,125 kg/m·s) to remain on the eye for 3 - 6 h. Medical-grade Dimethicone (970 kg/m·s), which is produced with higher manufacturing, biocompatibility, and safety standards for use in pharmaceuticals and medical devices, was included to assess if it would elicit a variable eye irritation response. The oil was only replaced if the eye cup leaked or if the animal moved. The eyes were examined with fluorescein by slit lamp immediately after treatment, and were either enucleated immediately or 3 - 7 d later. Compared to the control eye, which was treated with a balanced saline solution, the eyes treated with Dimethicone exhibited increased epithelial and whole corneal thickness, which persisted for several days and was most noticeable ≥ 3 d post-treatment. Although there appeared to be better ocular tolerance for the medical-grade Dimethicone, it also caused some corneal changes; under light microscopy, all eyes treated with Dimethicone showed various degrees of intracellular epithelial and stromal edema. The authors concluded that both non-medical grade and medical-grade Dimethicone are mildly irritating to the corneal epithelium.

The ocular irritancy of Dimethicone was evaluated in a study using groups of 3 guinea pigs or 3 rabbits, to test 5 separately-manufactured samples of Dimethicone (100 cm^2/s; dynamic viscosity or specific gravity values unavailable).[26] For the test, a drop of Dimethicone was instilled once daily for 10 d into the lower eyelid of the animals, and conjunctival irritancy and reflex response to light and touch were observed for 15 d. The first sample did not produce inflammation or ocular opacity; however, all tested guinea pigs died by day 8 - 10. The second sample caused inflammation in the eye of one rabbit after 10 d, while 2 guinea pigs and 1 rabbit died. The eyes of animals treated with the second sample were also opaque. No adverse effects were observed in the eyes of the rabbits or guinea pigs treated with 3 remaining samples; the researchers opined that the ocular irritancy and inflammatory effects of silicone fluids may be dependent upon the acidity of the samples.

MUCOUS MEMBRANE IRRITATION STUDIES

A mucoadhesive paste (53% Dimethicone) was introduced (0.5 g) via syringe into the vaginal cavity of 6 albino rabbits.[1] Two control rabbits were dosed with a sodium chloride solution. Tissue was scored according to the Draize scale (maximum score of 8) at 24, 48, and 72 h post dosing. Erythema was noted in 3 rabbits at 24 h, and in one rabbit at 48 h after treatment. None had erythema at 72 h. No edema or signs of toxicity were observed. The irritation score for the paste was 0.22.

Dimethicone

Five samples of Dimethicone (100 cm^2/s; dynamic viscosity or specific gravity values unavailable), each not requiring more than 0.1 ml of 0.05 N alcoholic KOH to neutralize 15 g of the fluid, were tested for irritation of vaginal mucosa.[26] A sample of 0.05 ml of Dimethicone was instilled into the vagina of rats (number of animals not specified) daily for 8 d, the vaginal mucous membrane was observed to determine irritancy, and the effect on leukocyte count was determined. A 77.8 - 88% increase in leukocytes was observed in the vaginal smears of rats treated with two samples of Dimethicone. A similar increase was observed for rats instilled with formaldehyde as the reference irritant. Leukocyte increases in the rats treated

with the 3 remaining samples was markedly lower. The authors concluded that 2 of the silicone samples with a higher acidity (0.17) and acid value of 0.3 were more likely to be mucous membrane irritants than the other 3 samples, in which the increase of leukocytes was relatively low (0.05 - 0.10 acidity; acid values were not provided).

CLINICAL STUDIES

Case Reports

Dimethicone

A 23-d old, premature twin male infant suffering with nasal congestion was accidentally sprayed intranasally with diaper rash protectant spray (instead of nasal saline spray), which listed 10% Dimethicone as the only active ingredient.[29] The child went into a choking and coughing spell, and was rushed to the emergency department. After 2 h, he was still in respiratory distress, wherein his oxygen saturation had dropped to 85% and his chest x-ray showed diffuse bilateral infiltrates, suggestive of bilateral chemical pneumonitis. By the 3rd day, he developed an eosinophilia of 31 - 37%, with an absolute eosinophilic count of 3100 - 4250 per µl. He was treated with frequent saline bronchial lavages and chest physical therapy to remove mucus plugs blocking his endotracheal tube and was weaned off the ventilator by the 7th day after exposure. Referring to the Expert Panel evaluation that Dimethicone is safe for cosmetic use and when inhaled short term,[1] the researchers were of the opinion that Dimethicone did not cause the patient's symptoms. They found that the inactive ingredients of the product were aloe oil extract, caprylic/capric triglyceride, mineral oil, Peruvian balsam oil, shea liquid, and tocopheryl acetate/vitamin E. The authors concluded that the massive dose of mineral oil exposure was the most likely cause for acute pneumonitis, as was the Peruvian balsam oil for eosinophilia.

SUMMARY

According to the *Dictionary*, these 30 methicone ingredients are reported to function in cosmetics as skin conditioning agents, hair conditioning agents, and/or viscosity increasing agents. Of the ingredients in this report, Dimethicone and Methicone have the greatest frequency of use, according to 2021 VCRP data. Reported use for Dimethicone increased from use in 1659 formulations in 1998 to 7656 in 2021, and reported frequency of use of Methicone increased from no reported uses in 1998 to use in 579 formulations in 2021. The highest concentration of use reported in 2019 was for Dimethicone, at a concentration of 85% in moisturizing products; the maximum concentration of use reported previously for Dimethicone was 80%. Maximum use concentrations for Dimethicone increased for several product categories, including those resulting in dermal contact (30% to 85%), exposure near the eye area (13% to 37.8%), incidental ingestion (20% to 71.3%), incidental inhalation from sprays (16% to 85%), and incidental inhalation from powders (30% to 53%).

Penetration of Dimethicone (9.5 kg/m·s and 332.5 kg/m·s) in human abdominal skin and vaginal tissue was examined after a 96-h application. A low penetration rate was observed for both viscosities, with more rapid penetration in vaginal tissue. In a dermal penetration study, the interaction of Dimethicone with the stratum corneum lipid microstructure in healthy excised human tissue was evaluated. All results indicated that Dimethicone did not disturb or interact with the upper layer of epidermis, and is not likely to penetrate the skin barrier. Male rats were exposed to both occlusive and non-occlusive patches of [^{14}C]Dimethicone to observe dermal absorption and excretion over 3 days. Radioactivity tracing demonstrated that 70% of the applied dose remained on the patches, 11.4% of the applied dose was at the site of application, and minimal amounts were found in feces and carbon dioxide traps. According to an estimated blood: air partition coefficient of 1.7×10^{-4}:1 for human inhalation, systemic circulation of Caprylyl Methicone is not likely. The algorithm-based soluble fraction of Caprylyl Methicone in the blood (<< 1%) suggests the minimal likelihood of excretion in urine as water-soluble metabolites.

The acute dermal LD_{50} of C30-45 Alkyl Dimethicone was determined to be > 2000 mg/kg bw in rats. In two separate acute dermal studies, undiluted Caprylyl Methicone and Dimethicone (54,150 kg/m·s) were applied, under occlusion, to the shaved backs of 10 Wistar rats and 10 New Zealand white rabbits, respectively, at doses of 2000 mg/kg bw for 24 h. No mortality and signs of toxicity were observed in either study and the acute dermal LD_{50} for each ingredient was determined to be > 2000 mg/kg bw in rats and rabbits, respectively. A single, 2008 mg/kg bw dermal application of Dimethicone did not cause mortality or noticeable abnormalities in 5 male and 5 female Sprague-Dawley rats; under these study conditions the acute dermal LD_{50} was determined to be > 2008 mg/kg bw. Three groups of 10 New Zealand white rabbits were exposed to an occlusive patch of Dimethicone (332.5 kg/m·s) for 28 d at doses up to 1000 mg/kg/d. No deaths or adverse events related to the exposure occurred, and the NOAEL for dermal application in rabbits was determined to be 1000 mg/kg/d.

Three female Wistar rats were administered a single dose of 2000 mg/kg bw Capryl Methicone, via gavage; no mortality or signs of systemic toxicity were observed, and the acute LD_{50} was determined to be > 2000 mg/kg bw. Five male and female Sprague-Dawley rats were administered a single oral dose of 2000 mg/kg bw Dimethicone in corn oil. No toxic effects or gross necropsy lesions were observed, and the acute LD_{50} was determined to be > 2000 mg/kg bw in rats. Caprylyl Methicone was administered in corn oil, via gavage, at doses of 0, 100, 300, or 1000 mg/kg bw/d to groups of 10 male and 10 female Han rats for 28 d. No mortality or clinical abnormalities occurred during observation; statistically significant lower blood cell count in the 300 mg/kg females, slight vacuolation in the adrenal glands of males in the main study, and recovery

group, dosed with 1000 mg/kg/d, and minimal increases of the liver weights of females in the 300 and 1000 mg/kg groups, were all considered toxicologically irrelevant. The NOAEL of Caprylyl Methicone was determined to be > 1000 mg/kg bw/d. In another 28-d oral toxicity study of Caprylyl Methicone, groups of 10 male and 10 female Sprague-Dawley rats were orally dosed with 0, 500, 1000, or 5000 mg/kg bw/d, via gavage. Deaths of 2 females in the 500 mg/kg group, 1 male and 2 females in the 1000 mg/kg group, and 3 males and 1 female in the 5000 mg/kg group were attributed to aspiration of the test substance. Congested lungs, enlarged livers, and lower mean organ and body weights in the 5000 mg/kg group were statistically significant, and the NOAEL was determined to be 1000 mg/kg bw/d, while the NOEL was determined to be 500 mg/kg bw/d. In a 28-d oral toxicity study, Dimethicone was administered at up to 10% (100,000 ppm) in the diet of CDF-(F344)-CrlBr rats. Test article related symptoms included matted fur, increased incidence of corneal opacity, and significantly decreased mean triglycerides and LDL levels at higher doses. These symptoms were not considered adverse effects and the NOAEL of Dimethicone was determined > 100,000 ppm. Four groups of 30 male and 30 female Fischer 344 rats were orally administered Dimethicone (9.5 kg/m·s), in their diet, at doses up to 1000 mg/kg bw/d for 12 mo. Amongst the treated rats, four groups of 10 male and 10 female rats were necropsied after 12 mo, while a remaining 20 male and 20 female rats per group were observed for recovery for 12 mo after the treatment period. In both necropsied and recovery groups there was an increase in ocular opacity, and the NOEL for systemic toxicity was determined to be 1000 mg/kg bw/d.

Groups of 5 Wistar rats were exposed for 4 h, nose-only, to solutions of 25% Dimethicone (95,000 kg/m·s) dissolved in petroleum ether, or to two other solvents in separate control groups (control solvents not named). No mortality or clinical symptoms were attributed to Dimethicone exposure, and the LC_{50} was determined to be > 11,582 mg/m^3. Dimethicone (9500 kg/m·s) dissolved in dichloromethane was tested for acute inhalation toxicity, at concentrations up to 694.8 mg/m^3, in Wistar rats. No mortality or toxic effects were observed, and the LC_{50} was determined to be > 695 mg/m^3.

In a reproductive and developmental toxicity study, 4 groups of 10 male and 10 female Han rats were orally dosed with 0, 100, 300, or 1000 mg/kg bw/d Caprylyl Methicone, in corn oil, via gavage for 28 d. Fertility, maternal, birth, and fetal outcomes were not adversely affected; the NOAEL for Caprylyl Methicone was determined to be > 1000 mg/kg bw/d.

Bacterial reverse mutation assays were performed with C30-45 Alkyl Dimethicone and Caprylyl Methicone; the test substances were not found to be non-mutagenic. In a bacterial reverse mutation assay, *S. typhimurium* tester strains TA98, TA100, TA153, TA1537, and *E. coli* strains WP2 uvrA and WP2 uvrA (pKM 101) were tested with Dimethicone (57,000 kg/m·s), at a maximum dose of 5000 µg per plate, in the presence and absence of metabolic activation. Although precipitate was observed at ≥ 500 or ≥ 1500 µg per plate, Dimethicone was considered non-mutagenic under these study conditions. In vivo, Caprylyl Methicone was intravenously administered at up to 5010 mg/kg bw to groups of 5 ICR mice in a micronucleus test; no significant increases in PCEs were observed and the test substance was deemed non-genotoxic.

The carcinogenic potential of a silicone resin containing Dimethicone and silica was evaluated by feeding 50 male and 50 female F344/DuCrj rats diets containing up to 5.0% of the test article for 104 wk. There was a statistically significant, 2 - 18% increase in the incidence of C-cell adenomas in female rats in the highest dose group, while the male rats in the highest dose group experienced a decreased incidence of prostate cancer compared to the control group. The incidence of prostate cancer in the control group was relatively high, and thus the difference between treatment and control groups was considered incidental.

Three groups of 20 male and 20 female F344 rats were observed for oncogenic effects upon oral administration of Dimethicone (10 cm^2/s; dynamic viscosity or specific gravity unavailable) at doses of 100, 300, or 1000 mg/kg bw/d for up to 24 mo. Slightly increased incidence of corneal opacity was observed at the maximum dose, as well as a statistically significant increase in islet adenomas among males in the 100 mg/kg bw group. However, the lack of increased islet adenomas in female rats and the high incidence amongst control rats suggested that these effects were independent of Dimethicone exposure. The NOEL for oncogenicity of Dimethicone was determined to be 1000 mg/kg bw/d.

Twenty female A.SW mice received a single 0.5-ml i.p. injection of Dimethicone, while 3 groups of 20 mice were injected with either saline, pristane or silicone gel, to evaluate immunological reactions over 6 mo. Dimethicone-treated mice produced various antibody isotopes within 2 mo of injection, spontaneously secreted and produced greater, dose-dependent amounts of IL-6, and showed silicone droplets and expanded vacuoles within kidney glomeruli, indicating the possibility for systemic accumulation.

A skin irritation test using C30-45 Alkyl Dimethicone (test concentration not specified) was performed in rabbits; the test substance was determined to be non-irritating. Two studies evaluating the dermal irritation potential of a neat, 4-h, occlusive application of Caprylyl Methicone to New Zealand white rabbits were performed; the test substance was deemed non-irritating at a dose of 0.5 ml, while it was deemed slightly irritating at an unspecified dose of 97%, undiluted Caprylyl Methicone. Dimethicone did not cause dermal irritation or inflammation in rabbits and guinea pigs. Caprylyl Methicone was determined to be a non-sensitizer in guinea pigs. Dimethicone did not cause sensitization or irritation in a contact sensitization study of female mice. In an HRIPT, Dimethicone was tested neat (as a negative control), and as used as a vehicle for a 5% solution of an unspecified test substance, in 106 subjects. No evidence of sensitization to Dimethicone, as a control or vehicle, was observed.

The ocular irritancy potential of C30-45 Alkyl Dimethicone was tested in rabbits; slight conjunctivae were observed, but resolved in within 24 h of exposure, and the test substance was deemed non-irritating. Caprylyl Methicone (0.1 ml) was not deemed irritating to rabbit eyes; an unspecified dose of Caprylyl Methicone was considered slightly irritating to rabbit eyes in another study. Sixteen rabbits were exposed for to up to 6 h with 0.7 - 1.0 ml of generic or medical-grade Dimethicone, in one eye, to test for variance in ocular irritancy. All eyes treated with either generic or medical-grade Dimethicone evidenced mild irritation of the corneal epithelium. In a study using groups of 3 guinea pigs, or rabbits, 5 separately manufactured samples of Dimethicone (100 cm^2/s; dynamic viscosity or specific gravity values unavailable) were instilled into the lower eyelid of the animals once daily for 10 d. All guinea pigs exposed to the first sample died by days 8 - 10, and the second sample caused corneal inflammation in one rabbit after 10 d, and death in another rabbit and 2 guinea pigs. No adverse effects were observed with exposure to the 3 remaining samples. Both Dimethicone samples with positive results had a slightly more acidic profile, suggesting that the ocular irritancy and inflammatory effects of silicone fluids may be acidity-dependent.

The potential for five samples 0.5 ml of Dimethicone (100 cm^2/s; dynamic viscosity or specific gravity values unavailable) to cause vaginal mucosa irritation was tested in rats for 8 d. An ~88% increase in leukocytes was observed in the vaginal smears of rats treated with two Dimethicone samples. A similar increase was observed in rats treated with formaldehyde. The leukocyte increase in the rats treated with the 3 remaining Dimethicone samples was markedly lower. Irritation outcomes for each Dimethicone sample were deemed to be affected by higher acidity and acid values.

A 23-d old, premature twin male infant experienced severe respiratory distress, acute pneumonitis, and eosinophilia as a result of intranasal exposure to a 10% Dimethicone spray. Although Dimethicone was listed as the active ingredient, mineral oil and Peruvian balsam oil were considered to be causative agents for the severe reaction.

DISCUSSION

In accordance with the CIR Procedures & Support to the Expert Panel for Cosmetic Ingredient Safety, the Panel evaluates the conclusions of previously-issued reports approximately every 15 years. After considering the dramatic increases in frequency of use of the previously-reviewed ingredients, as well as the concentrations of use in products that could result in incidental inhalation for additional Dimethicone, Methicone, and substituted-methicone polymers, the Panel reopened this safety assessment. The Panel concluded that the available data are sufficient for determining the safety of these ingredients as reportedly used in cosmetics when formulated to be non-irritating, with the exception that the available data are insufficient to make a determination that these ingredients are safe for use in products which could be incidentally inhaled.

The Panel was concerned that the potential exists for dermal irritation with the use of products formulated using dimethicone, methicone, and substituted-methicone polymers. The Panel specified that products containing these ingredients should be formulated to be non-irritating. Additionally, the Panel noted that Dimethicone is now being used at, or above, concentrations at which ocular irritation was observed in studies cited in the original assessment. Subsequently, the Panel distinguished the difference between instilling 35% Dimethicone in the eye, as described in an animal ocular irritation study from the original report, compared to using a cosmetic product containing 37.8% Dimethicone, in which ocular contact is not intended. However, the Panel stated that manufacturers should be cognizant of incidental/accidental exposure to the eye, and specified that products containing the ingredients included in this report should be formulated to be non-irritating to the eye. Additionally, the Panel discussed the validity of results from an ocular irritation study included in the present assessment, in which test animals died following instillation of 100% Dimethicone (970 kg/m·s) in the eye for 10 d. The Panel remarked that mortality occurring during an ocular irritation study is very unusual, and toxicologically implausible.

The Panel was made aware, through alternative sources, that some of the ingredients named in this assessment are reported to be used in consumer products which are applied via airbrush devices. The Panel considered the available physico/chemical properties data on the size distribution of airborne particles produced by airbrush devices and other delivery systems that may result in incidental inhalation. The Panel delayed arriving at a final conclusion in order to consider past and present information suggesting that a fraction of airborne particles resulting from airbrush delivery are respirable. The Panel noted that final particle size distribution of a spray product is determined by the composition of the formula, the concentration of individual ingredients and other relevant spray parameters (e.g., spray nozzle, can size, propellant type and pressure). The Panel noted that particle characteristics, such as size, morphology, and surface chemistry, are unique to each formulation with a risk of incidental inhalation, and can affect the associated deposition in the respiratory tract. The Panel also recognized currently available data suggest the use of airbrush makeup products that might lead to respiratory exposure to ingredients, which poses a potential risk to public health. The Panel felt there is an absence of data on respiration potential, as well as present concentration, frequency, and duration of use for these ingredients in formulations that may be incidentally inhaled (from any application or device). Thus, the Panel determined the available data are insufficient to determine safety for these ingredients for use in products that may be incidentally inhaled. The additional data needed to determine safety in cosmetics that may be incidentally inhaled are:

- information on the regulation of spray, or other, delivery systems for incidentally inhaled cosmetics

- particle size distributions produced by all cosmetics with the potential for incidental inhalation
- methods of use, including concentration of use and exposure duration and frequency, for all cosmetics with the potential for incidental inhalation

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 30 dimethicone, methicone, and substituted-methicone polymers are safe in cosmetics in the present practices of use and concentration described in this 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.

Amino Bispropyl Dimethicone
Aminopropyl Dimethicone
Amodimethicone
Amodimethicone Hydroxystearate*
Behenoxy Dimethicone
C20-24 Alkyl Dimethicone
C20-24 Alkyl Methicone*
C24-28 Alkyl Dimethicone*
C24-28 Alkyl Methicone
C26-28 Alkyl Dimethicone
C26-28 Alkyl Methicone*
C30-45 Alkyl Dimethicone
C30-45 Alkyl Methicone
C30-60 Alkyl Dimethicone*
C32 Alkyl Dimethicone*
Capryl Dimethicone
Caprylyl Methicone
Cetearyl Methicone
Cetyl Dimethicone
Dimethicone
Dimethoxysilyl Ethylenediaminopropyl Dimethicone
Hexyl Dimethicone
Hexyl Methicone*
Hydroxypropyldimethicone*
Methicone
Stearamidopropyl Dimethicone*
Stearoxy Dimethicone
Stearyl Dimethicone
Stearyl Methicone
Vinyl Dimethicone

**Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.*

TABLES

Table 1. Definitions, idealized structures, and functions[2, CIR Staff]

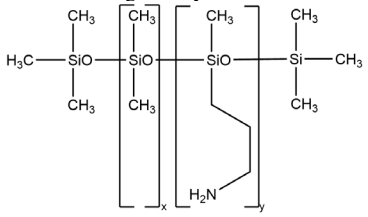
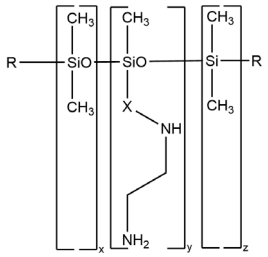
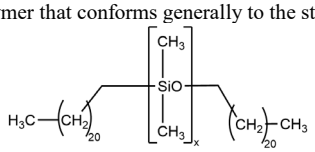
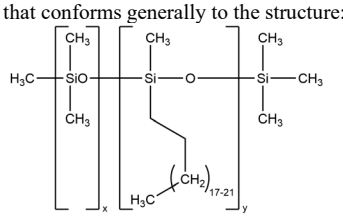
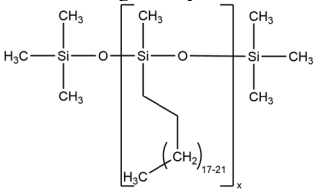
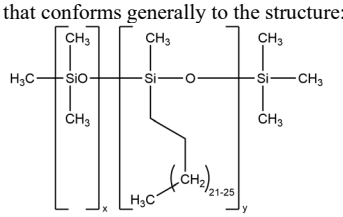
Name & CAS No.	Definition & Structure	Function(s)
Amino Bispropyl Dimethicone 189959-16-8	a complex three-dimensional siloxane polymer formed by the reaction between dimethiconol and 3-(trimethoxysilyl)-*N*-[3-(trimethoxysilyl)propyl]-1-propanamine.	Hair-conditioning agent
Aminopropyl Dimethicone 99363-37-8	the siloxane polymer that conforms generally to the structure: 	Hair-conditioning agent Skin-conditioning agent—miscellaneous
Amodimethicone 106842-44-8 68554-54-1 71750-79-3	a siloxane polymer that contains amino functional groups. It conforms generally to the structure:  where R=OH or CH_3, and X represents the propyl, isopropyl, or isobutyl group.	Hair-conditioning agent
Amodimethicone Hydroxystearate	the salt of Amodimethicone and Hydroxystearic Acid.	Hair-conditioning agent
Behenoxy Dimethicone	a dimethyl siloxane polymer that conforms generally to the structure: 	Skin-conditioning agent—emollient
C20-24 Alkyl Dimethicone 200074-76-6	is the siloxane polymer that conforms generally to the structure: 	Skin-conditioning agent—occlusive Viscosity increasing agent—nonaqueous
C20-24 Alkyl Methicone 200074-77-7	is the siloxane polymer that conforms generally to the structure: 	Skin-conditioning agent – emollient Viscosity increasing agent-- nonaqueous
C24-28 Alkyl Dimethicone 192230-29-8	is the siloxane polymer that conforms generally to the structure: 	Skin-conditioning agent—occlusive Viscosity increasing agent--nonaqueous

Table 1. Definitions, idealized structures, and functions[2, CIR Staff]

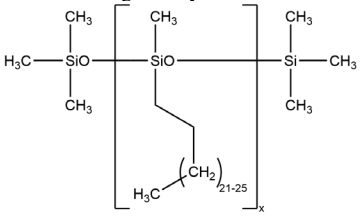
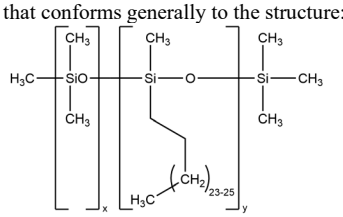
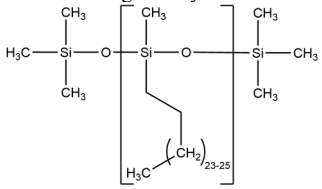
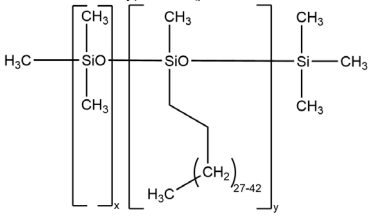
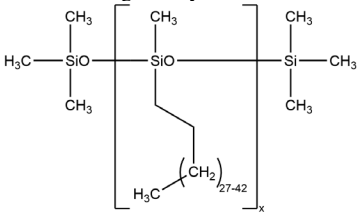
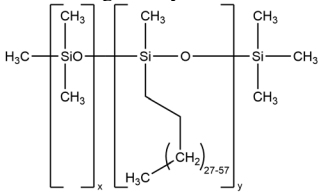
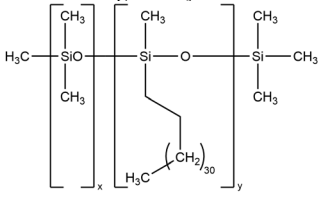
Name & CAS No.	Definition & Structure	Function(s)
C24-28 Alkyl Methicone 189378-12-9	the siloxane polymer that conforms generally to the structure: 	Skin-conditioning agent—emollient Viscosity increasing agent—non-aqueous
C26-28 Alkyl Dimethicone	is the siloxane polymer that conforms generally to the structure: 	Hair-conditioning agent Skin conditioning agent--occlusive
C26-28 Alkyl Methicone 189378-12-9	is the siloxane polymer that conforms generally to the structure: 	Skin-conditioning agent --occlusive
C30-45 Alkyl Dimethicone	the siloxane polymer that conforms generally to the structure: 	Skin-conditioning agent—occlusive
C30-45 Alkyl Methicone 189378-12-9 246864-88-0	the siloxane polymer that conforms generally to the structure: 	Skin-conditioning agent—occlusive Viscosity increasing agent—non-aqueous
C30-60 Alkyl Dimethicone	the siloxane polymer that conforms generally to the structure: 	Skin-conditioning agent—occlusive Viscosity increasing agent – non-aqueous
C32 Alkyl Dimethicone	is the silicone polymer that conforms generally to the structure: 	Skin- conditioning agent--emollient

Table 1. Definitions, idealized structures, and functions[2, CIR Staff]

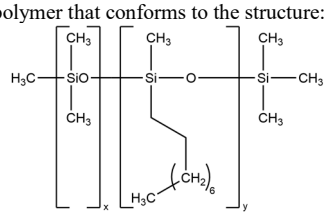
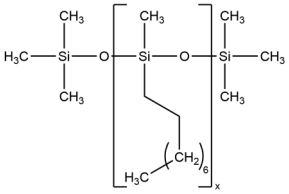
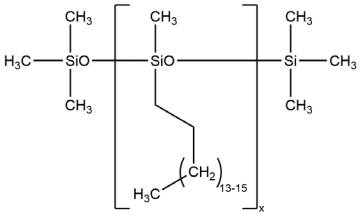
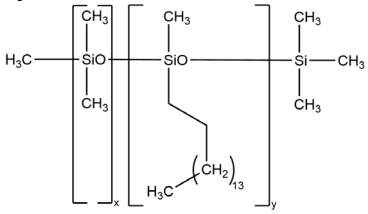
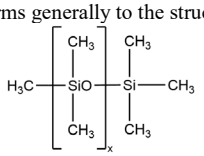
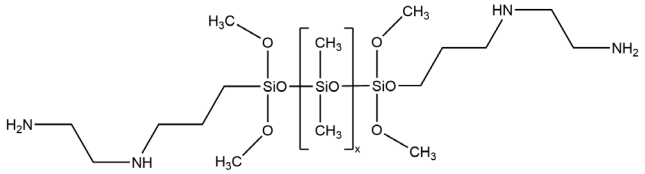
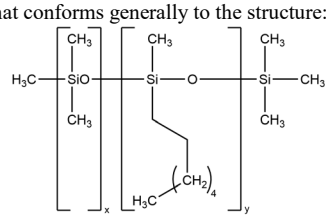
Name & CAS No.	Definition & Structure	Function(s)
Capryl Dimethicone	is a dimethyl siloxane polymer that conforms to the structure: 	Skin-conditioning agent--emollient
Caprylyl Methicone 17955-88-3	is the siloxane polymer that conforms to the structure: 	Skin-conditioning agent--occlusive
Cetearyl Methicone	a siloxane polymer that conforms to the structure: 	Skin-conditioning agent—occlusive
Cetyl Dimethicone 191044-49-2	a dimethyl siloxane polymer that conforms to the structure: 	Antifoaming agent Skin-conditioning agent—emollient and occlusive
Dimethicone 141-62-8 141-63-9 63148-62-9 9006-65-9 9016-00-6 107-52-8	a mixture of fully methylated linear siloxane polymers end blocked with trimethylsiloxy units. It conforms generally to the structure: 	Antifoaming agent Skin protectant Skin-conditioning agent—occlusive Solvent
Dimethoxysilyl Ethylenediaminopropyl Dimethicone 71750-80-6	the siloxane polymer that conforms generally to the structure: 	Hair conditioning agent
Hexyl Dimethicone	the siloxane polymer that conforms generally to the structure: 	Hair conditioning Skin conditioning agents - - miscellaneous

Table 1. Definitions, idealized structures, and functions[2, CIR Staff]

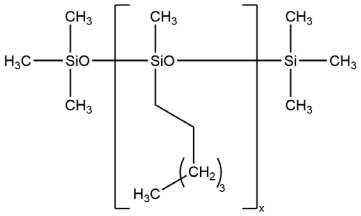
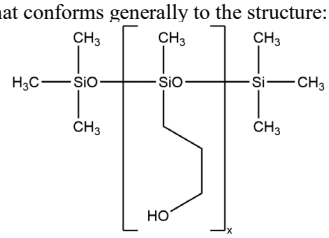
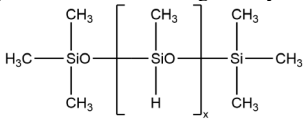
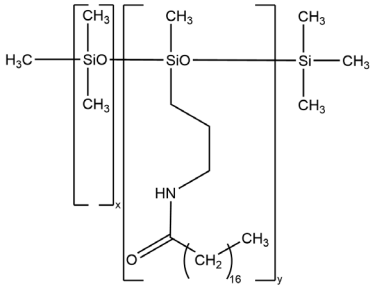
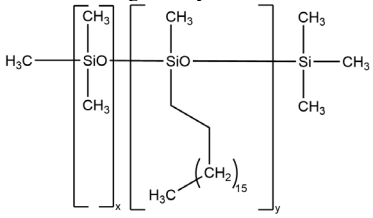
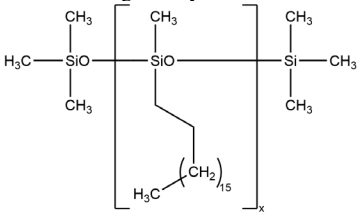
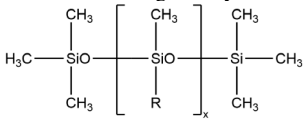
Name & CAS No.	Definition & Structure	Function(s)
Hexyl Methicone 1873-90-1	the siloxane polymer that conforms to the structure: 	Skin-conditioning—emollient
Hydroxypropyldimethicone 102782-61-6	the siloxane polymer that conforms generally to the structure: 	Hair-conditioning Skin-conditioning—miscellaneous
Methicone 63148-57-2 9004-73-3	a linear monomethyl polysiloxane. It conforms generally to the structure: 	Skin-conditioning agent—occlusive Surface modifier
Stearamidopropyl Dimethicone	the siloxane polymer that conforms to the structure: 	Corrosion inhibitor Film former
Stearoxy Dimethicone 68554-53-0	a polymer of dimethylpolysiloxane with some methyl groups replaced by stearoxy groups.	Skin-conditioning agent—emollient
Stearyl Dimethicone 67762-83-8	the siloxane polymer that conforms generally to the formula: 	Skin-conditioning agent—occlusive
Stearyl Methicone	the siloxane polymer that conforms generally to the structure: 	Skin-conditioning agent—occlusive
Vinyl Dimethicone 67762-94-1	a derivative of Dimethicone where some of the methyl groups have been replaced with vinyl groups. The vinyl groups can occur at the ends of the siloxane chain or pendant to the siloxane chain. It conforms generally to the structure:  wherein R is a methyl or vinyl group, and at least one vinyl group is present.	Not reported

Table 2. Frequency and concentration of use according to duration and exposure

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Amino Bispropyl Dimethicone				**Aminopropyl Dimethicone**			
	2021[9]	**1998[1]**	**2019[10]**	**1999[1]**	**2021[9]**	**1998[1]**	**2019[10]**	**1999[1]**
Totals*	**1**	**NR**	**NR**	**NR**	**35**	**NR**	**0.001-3**	**NR**
Duration of Use								
Leave-On	*1*	*NR*	*NR*	*NR*	*27*	*NR*	*0.001-3*	*NR*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*8*	*NR*	*0.3-0.66*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	14[a]; 5[b]	NR	0.1-0.5[a]	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	5[b]	NR	NR	NR
Dermal Contact	NR	NR	NR	NR	17	NR	0.001-3	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	Not spray: 0.001	NR
Hair - Non-Coloring	1	NR	NR	NR	17	NR	0.1-0.66	NR
Hair-Coloring	NR	NR	NR	NR	1	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
	Amodimethicone				**Behenoxy Dimethicone**			
	2021[9]	**1998[1]**	**2019[10]**	**1999[1]**	**2021[9]**	**1998[1]**	**2019[10]**	**1999[1]**
Totals*	**641**	**166**	**0.0051-5**	**0.0004-3**	**1**	**3**	**0.5**	**2-3**
Duration of Use								
Leave-On	*216*	*29*	*0.0051-4*	*0.0004-0.7*	*1*	*2*	*0.5*	*2*
Rinse-Off	*425*	*137*	*0.06-5*	*0.6-3*	*NR*	*1*	*NR*	*3*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	10	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	2	NR	NR	NR	1	NR	NR	NR
Incidental Inhalation-Spray	9; 84[a], 9[b]	3; 9[a]	0.3-2; 0.15-4[a]	0.0004-0.7[a]	NR	NR	NR	2[a]; 2[b]
Incidental Inhalation-Powder	3; 9[b]	NR	0.05[c]	NR	NR	NR	0.5[c]	2[b]
Dermal Contact	48	1	0.0051-0.49	NR	NR	NR	0.5	2-3
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	554	121	0.06-5	0.0004-3	NR	3	NR	NR
Hair-Coloring	37	44	0.18-1.3	2	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	7	NR	NR	NR	1	NR	NR	NR
Baby Products	2	NR	NR	NR	NR	NR	NR	NR
	C20-24 Alkyl Dimethicone				**C24-28 Alkyl Methicone**			
	2021[9]	**1998[1]**	**2020[12]**	**1999[1]**	**2021[9]**	**1998[1]**	**2019[10]**	**1999[1]**
Totals*	**34**	**NA**	**8**	**NA**	**3**	**NR**	**NR**	**2**
Duration of Use								
Leave-On	*34*	*NA*	*8*	*NA*	*3*	*NR*	*NR*	*2*
Rinse-Off	*NR*	*NA*	*NR*	*NA*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NA*	*NR*	*NA*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	3	NA	8	NA	NR	NR	NR	NR
Incidental Ingestion	23	NA	NR	NA	NR	NR	NR	2
Incidental Inhalation-Spray	3[a]; 4[b]	NA	NR	NA	NR	NR	NR	NR
Incidental Inhalation-Powder	4[b]	NA	NR	NA	NR	NR	NR	NR
Dermal Contact	11	NA	8	NA	3	NR	NR	NR
Deodorant (underarm)	NR	NA	NR	NA	NR	NR	NR	NR
Hair - Non-Coloring	NR	NA	NR	NA	NR	NR	NR	NR
Hair-Coloring	NR	NA	NR	NA	NR	NR	NR	NR
Nail	NR	NA	NR	NA	NR	NR	NR	NR
Mucous Membrane	23	NA	NR	NA	NR	NR	NR	2
Baby Products	NR	NA	NR	NA	NR	NR	NR	NR

Table 2. Frequency and concentration of use according to duration and exposure

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	C26-28 Alkyl Dimethicone				**C30-45 Alkyl Dimethicone**			
	2021[9]	**1998[1]**	**2020[12]**	**1999[1]**	**2021[9]**	**1998[1]**	**2019[10]**	**1999[1]**
Totals*	**5**	**NA**	**0.8-2.8**	**NA**	**51**	**NR**	**0.16-5.1**	**2**
Duration of Use								
Leave-On	*5*	*NA*	*0.8-2.8*	*NA*	*48*	*NR*	*0.16-5.1*	*2*
Rinse-Off	*NR*	*NA*	*NR*	*NA*	*3*	*NR*	*0.5*	*NR*
Diluted for (Bath) Use	*NR*	*NA*	*NR*	*NA*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	5	NA	0.8-2.8	NA	4	NR	0.16-5.1	NR
Incidental Ingestion	NR	NA	NR	NA	35	NR	0.4-2.9	NR
Incidental Inhalation-Spray	NR	NA	NR	NA	1[a]; 2[b]	NR	2.3[a]	2[a]
Incidental Inhalation-Powder	NR	NA	NR	NA	2[b]	NR	4; 0.5-4[c]	NR
Dermal Contact	5	NA	2-2.8	NA	12	NR	0.16-5.1	2
Deodorant (underarm)	NR	NA	NR	NA	NR	NR	NR	NR
Hair - Non-Coloring	NR	NA	NR	NA	3	NR	0.5-2.3	NR
Hair-Coloring	NR	NA	NR	NA	NR	NR	NR	NR
Nail	NR	NA	NR	NA	NR	NR	NR	NR
Mucous Membrane	NR	NA	NR	NA	35	NR	0.4-2.9	NR
Baby Products	NR	NA	NR	NA	NR	NR	NR	NR
	C30-45 Alkyl Methicone				**Capryl Dimethicone**			
	2021[9]	**1998[1]**	**2019[10]**	**1999[1]**	**2021[9]**	**1998[1]**	**2020[12]**	**1999[1]**
Totals*	**51**	**NR**	**0.0054-2.2**	**NR**	**NR**	**NR**	**1-5.5**	**NR**
Duration of Use								
Leave-On	*29*	*NR*	*0.0054-2.2*	*NR*	*NR*	*NR*	*1-5.5*	*NR*
Rinse-Off	*22*	*NR*	*NR*	*NR*	*NR*	*NR*	*1*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	9	NR	NR	NR	NR	NR	1.5	NR
Incidental Ingestion	8	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	6[a];1[b]	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	1[b]	NR	0.0054-2.2[c]	NR	NR	NR	1[c]	NR
Dermal Contact	39	NR	0.0054-2.2	NR	NR	NR	1-5.5	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	2	NR	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	1	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	8	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	1	NR
	Caprylyl Methicone				**Cetearyl Methicone**			
	2021[9]	**1998[1]**	**2020[12]**	**1999[1]**	**2021[9]**	**1998[1]**	**2019[10]**	**1999[1]**
Totals*	**183**	**NA**	**0.0075-16**	**NA**	**9**	**1**	**0.75-1.1**	**0.5-1**
Duration of Use								
Leave-On	*179*	*NA*	*0.0075-16*	*NA*	*9*	*1*	*0.75-1.1*	*0.5-1*
Rinse-Off	*4*	*NA*	*0.22-12*	*NA*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NA*	*NR*	*NA*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	50	NA	0.22-16	NA	1	NR	NR	NR
Incidental Ingestion	20	NA	2.8-7.5	NA	NR	1	NR	0.6-1
Incidental Inhalation-Spray	3; 40[a]; 29[b]	NA	0.8-6.2	NA	4[a];2[b]	NR	0.75[a]	0.5[b]
Incidental Inhalation-Powder	6; 29[b]	NA	0.014-6[c]; 0.0075-4	NA	2[b]; 1[c]	NR	1.1[c]	0.5[b]
Dermal Contact	152	NA	0.0075-16	NA	9	NR	0.9-1.1	0.5
Deodorant (underarm)	NR	NA	NR	NA	NR	NR	NR	NR
Hair - Non-Coloring	10	NA	0.5-6	NA	NR	NR	0.75	NR
Hair-Coloring	NR	NA	NR	NA	NR	NR	NR	NR
Nail	1	NA	NR	NA	NR	NR	NR	NR
Mucous Membrane	20	NA	2.8-7.5	NA	NR	1	NR	0.6-1
Baby Products	NR	NA	NR	NA	1	NR	NR	NR

Table 2. Frequency and concentration of use according to duration and exposure

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Cetyl Dimethicone				**Dimethicone**			
	2021[9]	**1998[1]**	**2019[10]**	**1999[1]**	**2021[9]**	**1998[1]**	**2019[10]**	**1999[1]**
Totals*	**87**	**27**	**0.001-11.8**	**0.5-10**	**7656**	**1659**	**0.0000014-85**	**0.0001-80**
Duration of Use								
Leave-On	*83*	*26*	*0.1-11.8*	*0.5-10*	*6704*	*1333*	*0.002-85*	*0.0001-80*
Rinse-Off	*4*	*1*	*0.001-6*	*NR*	*947*	*320*	*0.0000014-23.4*	*0.001-10*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*5*	*6*	*2.5-3*	*NR*
Exposure Type								
Eye Area	31	5	1-6	0.5	1146	111	0.25-37.8	0.3-13
Incidental Ingestion	10	NR	1.1-10	4-5	392	12	0.4-71.3	0.001-20
Incidental Inhalation-Spray	12[a]; 5[b]	4[a]; 2[b]	0.5-4[a]	2[a]; 2[b]	46; 2530[a]; 1107[b]	56; 336[a]; 299[b]	1-85; 0.3-63.5[a]; 1-2.9[b]	0.2-16; 0.3-15[a]; 0.0001-10[b]
Incidental Inhalation-Powder	3; 5[b]	2; 2[b]	6; 0.1-11.8[c]	0.9-3; 2[b]	217; 1107[b]; 20[c]	87; 299[b]; 7[c]	0.33-53; 1-2.9[b]; 0.5-66.9[c]	0.3-30; 0.0001-10[b]; 2[c]
Dermal Contact	72	24	0.001-11.8	0.9-10	6003	1313	0.0022-85	0.0001-30
Deodorant (underarm)	NR	NR	NR	NR	5[a]	9[a]	spray: 2-18.6; not spray: 5-40	0.5-23[a]
Hair - Non-Coloring	3	1	0.5-6	NR	838	249	0.0000014-63.5	0.08-80
Hair-Coloring	NR	NR	NR	NR	201	29	0.00015-3.3	0.5
Nail	NR	NR	NR	NR	172	36	0.002-75	0.001-3
Mucous Membrane	10	NR	0.001-10	4-5	427	54	0.0022-71.3	0.001-20
Baby Products	NR	NR	5	NR	21	8	0.21-10	2
	Dimethoxysilyl Ethylenediaminopropyl Dimethicone				**Hexyl Dimethicone**			
	2021[9]	**1998[1]**	**2019[10]**	**1999[1]**	**2021[9]**	**1998[1]**	**2019[10]**	**1999[1]**
Totals*	**NR**	**NR**	**0.043-2.1**	**NR**	**NR**	**NA**	**0.17**	**NA**
Duration of Use								
Leave-On	*NR*	*NR*	*0.043*	*NR*	*NR*	*NA*	*0.17*	*NA*
Rinse-Off	*NR*	*NR*	*2.1*	*NR*	*NR*	*NA*	*NR*	*NA*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NA*	*NR*	*NA*
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NA	0.17	NA
Incidental Ingestion	NR	NR	NR	NR	NR	NA	NR	NA
Incidental Inhalation-Spray	NR	NR	0.043[a]	NR	NR	NA	NR	NA
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NA	NR	NA
Dermal Contact	NR	NR	NR	NR	NR	NA	0.17	NA
Deodorant (underarm)	NR	NR	NR	NR	NR	NA	NR	NA
Hair - Non-Coloring	NR	NR	0.043	NR	NR	NA	NR	NA
Hair-Coloring	NR	NR	2.1	NR	NR	NA	NR	NA
Nail	NR	NR	NR	NR	NR	NA	NR	NA
Mucous Membrane	NR	NR	NR	NR	NR	NA	NR	NA
Baby Products	NR	NR	NR	NR	NR	NA	NR	NA
	Methicone				**Stearoxy Dimethicone**			
	2021[9]	**1998[1]**	**2019[10]**	**1999[1]**	**2021[9]**	**1998[1]**	**2019[10]**	**1999[1]**
Totals*	**579**	**NR**	**0.00014-3.6**	**0.009-5**	**18**	**21**	**0.8-1.5**	**0.1-3**
Duration of Use								
Leave-On	*566*	*NR*	*0.00014-3.6*	*0.009-5*	*17*	*20*	*0.8-1.5*	*0.1-3*
Rinse-Off	*12*	*NR*	*0.15-0.46*	*0.05-0.3*	*1*	*1*	*NR*	*0.5*
Diluted for (Bath) Use	*1*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	126	NR	0.1-3.6	0.02-0.9	3	NR	NR	2-3
Incidental Ingestion	232	NR	0.36	0.06	NR	NR	0.8	3
Incidental Inhalation-Spray	4[a]; 6[b]	NR	NR	0.3[b]	4[a]; 8[b]	6[a]; 10[b]	NR	0.1; 0.2-3[a]; 2[b]
Incidental Inhalation-Powder	31; 6[b]	NR	0.064-1.5; 0.048-1.9[c]	0.08-5; 0.3[b]; 0.3[c]	8[b]	1; 10[b]	NR	2[b]
Dermal Contact	318	NR	0.00014-3.6	0.01-5	17	21	1.5	0.5-3
Deodorant (underarm)	NR	NR	spray: 0.25	NR	NR	NR	NR	NR
Hair - Non-Coloring	12	NR	0.46	NR	NR	NR	NR	0.1-0.2
Hair-Coloring	NR	NR	NR	0.3	NR	NR	NR	NR
Nail	11	NR	0.0035-2.5	0.009	NR	NR	NR	NR
Mucous Membrane	236	NR	0.36	0.06	NR	NR	0.8	3
Baby Products	NR	NR	0.46	0.3	NR	NR	NR	NR

Table 2. Frequency and concentration of use according to duration and exposure

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Stearyl Dimethicone				**Stearyl Methicone**			
	2021[9]	**1998[1]**	**2019[10]**	**1999[1]**	**2021[9]**	**1998[1]**	**2019[10]**	**1999[1]**
Totals*	**79**	**7**	**0.2-8.3**	**0.8-6**	**1**	**NR**	**NR**	**NR**
Duration of Use								
Leave-On	*78*	*6*	*0.2-8.3*	*0.8-6*	*1*	*NR*	*NR*	*NR*
Rinse-Off	*1*	*1*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	18	2	3.6-8.3	0.8-6	NR	NR	NR	NR
Incidental Ingestion	5	2	0.38-2.6	4-6	NR	NR	NR	NR
Incidental Inhalation-Spray	1; 11[a]; 14[b]	1[a]	0.38[a]	4[b]	NR	NR	NR	NR
Incidental Inhalation-Powder	1; 14[b]	NR	0.2-2.3[c]	4[b]	NR	NR	NR	NR
Dermal Contact	70	3	0.2-8.3	1-6	1	NR	NR	NR
Deodorant (underarm)	NR	NR	not spray:1.2	NR	NR	NR	NR	NR
Hair - Non-Coloring	4	NR	0.3	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	5	2	0.38-2.6	4-6	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
	Vinyl Dimethicone							
	2021[9]	**1998[1]**	**2019[10]**	**1999[1]**				
Totals*	**8**	**NR**	**NR**	**NR**				
Duration of Use								
Leave-On	*8*	*NR*	*NR*	*NR*				
Rinse-Off	*NR*	*NR*	*NR*	*NR*				
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*				
Exposure Type								
Eye Area	NR	NR	NR	NR				
Incidental Ingestion	NR	NR	NR	NR				
Incidental Inhalation-Spray	5[a]; 3[b]	NR	NR	NR				
Incidental Inhalation-Powder	3[b]	NR	NR	NR				
Dermal Contact	8	NR	NR	NR				
Deodorant (underarm)	NR	NR	NR	NR				
Hair - Non-Coloring	NR	NR	NR	NR				
Hair-Coloring	NR	NR	NR	NR				
Nail	NR	NR	NR	NR				
Mucous Membrane	NR	NR	NR	NR				
Baby Products	NR	NR	NR	NR				

*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.
[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
NR – no reported use
NA – ingredient was not included in the original safety assessment.

Table 3. Methicone ingredients not reported to be in use[9-12]

Amodimethicone Hydroxystearate
C20-24 Alkyl Methicone
C24-28 Alkyl Dimethicone
C26-28 Alkyl Methicone
C30-60 Alkyl Dimethicone
C32 Alkyl Dimethicone
Hexyl Methicone
Hydroxypropyldimethicone
Stearamidopropyl Dimethicone

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Final Report on the Safety Assessment of Stearoxy Dimethicone, Dimethicone, Methicone, Amino Bispropyl Dimethicone, Aminopropyl Dimethicone, Amodimethicone, Amodimethicone Hydroxystearate, Behenoxy Dimethicone, C24–28 Alkyl Methicone, C30–45 Alkyl Methicone, C30–45 Alkyl Dimethicone, Cetearyl Methicone, Cetyl Dimethicone, Dimethoxysilyl Ethylenediaminopropyl Dimethicone, Hexyl Methicone, Hydroxypropyldimethicone, Stearamidopropyl Dimethicone, Stearyl Dimethicone, Stearyl Methicone, and Vinyldimethicone[1]

Dimethicone is a fluid mixture of fully methylated linear siloxane polymers end-blocked with trimethylsiloxy units. Methicone is a linear monomethyl polysiloxane. The other dimethicones and methicones covered in this review are siloxane polymers of Dimethicone and Methicone. Most of these ingredients function as conditioning agents in cosmetic formulations at current concentrations of use of ≤15%. Clinical and animal absorption studies reported that Dimethicone was not absorbed following oral or dermal exposure. *Dimethicone, Methicone, and Vinyldimethicone* were not acutely toxic following oral exposure. No adverse reactions were found in rabbits following short-term dermal dosing with 6% to 79% Dimethicone, yet adverse effects were noted with a hand cream formulation containing 1% Dimethicone, suggesting something else in the preparation was toxic. Mice and rats were dosed for 90 days with up to 10% Dimethicone without adverse effect. Dimethicone did not produce adverse effects in acute and short-term inhalation-route studies, Methicone and Vinyldimethicone were negative in acute exposure studies using rats, but Hexyl Methicone was toxic to rats at 5 mg/L delivered in small particle (mean diameter of 0.29 μ) aerosols. Most dermal irritation studies using rabbits classified Dimethicone as a minimal irritant. Dimethicone (tested undiluted and at 79%) was not a sensitizer in four assays using mice and guinea pigs. It was not a sensitizer at 5.0% in a clinical repeated insult patch test using 83 panelists. Most ocular irritation studies using rabbits classified Dimethicone as a mild to minimal irritant. Dimethicone was tested in numerous oral-dose (using rats) and dermal-dose (using rats, rabbits, and monkeys) reproductive and developmental toxicity studies. In a few studies, treated males had significantly decreased body weight and/or decreased testes or seminal vesicles weights. No treatment-related adverse findings were noted in dosed pregnant females or fetuses. Dimethicone was negative in all genotoxicity assays. It was negative in both an oral (tested at 91%) and dermal (tested at an unknown concentration) dose carcinogenicity assay using mice. The Cosmetic Ingredient Review (CIR) Expert Panel considered it unlikely that any of these polymers would be significantly absorbed into the skin due to their large molecular weight. Although adverse effects were noted in one inhalation study with small aerosol particles, the expected particle sizes for cosmetic products would primarily be in the range of 60 to 80 μ, and less than 1% would be under 10 μ, which is an upper limit for respirable particles. Overall, the safety test data support the safety of these ingredients at the concentrations they are known to be used in cosmetic formulations. Accordingly, the CIR Expert Panel was of the opinion that Stearoxy Dimethicone, Dimethicone, Methicone, Amino Bispropyl Dimethicone, Aminopropyl Dimethicone, Amodimethicone, Amodimethicone Hydroxystearate, Behenoxy Dimethicone, C24–28 Alkyl Methicone, C30–45 Alkyl Methicone, C30–45 Alkyl Dimethicone, Cetearyl Methicone, Cetyl Dimethicone, Dimethoxysilyl Ethylenediaminopropyl Dimethicone, Hexyl Methicone, Hydroxypropyldimethicone, Stearamidopropyl Dimethicone, Stearyl Dimethicone, Stearyl Methicone, and Vinyldimethicone are safe as used in cosmetic formulations.

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[1]Reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel. This report was prepared by Bindu Nair, with the assistance of Amy R. Elmore, both former CIR staff.

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INTRODUCTION

This report is a compilation of data relevant to assessing the safety of Stearoxy Dimethicone, Dimethicone, Methicone,

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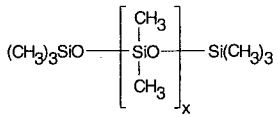
Amino Bispropyl Dimethicone, Aminopropyl Dimethicone, Amodimethicone, Amodimethicone Hydroxystearate, Behenoxy Dimethicone, C24–28 Alkyl Methicone, C30–45 Alkyl Methicone, C30–45 Alkyl Dimethicone, Cetearyl Methicone, Cetyl Dimethicone, Dimethoxysilyl Ethylenediaminopropyl Dimethicone, Hexyl Methicone, Hydroxypropyldimethicone, Stearamidopropyl Dimethicone, Stearyl Dimethicone, Stearyl Methicone, and Vinyldimethicone for use in cosmetic formulations. Almost all of the studies were done on Dimethicone identified under the CAS no. 63148-62-9 and defined as "dimethyl silicones and siloxanes." Heading names are used to identify studies that were done on other ingredients.

CHEMISTRY

Definition and Structure

Stearoxy Dimethicone (CAS no. 68554-53-0) is a polymer of dimethylpolysiloxane end-blocked with stearoxy groups. No structure is available. Synonyms include Dimethylsiloxane·Methylstearoxysiloxane Copolymer; Dimethyl Siloxy Stearoxy Siloxane Polymer; Poly(dimethylsiloxy) Stearoxysiloxane; Siloxanes and Silicones, Dimethyl, (Octadecyloxy)-Terminated; and Stearoxymethylpolysiloxane (Wenninger, Canterbery, and McEwen 2000).

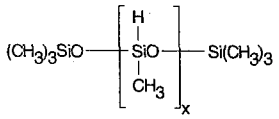
Dimethicone (CAS no. 9006-65-9, 63148-62-9, and 9016-00-6) is a mixture of fully methylated linear siloxane polymers $[-(CH_3)_2SiO-]_x$ end-blocked with trimethylsiloxy units $[-(CH_3)_3SiO-]$. It conforms generally to the formula (Wenninger, Canterbery, and McEwen 2000; Committee on Revision of the United States Pharmacopeial Convention 1995):



Dimethicone

Synonyms include Dimethylpolysiloxane; Dimethyl Silicone; Highly Polymerized Methyl Polysiloxane (1) and (2); Methyl Polysiloxane; Poly[oxy(dimethylsilylene)], α-(trimethylsilyl)-ω-methyl-; Silicone L-45 (Wenninger, Canterbery, and McEwen 2000), and α-(trimethylsilyl)-ω-methylpolydimethylsiloxane poly[oxy(dimethylsilylene)] (Committee on Revision of the United States Pharmacopeial Convention 1995). The Food and Agriculture Organization (FAO) of the World Health Organization (WHO) also lists the following three synonyms: Dimethylsilicone Fluid, Dimethylsilicone Oil, and Poly(dimethylsiloxane) (FAO/WHO 1994).

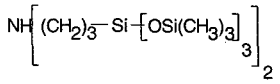
Methicone (CAS no. 9004-73-3) is a linear monomethyl polysiloxane. It conforms generally to the formula (Wenninger, Canterbery, and McEwen 2000):



Methicone

Synonyms include Hydrogen Methyl Polysiloxane, Methyl Hydrogen Polysiloxane, and Poly[oxy(methylsilylene)] (Wenninger, Canterbery, and McEwen 2000).

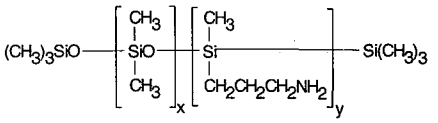
Amino Bispropyl Dimethicone is a substituted siloxane amine that conforms generally to the formula (Wenninger, Canterbery, and McEwen 2000):



Amino Bispropyl Dimethicone

No synonyms for Amino Bispropyl Dimethicone were found.

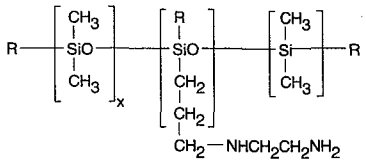
Aminopropyl Dimethicone is a silicone polymer that conforms generally to the formula (Wenninger, Canterbery, and McEwen 2000):



Aminopropyl Dimethicone

No synonyms for Aminopropyl Dimethicone were found.

Amodimethicone is a silicone polymer end blocked with amino functional groups. It conforms generally to the formula (Wenninger, Canterbery, and McEwen 2000):



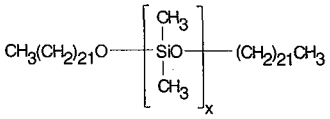
Amodimethicone

where R represents OH or CH3

Synonyms for Amodimethicone include Aminoethylaminopropylsiloxane · Dimethylsiloxane Copolymer Emulsion (Wenninger, Canterbery, and McEwen 2000).

Amodimethicone Hydroxystearate is the salt of Amodimethicone (q.v.) and Hydroxystearic Acid (q.v.) (Wenninger, Canterbery, and McEwen 2000). No structure was available and no synonyms were found.

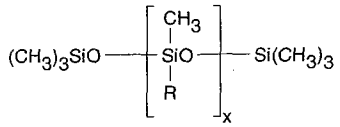
Behenoxy Dimethicone is a dimethyl siloxane polymer that conforms generally to the formula (Wenninger, Canterbery, and McEwen 2000):



Behenoxy Dimethicone

No synonyms for Behenoxy Dimethicone were found.

C24–28 Alkyl Methicone is the silicone polymer that conforms to the formula (Wenninger, Canterbery, and McEwen 2000):

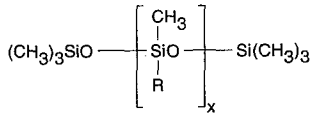


C24-28 Alkyl Methicone

where R represents the C24-28 alkyl group

No synonyms for C24–28 Alkyl Methicone were found.

C30–45 Alkyl Methicone is the silicone polymer that conforms to the formula (Wenninger, Canterbery, and McEwen 2000):

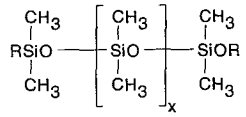


C30-45 Alkyl Methicone

where R represents the C30-45 alkyl group

No synonyms for C30–45 Alkyl Methicone were found.

C30–45 Alkyl Dimethicone is a silicone polymer that conforms generally to the formula (Wenninger, Canterbery, and McEwen 2000):

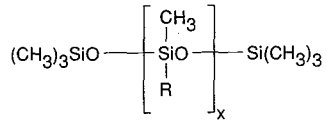


C30-45 Alkyl Dimethicone

where R represents the C30-45 alkyl group

No synonyms for C30–45 Alkyl Dimethicone were found.

Cetearyl Methicone is the silicone polymer that conforms to the formula (Wenninger, Canterbery, and McEwen 2000):

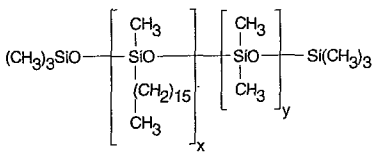


Cetearyl Methicone

where R represents the C16-18 alkyl group

No synonyms for Cetearyl Methicone were found.

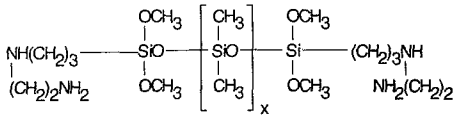
Cetyl Dimethicone is a dimethyl siloxane polymer that conforms to the formula (Wenninger, Canterbery, and McEwen 2000):



Cetyl Dimethicone

No synonyms for Cetyl Dimethicone were found.

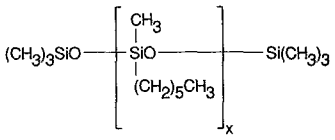
Dimethyoxysilyl Ethylenediaminopropyl Dimethicone (CAS no. 71750-80-6) is the silicone polymer that conforms generally to the formula:



Dimethyoxysilyl Ethylenediaminopropyl Dimethicone

Synonyms include Siloxanes and Silicones, Dimethyl, Mono-[[3-[(2-aminoethyl)amino]propyl]dimethoxysilyl]oxy-terminated (Wenninger, Canterbery, and McEwen 2000).

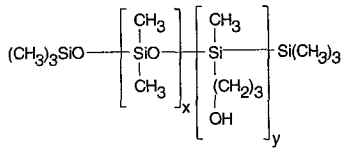
Hexyl Methicone (CAS no. 1873-90-1) is the silicone polymer that conforms to the formula:



Hexyl Methicone

Synonyms for Hexyl Methicone include trisiloxane, 3-Hexyl-1,1,1,3,5,5,5-Heptamethyl- (Pepe, Wenninger, and McEwen 2002), and 1,1,1,3,5,5,5-Heptamethyl-6-Hexyltrisiloxane (IIT Research Institute 1994).

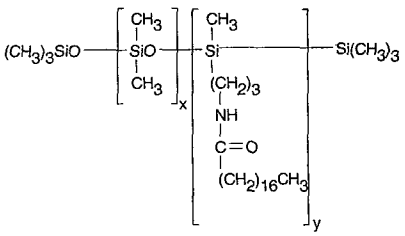
Hydroxypropyldimethicone (CAS no. 102782-61-6) is the silicone polymer that conforms generally to the formula:



Hydroxypropyldimethicone

A synonym is Siloxanes and Silicones, Dimethyl, 3-Hydroxypropyl Methyl (Wenninger, Canterbery, and McEwen 2000).

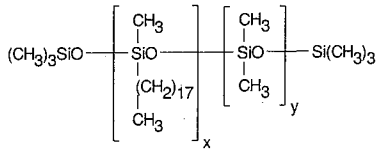
Stearamidopropyl Dimethicone is the silicone polymer that conforms to the formula (Wenninger, Canterbery, and McEwen 2000):



Stearamidopropyl Dimethicone

No synonyms for Stearamidopropyl Dimethicone were found.

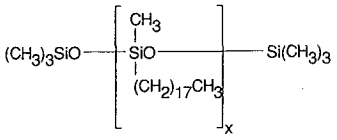
Stearyl Dimethicone is the silicone polymer that conforms generally to the formula (Wenninger, Canterbery, and McEwen 2000):



Stearyl Dimethicone

No synonyms for Stearyl Dimethicone were found.

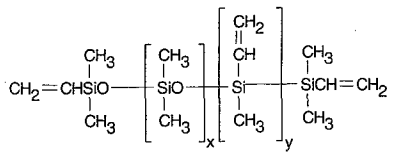
Stearyl Methicone is the silicone polymer that conforms to the formula (Wenninger, Canterbery, and McEwen 2000):



Stearyl Methicone

No synonyms for Stearyl Methicone were found.

Vinyldimethicone is a polymer of dimethylsiloxane containing vinyl functional groups. It conforms generally to the formula (Wenninger, Canterbery, and McEwen 2000):



Vinyldimethicone

The Registry of Toxic Effects of Chemical Substances (RTECS 1998) identifies "vinyl dimethylsiloxy-terminated polydimethylsiloxane" with the CAS no. 68083-19-2.

Physical and Chemical Properties

Dimethicone is a white, almost odorless fluid polymer. The Cosmetic, Toiletry, and Fragrance Association (CTFA) specifications for Dimethicone state that the color and odor are specified by the buyer. Also specified by the buyer are the refractive index at 25°C (within the range of 1.4000 to 1.4035), and the kinematic viscosity (provided that the specified mean viscosity at 25°C is not less than 20 centistokes [cs] and not greater than 60,000 cs, and that the specification limits are not greater than ±5% of the specified mean). It contains 98.5% to 101.1% Dimethicone and the total acid number is 0.01 maximum (Nikitakis and McEwen 1990).

One supplier of Dimethicone noted that 100 and 350 cs fluids are generally used for cosmetics (Dow Corning no date).

The National Formulary specifies that Dimethicone have a nominal viscosity in the discrete range between 20 and 12,500 cs and contain between 97.0% and 103.0% of polydimethylsiloxane. Minimum and maximum viscosity cs values were established for nominal viscosity cs values of 20, 100, 200, 350, 500, 1000, and 12500. The specific gravity ranged from 0.946 for the 20-cs nominal viscosity to 0.975 for the 1000-cs nominal viscosity (specific gravity values were not given for the 12500-cs nominal viscosity). The refractive index ranged from 1.3980 for the 20-cs nominal viscosity to 1.4055 for the 12500-cs nominal viscosity (Committee of Revision of the United States Pharmacopeial Convention 1995).

Method of Manufacture

Stearoxy Dimethicone is produced by the reaction of dichloropolydimethylsiloxane with stearyl alcohol (Goldschmidt Chemical Corp. 1998).

Dimethicone is produced by polymerization/equilibration (Goldschmidt Chemical Corp. 1998).

Cetyl Dimethicone is produced by hydrosilylation of C_{16} alpha-olefins (Goldschmidt Chemical Corp. 1998).

Stearyl Dimethicone is produced by hydrosilylation of C_{18} alpha-olefins (Goldschmidt Chemical Corp. 1998).

Manufacturing methods were not available for other ingredients.

Impurities

One supplier of these ingredients noted that Stearoxy Dimethicone, Dimethicone, Cetyl Dimethicone, and Stearyl Dimethicone contain no antioxidants or preservatives. Heavy metals are at 5 ppm maximum, and D4/D5 cyclomethicone is at less than 1% (Goldschmidt Chemical Corp. 1998).

USE

Cosmetic

The functions of Stearoxy Dimethicone and the related cosmetic ingredients are listed in Table 1. Almost all function as conditioning agents for either the hair or skin; the exceptions are Stearamidopropyl Dimethicone (corrosion inhibitor, film former) and Vinyldimethicone (chemical additive). In addition to being conditioning agents, Dimethicone and Cetyl Dimethicone also function as antifoaming agents. C24–28 Alkyl Methicone and C30–45 Alkyl Methicone are also viscosity-increasing agents—nonaqueous (Pepe, Wenninger, and McEwen 2002). One supplier noted that Stearoxy Dimethicone, Cetyl Dimethicone, and Stearyl Dimethicone are also used as "spreading agents" (Goldschmidt Chemical Corp. 1998).

Seven of the 20 ingredients were reported to the Food and Drug Administration (FDA) as in use in January 1998 (FDA 1998). These seven were used in a total of 1884 formulations (Table 2). Two uses of C14–20 polyalkylmethicone were also reported to the FDA, although this ingredient is not listed in the *International Cosmetic Ingredient Dictionary and Handbook* (Pepe, Wenninger, and McEwen 2002).

Recent data submitted to the Cosmetic Ingredient Review (CIR) from one source indicated use of Stearoxy Dimethicone at ≤3.0%, Dimethicone at ≤15%, Cetyl Dimethicone at ≤3.0%, and Stearyl Dimethicone at ≤5.0% (Goldschmidt Chemical

TABLE 1
Cosmetic function of Dimethicones and Methicones

Ingredient	Function[1]	Used in 1998[2]
Stearoxy Dimethicone	Skin-conditioning agent—emollient; spreading agent[3]	Yes
Dimethicone	Antifoaming agent; skin-conditioning agent—emollient	Yes
Methicone	Skin-conditioning agent—occlusive	
Amino Bispropyl Dimethicone	Hair-conditioning agent	
Aminopropyl Dimethicone	Hair-conditioning agent	
Amodimethicone	Hair-conditioning agent	Yes
Amodimethicone Hydroxystearate	Hair-conditioning agent	
Behenoxy Dimethicone	Skin-conditioning agent—emollient	Yes
C24–28 Alkyl Methicone	Skin-conditioning agent—emollient; viscosity increasing agent—nonaqueous	
C30–45 Alkyl Methicone	Skin-conditioning agent—occlusive; viscosity increasing agent—nonaqueous	
C30–45 Alkyl Dimethicone	Skin-conditioning agent—occlusive	
Cetearyl Methicone	Skin-conditioning agent—occlusive	Yes
Cetyl Dimethicone	Antifoaming agent; skin-conditioning agent—occlusive; spreading agent[3]	Yes
Dimethoxysilyl Ethylenediaminopropyl Dimethicone	Hair-conditioning agent	
Hexyl Methicone	Skin-conditioning agent—emollient	
Hydroxypropyldimethicone	Hair-conditioning agent; skin-conditioning agent—miscellaneous	
Stearamidopropyl Dimethicone	Corrosion inhibitor; film former	
Stearyl Dimethicone	Skin-conditioning agent—occlusive; spreading agent[3]	Yes
Stearyl methicone	Skin-conditioning agent—occlusive	
Vinyldimethicone	Chemical additive	

[1]Pepe, Wenninger, and McEwen 2002.
[2]FDA 1998.
[3]Goldschmidt Chemical Corp. 1998.

Corp. 1998). Concentration of use data provided by the CTFA are given in Table 2 (CTFA 1999).

Current concentrations of use may be compared with historical data from industry reports to FDA in 1984 in which Stearoxy Dimethicone was used at ≤5% (51 uses total), Dimethicone was used predominately at ≤25%, with one use at 25% to 50% (1012 uses total), Methicone was used in two formulations at ≤1% but also in one formulation at >50%, and Amodimethicone was used in nine products at unknown concentrations (FDA 1984).

According to the Ministry of Health, Labor and Welfare (MHLW) in Japan, Stearoxy Dimethicone, Dimethicone, Methicone, Amino Bispropyl Dimethicone, Aminopropyl Dimethicone, Amodimethicone, Amodimethicone Hydroxystearate, Behenoxy Dimethicone, C24–28 Alkyl Methicone, C30–45 Alkyl Methicone, C30–45 Alkyl Dimethicone, Cetearyl Methicone, Cetyl Dimethicone, Dimethoxysilyl Ethylenediaminopropyl Dimethicone, Hexyl Methicone, Hydroxypropyldimethicone, Stearamidopropyl Dimethicone, Stearyl Dimethicone, Stearyl Methicone, and Vinyldimethicone are not restricted in any manner in cosmetic formulations (MHLW 2001).

Stearoxy Dimethicone, Dimethicone, Methicone, Amino Bispropyl Dimethicone, Aminopropyl Dimethicone, Amodimethicone, Amodimethicone Hydroxystearate, Behenoxy Dimethicone, C24–28 Alkyl Methicone, C30–45 Alkyl Methicone, C30–45 Alkyl Dimethicone, Cetearyl Methicone, Cetyl Dimethicone, Dimethoxysilyl Ethylenediaminopropyl Dimethicone, Hexyl Methicone, Hydroxypropyldimethicone, Stearamidopropyl Dimethicone, Stearyl Dimethicone, Stearyl Methicone, and Vinyldimethicone are not listed in Annex II (list of substances that must not form part of the composition of cosmetic products) or Annex III (list of substances that cosmetic products must not contain except subject to the restrictions and conditions laid down) of the *Cosmetics Directive of the European Union* (European Commission, 2003).

TABLE 2
Product formulation data

Product category (number of formulations reported to FDA) (FDA 1998)	Number of formulations containing ingredient (FDA 1998)	Current concentration of use (CTFA 1999)
Stearoxy Dimethicone		
Eye shadow (506)	—	3%
Eye lotion (18)	—	2%
Hair spray (aerosol fixative) (261)	—	0.1%
Tonics, dressings, and other hair-grooming aids (549)	—	0.2%
Foundations (287)	—	0.7%
Lipstick (790)	—	3%
Face powders (250)	1	—
Makeup bases (132)	1	0.9%
Skin cleansing (653)	1	0.5%
Face and neck skin care (excluding shaving) (263)	3	2%
Body and hand skin care (excluding shaving) (796)	7	2%
Moisturizing creams, lotions, powders, and sprays (excluding shaving preparations) (769)	5	2%
Night skin care (188)	1	—
Other skin care preparations (692)	2	—
Suntan gels, creams, and liquids (136)	—	3%
1998 total for Stearoxy Dimethicone	21	
Dimethicone		
Baby lotions, oils, powders, and creams (53)	7	2%
Other baby products (29)	1	2%
Bath oils, tablets, and salts (124)	1	—
Bubble baths (200)	1	—
Other bath preparations (159)	4	—
Eyebrow pencil (91)	1	13%
Eyeliner (514)	6	1%–5%
Eye shadow (506)	55	1%–10%
Eye lotion (18)	5	0.5%–1%
Eye makeup remover (84)	2	4%
Mascara (167)	20	0.3%–4%
Other eye makeup preparations (120)	22	—
Colognes and toilet waters (656)	3	—
Sachets (28)	1	—
Perfumes (28)	—	16%
Other fragrance preparations (148)	30	5%–6%
Hair conditioners (636)	103	0.2%–10%
Hair sprays (aerosol fixatives) (261)	23	0.2%–0.6%
Hair straighteners (63)	1	—
Permanent waves (192)	2	—
Rinses (noncoloring) (40)	4	0.4%–3%
Shampoos (noncoloring) (860)	72	0.08%–4%
Tonics, dressings, and other hair-grooming aids (549)	28	1%–10%
Wave sets (55)	1	—
Other hair preparations (276)	15	10%–80%
Hair dyes and colors (1572)	1	—
Hair tints (54)	28	—

(Continued on next page)

TABLE 2
Product formulation data *(Continued)*

Product category (number of formulations reported to FDA) (FDA 1998)	Number of formulations containing ingredient (FDA 1998)	Current concentration of use (CTFA 1999)
Other hair-coloring preparations (59)	—	0.5%
Blushers (all types) (238)	86	3%–23%
Face powders (250)	87	0.3%–30%
Foundations (287)	122	1%–16%
Lipstick (790)	12	0.6%–20%
Makeup bases (132)	11	4%–23%
Rouges (12)	1	1%
Makeup fixatives (11)	2	24%
Other makeup preparations (135)	14	3%
Basecoats and undercoats (48)	3	0.001%
Cuticle softeners (19)	2	—
Nail creams and lotions (17)	4	0.6%–1%
Nail extenders (<4)	1	0.001%
Nail polish and enamel (80)	16	0.001%–3%
Other manicuring preparations (61)	10	—
Other oral hygiene products (6)	—	0.001%
Bath soaps and detergents (385)	6	0.5%–0.8%
Deodorants (underarm) (250)	9	0.5%–23%
Other personal cleanliness products (291)	30	3%
Aftershave lotion (216)	18	0.5%–2%
Preshave lotions (all types) (14)	1	—
Shaving cream (139)	8	0.5%–1%
Other shaving preparation products (60)	5	3%
Cleansing (653)	43	0.07%–3%
Depilatories (28)	—	0.5%–3%
Face and neck skin care (excluding shaving) (263)	63	0.0001%–10%
Body and hand skin care (excluding shaving) (796)	228	0.5%–10%
Foot powders and sprays (35)	8	—
Moisturizing (769)	200	0.5%—10%
Night skin care (188)	41	1%–2%
Paste masks (mud packs) (255)	13	2%
Skin fresheners (184)	2	0.3%–5%
Other skin care preparations (692)	111	5%
Suntan gels, creams, and liquids (136)	27	1%–15%
Indoor tanning preparations (62)	29	1%–5%
Other suntan preparations (38)	9	4%
1998 total for Dimethicone	1695	
Amodimethicone		
Colognes and toilet waters (656)	1	—
Hair conditioners (636)	67	0.7%–3%
Hair sprays (aerosol fixatives) (261)	2	—
Hair straighteners (63)	2	0.6%
Permanent waves (192)	18	—
Rinses (noncoloring) (40)	1	—
Shampoos (noncoloring) (860)	5	—
Tonics, dressings, and other hair-grooming aids (549)	9	0.0004%–0.7%

(Continued on next page)

TABLE 2
Product formulation data (*Continued*)

Product category (number of formulations reported to FDA) (FDA 1998)	Number of formulations containing ingredient (FDA 1998)	Current concentration of use (CTFA 1999)
Other hair preparations (276)	17	—
Hair dyes and colors (1572)	41	—
Hair bleaches (113)	1	—
Other hair-coloring preparations (59)	1	2%
Hair lighteners with color (6)	1	—
Wave sets (55)	—	0.7%
1998 total for Amodimethicone	166	
Behenoxy Dimethicone		
Foundations (287)	—	2%
Face and neck creams, powders, lotions and sprays (excluding shaving preparations) (263)	—	2%
Paste masks (mud packs) (255)	—	3%
Hair conditioners (636)	1	—
Other hair preparations (276)	2	—
Suntan gels, creams, and liquids (136)	—	2%
1998 total for Behenoxy dimethicone	3	
C14–20 Polyalkylmethicone[a]		
Eyebrow pencil (91)	1	—
Lipstick (790)	1	—
1998 total for C14-20 Polyalkylmethicone	2	
C24–28 Alkyl Dimethicone		
Lipstick (790)	—	2%
1998 total for C24–28 Alkyl Methicone	—	
C30–45 Alkyl Dimethicone		
Suntan gels, creams, and liquids (136)	—	2%
1998 total for C30–45 Alkyl Methicone	—	
Cetearyl Methicone		
Face and neck creams, powders, lotions and sprays (excluding shaving preparations) (263)	—	0.5%
Lipstick (790)	1	0.6%–1%
1998 total for Cetearyl Methicone	1	
Cetyl Dimethicone		
Eye shadow (506)	1	—
Mascara (167)	2	0.5%
Other eye makeup preparations (120)	2	—
Tonics, dressings, and other hair-grooming aids (549)	1	—
Blushers (all types) (238)	5	4%–10%
Face powders (250)	2	0.9%–3%
Foundations (287)	2	6%
Lipstick (790)	—	4%–5%
Makeup bases (132)	4	—
Other makeup preparations (135)	2	4%
Cleansing (653)	1	—
Face and neck skin care (excluding shaving) (263)	1	—
Body and hand skin care (excluding shaving) (796)	1	2%
Moisturizing (769)	2	—

(Continued on next page)

TABLE 2
Product formulation data (*Continued*)

Product category (number of formulations reported to FDA) (FDA 1998)	Number of formulations containing ingredient (FDA 1998)	Current concentration of use (CTFA 1999)
Suntan gels, creams, and liquids (136)	—	2%
Other suntan preparations (38)	1	—
1998 total for Cetyl Dimethicone	27	
Stearyl Dimethicone		
Mascara (167)	2	0.8%
Eye shadow (506)	—	1%–6%
Makeup bases (132)	—	6%
Makeup fixatives (11)	—	5%
Foundations (287)	1	1%–6%
Lipstick (790)	2	4%–6%
Blushers (all types) (238)	—	6%
Moisturizing (769)	1	—
Paste masks (mud packs) (255)	1	—
Other skin preparations (692)	—	4%
Suntan gels, creams, and liquids (136)	—	4%
1998 total for Stearyl Dimethicone	7	
Methicone		
Baby lotions, oils, powder, and creams (53)	—	0.3%
Eyebrow pencil (91)	—	0.2%–0.9%
Eyeliner (514)	—	0.05%–0.8%
Eye shadow (506)	—	0.05%–0.9%
Eye makeup remover (84)	—	0.05%
Mascara (167)	—	0.1%–0.2%
Other eye makeup preparations (120)	—	0.02%
Other hair coloring preparations (59)	—	0.3%
Blushers (all types) (238)	—	0.5%–0.9%
Face powders (250)	—	0.08%–5%
Foundations (287)	—	0.03%–2%
Lipstick (790)	—	0.06%
Makeup bases (132)	—	0.7%
Makeup fixatives (11)	—	0.6%
Other makeup preparations (135)	—	0.01%
Nail polish and enamel (80)	—	0.009%
Body and hand skin care (excluding shaving) (796)	—	0.3%
1998 total for Methicone	0	

[a]C14–20 Polyalkylmethicone is not listed in the *International Cosmetic Ingredient Dictionary and Handbook* (Wenninger, Canterbery, and McEwen 2000).

Noncosmetic

Food

In 1979, the Joint Expert Committee on Food Additives (JECFA) of the WHO established an acceptable daily intake (ADI) level for Dimethicone of 0 to 1.5 mg/kg body weight. The ADI applied, "only to compounds with a relative molecular mass in the range of 200–300" (FAO/WHO 1994).

The Select Committee of GRAS Substances (SCOGS) of the Federation of American Societies for Experimental Biology (FASEB) evaluated the safety of Dimethicone (under the name methylpolysilicones) for food use. The Select Committee was of the opinion:

> The bulk of food grade methylpolysilicones consists of high molecular weight compounds which are not absorbed to any appreciable extent from the intestinal tract. However, these silicones may also contain some low molecular weight (<1000) polymers which might be absorbed. Prudence dictates that food grade specifications should be modified to minimize the presence of absorbable components.

The Select Committee concluded that there was no evidence that demonstrated or suggested grounds to suspect that Dimethicone was hazard to the public when used at levels, "that are now current or that might be reasonably expected in the future." At the time, daily intake was estimated at 0.1 μg/kg/body weight (FASEB 1981).

The FDA has included "siloxanes and silicones, dimethyl . . ." as acceptable defoaming agents in the manufacture of paper and paperboard for use in packaging, transporting, or holding food. The regulation appears in the Code of Federal Regulations (CFR) at 21 CFR §176.210.

Pharmaceutical

The FDA has proposed classifying Dimethicone as Category 1 (recognized as safe and effective) for use as a skin protectant up to 30% in infants, children, and adults with the labeling: *Warning. Not to be applied over puncture wounds, infections, or lacerations* (FDA 1978). The FDA has also proposed Dimethicone as Category 1 in the treatment and prevention of diaper rash (FDA 1990).

At one time, Dimethicone was used in antacid formulations (Locock 1971). Now, simethicone (not contained in this report) is used (Harvey 1990).

GENERAL BIOLOGY

Dimethicone Absorption and Excretion

Oral Delivery—Animal Studies

Dow Corning Corp. (1956) orally administered an antifoam compound containing 28% [^{14}C]-Dimethicone to two lactating dogs (25 g given to ~9-kg animals) and one albino rat (0.58 g given to ~170-g animal, sex not given). No evidence of assimilation was observed in the rat. Traces of siloxanes were found throughout the body of both dogs. It was estimated that 0.0001% of the dose had been absorbed from the gastrointestinal (GI) tract.

The University of Birmingham (1968) reported a study in which four beagle dogs (two of each sex) were fed an antifoam compound (91% Dimethicone) at a dose of 300 mg/kg/day for 120 days. The material was mixed with a small amount of meat and given prior to the main meal to ensure that all of the dose was eaten. Total silicon consumption was between 300 and 500 g. A control group received untreated feed. Urine and feces were collected periodically. At the end of dosing, dogs were fed untreated feed for 5 days and then killed. Blood samples were taken and major organs were weighed and examined for microscopic and histopathologic changes and for silicon content. Average output of urinary silicate was not increased in treated dogs. Fecal silicon output was approximately equal to the amount ingested. Silicon was not detected in any organ. One dosed male had a healed gastric ulcer. The spleen of one dosed female had areas of atrophy with wide fibrous trabeculation. The other treated female had a slightly reddened rugae in an area of the stomach and adherent mucus in the intestine, but was microscopically normal. The antifoam compound was considered not absorbed by beagle dogs.

Dow Corning Corp. (1972a) gave a 41.8-mg/kg oral dose of [^{14}C]-Dimethicone (360 fluid with a specific activity of 0.5 mCi/g) to a male rhesus monkey. The animal was held in a unit that prevented respiratory air from being contaminated with volatile products from feces and urine. Air, feces, and urine were analyzed. Virtually all radioactive label was found in the feces. By 70.5 h after dosing, 65.4% of the dose was recovered in the feces. An additional 27.3% of the dose was recovered over the next hour, with only trace amounts after that. Analysis of toluene extracts of the fecal samples established that Dimethicone was excreted unchanged.

Dow Corning Corp. (1989a) gave male Sprague-Dawley rats a single oral dose of [^{14}C]-Dimethicone fluid (either 35 or 1000 cs, with unspecified specific activity) at either 250 or 2500 mg/kg. In a repeated-dose study, rats were fed 0.5% or 5.0% Dimethicone for 13 days followed by a single oral dose of the radioactive Dimethicone at either 250 or 2500 mg/kg. Plasma, excreta, organs, and tissues were collected at 4, 8, 24, and 48 h post dosing and analyzed for radioactivity via liquid scintillation spectrophotometry. Most of the test material was found in the GI tract at 4 and 8 h and in the feces at 24 and 48 h after administration of [^{14}C]-Dimethicone fluid. Anal leakage was observed with the 35 cs fluid at the 2500-mg/kg dose. Trace activity was detected in the urine and scattered tissue samples until 8 h; no activity was detected in tissues or organs at 48 h. Dimethicone was considered to be rapidly excreted from the GI tract following gavage.

Oral Delivery—Human Studies

In a report from the University of Birmingham (1967a), four subjects were instructed to ingest a capsule containing 376.5 mg silicone (an antifoam product containing 91% Dimethicone) twice a day for 10 days. Two subjects completed the protocol. Daily fecal samples were collected from the two during the last 3 days of the dosing period, and 24-h urine samples were collected from all four during the last 5 days. Fecal analysis detected a silicone output that was slightly greater than the intake. The authors considered that the short sampling time had not established a quanitative balance between oral intake and fecal output. No significant increase in soluble silicate was detected in the urine. In studies with other species, the authors stated that almost 99% and 82.5% of the administered silicone was recovered in the 4-day feces of rats and rabbits, respectively. They concluded that Dimethicone was unlikely to be absorbed from the GI tract of humans, rats, and rabbits.

Dow Corning Corp. (1974) studied the absorption and elimination of silicon contained in two Dimethicone antifoam preparations in human tests. Each of the two samples was given as a single oral dose of 100 mg/kg to six humans or as a single dose (100 mg/kg) of an emulsion (30 mg/kg solids) to five humans. Total and organosoluble urinary silicon output (for 72 h post administration) and organosoluble silicon output in expired

air (8-h value) were measured. The compound that contained <0.22% low-molecular-weight polymers (in 91% Dimethicone) did not produce a significant increase in total or organosoluble urinary silicon. Further, no organosilicon compounds were detected in the expired air. An increase in all three parameters was observed with the second compound, which contained 10% low-molecular-weight polymers (in 93% Dimethicone). The urine contained 1.8% and 3.3% of the administered dose of the compound and emulsion, respectively. The expired air contained approximately 0.25% of the given dose. It was suggested that the increased silicon concentrations found with the second Dimethicone sample represented organosoluble silicon rather than inorganic silicon (silica). Approximately 25% of the urinary silicon was an unidentified form of a soluble organosilicon compound. The exhaled material contained primarily octamethylcyclotetrasiloxane and small amounts of decamethylcyclopentasiloxane.

Dermal Delivery—Human Studies

Hobbs, Fancher, and Calandra (1972) applied a 100 cs Dimethicone fluid (TX-225) once daily (50 mg/kg) to the back of five Caucasian males for 10 days. The material was evenly distributed over the entire back surface and no special covering was required. After 20 h of exposure, the excess material was rinsed off. Daily logs of diet were maintained and subjects were asked to refrain from eating raw leafy vegetables during the study. Subjects provided samples of home drinking water and beer, so that dietary silicon contributions could be quantified.

Absorption was measured as silicon in blood and urine. Baseline concentrations were established for several days (up to 25) prior to dosing. Samples were taken on days 1, 3, 6, 8, and 10 during the dosing period. No significant difference between pretest and test urinary silicon concentrations were found in four subjects. One subject had increased urinary silicon ($p = 0.05$) that was attributed to a large value on day 10, accompanied by large urine output on that day. Another two subjects had consistently greater total urinary silicon concentrations throughout the study compared to other subjects. The finding was attributed to relatively high concentrations of silicon in the subjects' home drinking water, high beer intake, and generally greater urine output. Statistical analysis of group data indicated no significant increase in urine silicon concentrations. No increase in blood silicon concentrations was noted in any subjects. The investigators concluded that there was no evidence of dermal absorption of Dimethicone (Hobbs, Fancher, and Calandra 1972).

Absorption Enhancement by Dimethicone

Two clinical studies investigated the effects of various lipophilic vehicles on the skin penetration of methyl nicotinate. Dimethicone 100 was selected as the standard because it was not expected to exert "specific vehicle effects" due to its high molecular weight (6700 Da). As expected, Dimethicone did not alter drug penetration (Leopold and Lippold 1995; Leopold and Maibach 1996).

ANIMAL TOXICOLOGY

Acute Oral Toxicity

Dimethicone

The acute oral LD_{50} values for various Dimethicone samples, summarized in Table 3, are consistent with the conclusion that Dimethicone is not acutely toxic.

Methicone

Methicone (as L-31) had an oral LD_{50} of >64 ml/kg in male albino rats. No deaths occurred in five rats given that dose (Mellon Institute 1993).

Vinyldimethicone

A substance identified as "vinyl dimethylsiloxy-terminated polydimethylsiloxane" (CAS no. 68083-19-2) had an oral LD_{50} of >16.0 ml/kg in 10 Sprague Dawley rats. Greasy-textured fur was noted. One rat had pneumonia, and pleuritis was observed at necropsy (Myers and Ballantyne 1993).

Short-Term Oral Toxicity

Dimethicone

MacDonald, Lanier, and Deichmann (1960) fed groups of 50 Sprague-Dawley rats (10 of each sex) 1% Dimethicone at one of five viscosities, 30, 350, 1000, 10000, and 60000 cs, for 90 days. A control group received untreated feed. Rats were killed after the dosing period and examined for gross lesions. Feed consumption, weight gain, hematological parameters (total and differential leukocyte counts, hematocrit, and hemoglobin measured on days 45 and 90), organ weights (heart, lungs, liver, spleen, kidneys, and testes), microscopic examination (spleen, kidneys, liver, testes/ovaries, uterus, aorta, stomach, intestines) were similar between dosed and control rats. One rat of the 60,000-cs group had an aggregation of leukocytes in the myocardium of the right ventricle of the heart. Varying degrees of inflammation were noted in the lungs.

In a study at the University of Birmingham (1967b), groups of 20 rats (10 of each sex) were fed 0.1% or 1% of an antifoam preparation containing 91% Dimethicone for 90 days. It was estimated that rats consumed almost 22.5 g of the compound during the dosing period. Rats were then transferred to a control diet and a 24-h urine specimen was collected for silicate content analysis. Rats were killed after 2 weeks of feeding the control diet and were necropsied. Blood samples were taken from the caudal vein and the lungs; any detectable lymphoid tissue was examined microscopically. The liver, kidneys, spleen, testes, and intestine were analyzed for silicone content.

No significant differences were observed in body weight gain, serum parameters (sodium, potassium, serum glutamic oxaloacetic transaminase [SGOT], serum pyruvic glutamic transaminase [SPGT], total protein, albumin, globulin, hemoglobin concentration, packed cell volume [PCV], total white cells, polymorphonuclear leukocytes, eosinophils, lymphocytes, and monocytes), urine-concentrating ability, protein content,

TABLE 3
Acute oral toxicity of Dimethicone

Dimethicone sample	Oral LD_{50}	Reference
	Mice	
35% aqueous dispersion as TX 184A and 184B	>10.0 ml/kg	Hill Top Research 1967
	Rats	
3.26% in a caulking compound	26.85 g/kg	Food and Drug Research Labs 1978
3.26% in a caulking compound	>17.22 g/kg (approximate) Substance blocked airways	Food and Drug Research Labs 1979a
6.9% in rubber adhesive sealant	>8.49 g/kg (approximate) Substance blocked airways	Food and Drug Research Labs 1979b
15% in emulsion	12.3 ml/kg (males) 6.50 ml/kg (females)	Bushy Run Research Center 1984
15.7% in a rubber adhesive sealant	23.12 g/kg (approximate) Substance blocked airways	Food and Drug Research Labs 1980
15.7% in caulking	6.98 g/kg	Food and Drug Research Labs 1981
35.0% in emulsion	>40 ml/kg	Food and Drug Research Labs 1977a
38.0% in emulsion	>40 ml/kg	Food and Drug Research Labs 1977b
50% aqueous dispersion	>10.0 ml/kg	Dow Corning Corp. 1972b
81.8% in a putty	21.2 g/kg	Food and Drug Research Labs 1977c
85.8% in putty	19.9 g/kg	Food and Drug Research Labs 1977d
85.8% in a putty (given as a 75% suspension in 95% ethanol)	31.9 g/kg (discounting ethanol effects)	Food and Drug Research Labs 1977e
XF-1-3753	>10.0 g/kg	Dow Corning Corp. 1970
XF-2-1075	>15.4 g/kg	Dow Corning Corp. 1975
X2-1133 heat-transfer fluid	≥15.4 g/kg	Dow Corning Corp. 1977
X2-1162 heat-transfer fluid	≥15.4 g/kg	Dow Corning Corp. 1978a
Heat-transfer fluid	≥15.4 g/kg	Dow Corning Corp. 1978b
Trade compound (>90% Dimethicone)	>17 g/kg	Springborn Labs 1991
	Guinea pigs	
Two 35% aqueous dispersions	>30.0 g/kg	Dow Corning Corp. 1949
Two 35% aqueous emulsions	>10.0 g/kg	Dow Corning Corp. 1950

silicate concentration, or organ weight. Male rats of the 1% group weighed significantly more ($p < 0.05$) than controls at the time of necropsy. No changes were noted at microscopic examination. Silicone was not detected in the spleen, kidneys, liver, testes, or intestine (University of Birmingham 1967b).

Atlas Chemical Industries (1969) fed an antifoam compound containing 95% Dimethicone to groups of six dogs (three of each sex) at concentrations of 120, 380, or 1200 mg/kg/day for 90 days. Body weight gain, serum chemistry parameters (urea, nitrogen, glucose, sodium, potassium, chloride, cholesterol, alkaline phosphatase, and SGOT), hematology parameters (PCV, hemoglobin, sedimentation rate, leukocyte count, differential count, and plasma prothrombin time [PTT]), urinary parameters, and gross and microscopic examination of tissues and organs were similar to controls groups.

Dow Corning Corp. (1972c) described Dimethicone fluids that contain low-molecular-weight linear and cyclic dimethylpolysiloxanes as "ubiquitous trace components" and conducted a study of the effects of a 4-week oral exposure to 20-cs Dimethicone fluid using rats. The study measured changes in organ weight, thyroid function, and tissue elemental silicon accumulation. Rats were fed either the 20 cs fluid containing not more than 0.04% linear/cyclic dimethylpolysiloxanes (where number of Si atoms ≤ 6) or a "spiked" solution containing 5% each of four linear/cyclic dimethylpolysiloxanes. Controls were sham-dosed. No changes were noted with respect to final body weights or organ weights. Whole body oxygen consumption was not altered by treatment. Changes were seen in serum total cholesterol concentrations, but were not consistent with regard to compound, sex, or route of administration. The authors observed that females accumulated more organosiloxane-derived silicone in depot fat than males. Administration of cyclic compounds resulted in greater fat silicone concentrations in fat compared to administration of linear compounds.

Dow Corning Corp. (1989b) investigated silicon oil as a low-calorie alternative to traditional edible oils. Groups of 30 CD-1 mice (15 of each sex) were fed diets containing 5% and 10% Dimethicone fluid for 90 days. A control group received

untreated feed. Mice were killed at the end of dosing and major organs were collected, weighed, and examined for microscopic lesions. No signs of toxicity, changes in behavior, or mortality were seen in any group. Mean body weights were comparable between treated and control mice. Treated mice consumed significantly more feed; the increased intake was considered to compensate for the non-nutritive components of the diet. Anal leakage was observed in treated mice and was greatest in females of the 10% group, but stool consistency was similar to controls. Organ weights were similar and no microscopic lesions were observed.

At the Dow Corning Corp. (1989c), groups of 40 Sprague-Dawley rats (20 of each sex) were fed 1%, 5%, or 10% Dimethicone at one of three viscosities, 35, 350, and 1,000 cs (total of nine treatment groups) for 90 days. Two control groups received untreated feed. Blood samples were obtained by cardiac puncture from 20 rats of each group (10 of each sex) and urine was collected from 10 of these 20 rats (5 of each sex) at the end of the study. All rats were killed and major organs were collected, weighed, and examined for microscopic lesions.

No signs of toxicity or changes in behavior were observed. One control female and two treated male rats were moribund and were killed. The authors did not consider the deaths treatment related. Slight-to-marked anal leakage was observed in rats of the 10% group; leakage decreased with increasing viscosity. Slight leakage was also observed in rats of the 5% group. Stool consistency was similar to controls. Although occasionally body weight increase was significantly greater in treated male rats, most of the mean body weight data was comparable between treated and control groups. Treated rats consumed more feed and, as in the mouse study, the finding was considered a compensatory response to the non-nutritive components of the diet.

Changes in blood, clinical chemistry, bone marrow, or urinary parameters were observed occasionally but were not considered biologically significant. Some mean absolute and relative organ weights were significantly different between treated and controls, but the findings were not considered of biological or toxicological significance.

Treatment-related changes were observed in the eyes (corneal opacities and neovascularization). Some rats also had mineralization of the cornea. Mild chronic inflammation of the cornea was observed microscopically. The ocular findings were not dose dependent and could have resulted from direct irritation from the Dimethicone fluid in the feed. Three lymphomas were observed in treated males (two lymphocytic lymphomas in the 10%, 1000-cs group, and one undifferentiated lymphoma in the 1%, 35-cs group). The neoplasms were not considered treatment related because the incidence was within that of the historical control and the incidence was not duplicated in the follow-up study (described below) using a larger group of rats (Dow Corning Corp. 1989c).

Because of the lymphomas seen in the study described above, male rats were selected for further study (Dow Corning Corp. 1989d). Groups of 100 were fed 10% Dimethicone fluid at one of three viscosities (35, 350, and 1000 cs) for 90 days. Two control groups received untreated feed. At the end of dosing all rats were killed, major organs and blood were collected and examined for microscopic and hematologic changes. No overt signs of toxicity or behavioral changes were observed. Two treated rats were killed; one was moribund. A statistically significant difference in mean body weight was observed between rats of the 35-cs group and one control group, but was not considered treatment related. Like earlier studies, treated rats had significantly greater mean feed consumption. No significant changes were observed in hematology parameters or at necropsy and histopathologic examination.

Subchronic Oral Toxicity

Dimethicone

Child, Paquin, and Deichmann (1951) reported a study in which groups of two mongrel dogs were fed Dimethicone (83% in an antifoam compound) at 0.3, 1.0, or 3.0 g/kg/day in ground horse meat 5 days per week for 3 months. A control group was fed untreated horse meat. Afterwards, dogs were fed the Dimethicone in commercial dog food for another 3 months. Dogs were killed at the end of the study; organs and tissues were weighed and examined for microscopic lesions. Both dogs of the 3.0-g/kg group had a thin layer of viscid, gray material covering the intestinal tract and enlarged lymphoid aggregates of the small intestine. The liver of dosed dogs had pigment deposits that were revealed to be bile; quantities deposited in the Kupffer and hepatic cells were directly related to the daily dosing. The authors concluded that the antifoam compound would be harmless should traces be absorbed by humans "from time to time."

Dow Corning Corp. (1954a) fed an antifoam compound (83% Dimethicone) in an emulsion to rats at concentrations of 0.1%, 0.3%, and 1.0% for 120 days. No adverse effect was noted in growth, appearance, behavior, mortality, hematologic parameters, or blood urea nitrogen (BUN). An increase in the spleen and liver weight was noted in rats of the 1.0% group.

Chronic Oral Toxicity

Dimethicone

Rowe, Spencer, and Bass (1950) fed 0.3% (by weight) Dimethicone antifoam compound to groups of 50 Wistar rats (25 of each sex) for 2 years. A control group received untreated feed. Rats were killed at the end of the study. Gross appearance, behavior, growth, and survival were comparable between treated and control animals. Treated rats had greater weight gains compared to controls. No significant differences were observed in the weights of the heart, liver, kidneys, spleen, and testes. BUN and hepatic lipid values were comparable. At microscopic examination, pulmonary lesions, changes in the ovaries and uterus, and mild fatty changes in the liver and tubular epithelium of the kidneys were observed in all treated rats.

Carson, Weinberg, and Oser (1966) fed Dimethicone, as it appeared in a fluid (50 or 350 cs) or in an antifoam compound, as 1% of the diet to groups of rats (for 1 year) and rabbits (for 8 months). The number of animals was not stated. Control groups received untreated feed. Feed and water were available ad libitum. Blood and urine samples were taken periodically. Necropsy was done at the end of dosing. No adverse effects were observed. At the same time, additional groups of rats and rabbits received Dimethicone plus 0.8% cholesterol. The control group for this portion of the study received the cholesterol-supplemented feed. Adverse effects were observed in animals fed cholesterol (both with and without Dimethicone) compared to basal controls. The changes were attributed to the cholesterol.

Acute Dermal Toxicity

Dimethicone

Bushy Run Research Center (1984) reported that a commercial emulsion containing 15% Dimethicone had a dermal LD_{50} of approximately 16.0 ml/kg in rabbits. At that dose, Dimethicone killed 2/5 males and 2/5 females. A Dimethicone dose of 8.0 ml/kg killed 1/5 males and 0/5 females.

Hazleton France (1988a) applied a colorless slightly viscous liquid containing Dimethicone (2008 mg/kg; 2.07 ml/kg volume applied) to the clipped skin of 10 Sprague-Dawley rats (5 of each sex). The exposure area was approximately 10% of the total body surface. The concentration of Dimethicone in the liquid was unreported. The site was covered for 24 h of exposure and then rinsed with water. Observations were made at 15 min, 1 h, 2 h, 4 h, and then once daily for 14 days. Necropsy was done at the end of the study. No adverse reactions were noted. The dermal LD_{50} was >2008 mg/kg.

Springborn Labs (1991) applied a trade mixture (containing >90% Dimethicone) in a single dermal application (2000 mg/kg) to a group of 10 rabbits (5 of each sex). Rabbits were killed on day 15 and necropsied. Decreased feed consumption, diarrhea, mucoid/soft stool, and application site dermal irritation were observed. No changes were noted at necropsy. The acute dermal LD_{50} was >2000 mg/kg.

Methicone

Methicone (as L-31) had a dermal LD_{50} of >20 ml/kg in albino rabbits. The dose was the maximum amount of fluid that could be kept in contact with the skin under impervious covering. At that dose (24-h contact), none of four rabbits died and no irritation was noted (Mellon Institute 1993).

Vinyldimethicone

A substance identified as "vinyl dimethylsiloxy-terminated polydimethylsiloxane" (CAS no. 68083-19-2) had a dermal LD_{50} of >16.0 ml/kg in New Zealand white rabbits. The rabbits (five of each sex) had received a 24-h occlusive exposure to the single dose and were observed for 14 days. Erythema and edema were noted, but no signs of systemic effects were observed. No gross lesions were noted at necropsy (Myers and Ballantyne 1993).

Short-Term Dermal Toxicity

Dimethicone

Dow Corning Corp. (1969) reported that three formulations intended for application to the feet, containing 6%, 11%, or 25% Dimethicone, were applied daily (2000 mg/kg) to clipped sites on male rabbits for 7 days. A control group was treated with a formulation containing 22% Dimethicone. Another control group was left untreated. Rabbits were killed at the end of the study and observed for gross lesions. No adverse reactions, effects on body weights, or pathologic changes were noted.

As described earlier, Dow Corning Corp. (1972c) conducted a study of the effects of a 4-week oral exposure to 20-cs Dimethicone fluid using rats. Rats also were dermally dosed with either the 20 cs fluid containing not more than 0.04% linear/cyclic dimethylpolysiloxanes (where number of Si atoms $\leq$ 6) or a "spiked" solution containing 5% each of four linear/cyclic dimethylpolysiloxanes. Controls were sham-dosed. The study measured changes in organ weight, thyroid function, and tissue elemental silicon accumulation. No changes were noted with respect to final body weights or organ weights. Whole body oxygen consumption was not altered by treatment. Changes were seen in serum total cholesterol concentrations, but were not consistent with regard to compound, sex, or route of administration. Dermal dosing resulted in less silicon accumulation in the fat than did oral administration.

Acute Inhalation Toxicity

Dimethicone

Hazleton Labs (1953) exposed two dogs, seven guinea pigs, and seven rats to a "200 fluid" aerosol (containing unspecified concentration of Dimethicone) at a concentration of 2.12 mg/L for 6 h. No particle size was reported. Three guinea pigs died during the study. At the end of dosing, almost all of the animals were killed for necropsy and collection of tissues. One dog was observed for an additional month before it was killed. Hyperventilation, excitability, and salivation were noted during exposure. All animals killed immediately after dosing had hyperemic lungs with hemorrhagic areas. At microscopic examination edema, hemorrhage, and mild interstitial irritation of the lungs were found. The dog killed 1 month later had small areas of dark coloration of the lungs, but microscopic findings were similar to those found in animals that had been immediately killed. The authors concluded that this fluid produced only minimal signs of toxicity and was essentially nontoxic.

Methicone

Methicone (as L-31) generated as a concentrated vapor caused no mortality when six female albino rats were exposed for 8 h. The calculated concentration was 0.78 mg/L. Rats appeared normal throughout the subsequent 2-week observation

period and no remarkable lesions were noted at necropsy. No further details were given (Mellon Institute 1993).

Hexyl Methicone

Aerosolized Hexyl Methicone was administered by whole-body inhalation exposure to groups of 10 Fischer F344/N rats (5 of each sex) for a 4-h exposure. The initial target dose was 5.0 mg/L (5.08 mg/L achieved) with particles having a mass median aerodynamic diameter (MMAD) of 0.27 μm. All exposed rats died within 24 h. A second exposure was done using a 2.0 mg/ml dose with an MMAD of 0.29 μm. Four males died within 2 h of exposure; the remaining six rats survived the 14-day observation period. A third exposure was then conducted with a targeted dose of 1.0 mg/L (0.95 mg/L achieved), with an MMAD of 0.27 μm. Two males died immediately after the exposure; the remaining rats survived through the observation period. Dyspnea and decreased activity or hypoactivity were clinically observed in surviving rats immediately after exposure. Lesions at necropsy of rats that died included dark red or mottled lungs and/or fluid filled trachea; no unusual findings were noted at necropsy of rats that had survived the observation period. The calculated LC_{50} was 1.12 mg/L for males, between 2.0 and 5.0 mg/L for females, and 1.8 mg/L for the combined sexes (IIT Research Institute 1994).

Vinyldimethicone

Sprague Dawley rats were placed in a sealed chamber and exposed for 6 h to a near-saturation vapor of a substance identified as "vinyl dimethylsiloxy-terminated polydimethylsiloxane" (CAS no. 68083-19-2). No particle size was reported. Rats were observed for 14 days after exposure. No deaths or gross lesions were observed. No further details were provided (Myers and Ballantyne 1993).

Short-Term Dermal Toxicity

Dimethicone

A cat, rabbit, guinea pig, two rats, and four mice were sprayed for 4 hours with an atomizer containing 10 ml/kg of a Dimethicone sample. The sample contained approximately 110 siloxane units and its viscosity was 140 cs at 20°C. No particle size was reported; but the atomizer output was described as a thick fog that settled rapidly on the animals and the cage. The treatment was repeated 29 days later. The cat, rabbit, guinea pig, and rats had no adverse effects from the exposure. Weight gain was normal during the exposure and 6-week postdosing observation periods, the urine was free from protein, and the blood had no changes in hemoglobin content or in erythrocyte and leukocyte counts. All four mice died. The first died after 20 exposures and the others died during the postdosing period. None were examined microscopically. The authors stated that there was a relatively high mortality rate in mice in the laboratory at the time and that the link between the treatment and deaths was not certain. Overall, the authors concluded that inhalation of silicone oil was harmless (Gloxhuber and Hecht 1955).

Vaginal Irritation

Dimethicone

A mucoadhesive paste (53% Dimethicone) was introduced (0.5 g) via syringe into the vaginal cavity of six albino rabbits. Two control rabbits were dosed with a sodium chloride solution. Tissue was scored according to the Draize scale (maximum score of 8) at 24, 48, and 72 h post dosing. Erythema was noted in three rabbits at 24 h, and in one rabbit at 48 h after treatment. None had erythema at 72 h. No edema or signs of toxicity were observed. The irritation score for the paste was 0.22 (Toxikon Corp. 1991).

Dermal Irritation

Dimethicone

Hazleton Labs (1975) reported a preliminary skin irritation study using six adult albino rabbits (species/sex not stated). A Dimethicone fluid (0.5 ml) was applied for 24 h under occlusive patches to an intact and abraded site (clipped of hair) on each of two rabbits. Sites were scored for erythema and edema at the time of patch removal (24 h) and again 48 h later. The maximum score was 8.0. The authors reported a primary irritation index (PII) of 6.54 and concluded that the material was a severe irritatnt to rabbit skin.

CTFA (1977a) reported no reactions when a Dimethicone sample (100%) was applied in a 24-h patch to the clipped backs of eight rabbits, four with abraded backs.

Dow Corning Corp. (1978a) evaluated intact and abraded sites on rabbits exposed to three heat-transfer fluids (for industrial use) at 24 and 72 h (presumably on a 0–8 scale). The protocol used to test was not reported. The three fluids had PII scores of 0.1, 0.0, and 0.0, respectively (Dow Corning Corp. 1977, 1978a, 1978b). Based on unreported findings, the investigators stated that one fluid, "may be absorbed through the skin in acutely toxic amounts" and recommended dermal absorption toxicity testing.

The Bushy Run Research Center (1984) reported that a 4-h occlusive exposure to 0.5 ml of a commercial emulsion (15% Dimethicone) produced moderate erythema in all six rabbits tested and minor-to-moderate edema in four. The erythema persisted in most of the rabbits for 10 days (rabbits were observed for 21 days). Desquamation developed within 7 days. One rabbit died on day 21; the death was not considered treatment related.

Hazleton France (1989) applied AK 350 (containing an unreported amount of Dimethicone) for 4 h on each of two sites on six New Zealand white rabbits. No irritation was reported at the 1 h scoring or the 72 h scoring.

Springborn Labs (1991) reported a study in which a trade mixture (containing >90% Dimethicone) were applied for 4 h on each of two sites on six New Zealand white rabbits. Slight-to-well-defined erythema and very slight edema was observed at almost all test sites at the 1-h scoring. The irritation diminished with time and had cleared by the 72 h scoring (last scoring). The calculated PII was 0.40. The maximum score was 8.0.

Vinyldimethicone

A substance identified as "vinyl dimethylsiloxy-terminated polydimethylsiloxane" (CAS no. 68083-19-2) was applied in a 4-h occlusive patch (0.5-ml dose) to the clipped, intact dorsal skin of six New Zealand white rabbits (2 to 3.5 kg, sex not given). Sites were scored using the Draize scale for 7 days. The PII was 0.0 (maximum possible = 8.0). No irritation was observed (Myers and Ballantyne 1993).

Cumulative Dermal Irritation

Dimethicone

Dow Corning Corp. (1949) applied two mold release emulsions each containing 35% Dimethicone (Type P and XE-18) in 10 applications over 14 days to the external ears and shaved abdomen of rabbits. The number of rabbits used and actual exposure time were not reported. No reactions were observed in the pinna, but both emulsions produced slight "simple" irritation to the abdomen. In a follow-up study, Dow Corning Corp. (1950) reported that another two 35% aqueous emulsions, tested under similar conditions, produced similar reactions.

Dow Corning Corp. (1953) reported that Dimethicone (as XF-409) applied to the intact skin of the external ear or abdomen of rabbits (number not stated) for a total of 10 applications produced very slight hyperemia after prolonged contact for several days.

Dow Corning Corp. (1954b) reported four irritation studies in which Dimethicone 200 fluid, tested at 99 parts (as XF1-3753) and as a 50% aqueous dispersion (as XEF-4-3561) was applied to three sites: the intact external ear (10 applications), the intact abdomen (10 applications), and abraded abdomen (3 applications) on an unspecified number of rabbits. Exposure time was not reported. The authors concluded that Dimethicone did not produce irritation in these studies.

Gloxhuber and Hecht (1955) painted a rabbit's external ear once daily for 60 consecutive working days with a Dimethicone sample. The sample contained approximately 110 siloxane units and its viscosity was 140 cs at 20°C. No changes were noted compared to the untreated pinna.

These same authors painted the ears of three rabbits twice daily with a 40% Dimethicone emulsion (60 cs at 20°C). One rabbit died on day 10; the death was not considered treatment related. The other two rabbits were painted 60 and 100 times, respectively, without adverse effect (Gloxhuber and Hecht 1955).

Hill Top Research (1967) applied two 35% Dimethicone aqueous dispersions (TX-184A and TX-184B) for an unspecified amount of time to two rabbits. Sites were evaluated for 15 days. No irritation was observed.

Dow Corning Corp. (1975) reported that when tested as a hydraulic fluid (99.7% as XF-21075), Dimethicone produced no reaction in the external ear, hyperemia after the sixth application to the intact abdomen that became moderate with slight edema after the ninth application, and slight hyperemia after the first application to the abraded abdomen.

CTFA (1977b) reported that Dimethicone (100%), applied to the clipped skin of three male Hartley guinea pigs once a day for 3 consecutive days (it was not stated whether or not the site was covered), produced no reaction.

Irritation Barrier

Dimethicone

A cream containing 10% Dimethicone was investigated as a barrier against dermal irritation. The cream was applied to one side of the clipped back of female guinea pigs. Plastic syringe reservoirs containing the irritants toluene, mineral oil, sodium hydroxide, and sodium lauryl sulfate (SLS) were applied for exposure times of 2 or 24 h. Each irritant was tested on three guinea pigs. Punch biopsies were taken from the test site and were examined for pathologic changes. The cream did not significantly protect against irritation by toluene or sodium hydroxide. It did protect against SLS-induced irritation when the SLS had been applied in a hydrophobic phase, but not when a water solution was used. The cream protected against mineral oil-induced skin changes (Mahmoud, Lachapelle, and van Neste 1984).

Dermal Sensitization

Dimethicone

Dow Corning Corp. (1985) applied a gel containing 79% Dimethicone (Q7-2167/68) to the clipped and depilated backs of 10 male Hartley albino guinea pigs. Four 48-h occlusive patches (0.1 ml) were applied in 10 days. At the third application, 0.2 ml Freund's complete adjuvant (FCA) was injected intradermally near the test site. Sites were evaluated at the time of patch removal. Following a 10-day nontreatment period, guinea pigs were challenged at an unexposed site. Challenge reactions were evaluated at 24, 48, and 72 h postapplication. Positive- and negative-control groups (five guinea pigs in each group) were maintained. Hyperemia and edema were each scored on 0–4 scales. Observations during induction were not reported. No reactions were observed at challenge.

Hazleton France (1989) tested a trade mixture (containing >90% Dimethicone) using the Magnusson-Kligman protocol. On induction day 1, groups of 20 Dunkin-Hartley guinea pigs (10 of each sex) received three series of two injections consisting of (1) FCA alone, (2) a 50% *w/w* solution of the test article alone, and (3) FCA plus test article. Because pretesting established that the test article was not an irritant, an SLS patch was applied on day 8. A 48-h occlusive patch of the test material as supplied was applied on day 9. Following an 11-day nontreatment period, a 24-h patch of the test article was applied to a previously unexposed site. Challenge sites were evaluated 24 and 48 h after patch removal. A control group was treated with water. No reactions were observed at challenge.

National Institute of Environmental Health Sciences (1990) reported a study in which Dimethicone fluid was applied (20 μl) to shaved and dermabraded dorsal sites on sixteen female B6C3F$_1$ mice daily for 8 days. Seven days later, mice were

challenged on the dorsal and ventral sides of the left external ear. A hypersensitivity reaction was measured by both the radioisotopic incorporation assay ([^{125}I]-Iododeoxyuridine (IUDR) was injected into the tail vein of all mice the day before challenge) and the mouse ear swelling test (MEST). Following the MEST test, all mice were killed except for eight of the Dimethicone group. The challenged and untreated external ears of killed mice were biopsied and counted in a gamma counter. Seven days later, the eight remaining mice were joined with another group of eight mice that had been treated with saline for 5 days. All of these mice were challenged with an application of Dimethicone on the left external ear and again analyzed by the MEST assay for 2 days. The authors concluded that Dimethicone did not produce a contact hypersensitivity reaction.

Dow Corning Corp. (1991) tested a Dimethicone liquid (Q7-2867) following a modified split-adjuvant protocol. The liquid (0.2 ml) was applied under gauze to 10 male Hartley guinea pigs. Four 48-h occlusive patches were applied in 10 days. FCA was injected at the third application and application of the fourth patch occurred 72 h later. Following a 12-day nontreatment period, a 24-h challenge patch was applied to an unexposed site. Challenge reactions were evaluated at 24, 48, and 72 h post application. Two negative-control groups (saline and alcohol), one positive-control group, and a vehicle-control group were maintained. No irritation was noted during induction, and the Dimethicone liquid did not produce any reactions at challenge.

Ocular Toxicity

Dimethicone

Dow Corning Corp. (1953) reported that Dimethicone (as XF-409) produced very slight pain and irritation for a few hours after instillation into rabbit eyes (number not stated) regardless of whether the eye was subsequently rinsed or unrinsed.

Dow Corning Corp. (1954b) tested Dimethicone as 200 fluid in four studies using rabbits. Dimethicone was reported to produce a slight conjunctival irritation that subsided in 24 h when tested undiluted in rinsed and unrinsed eyes.

Another study (Dow Corning Corp. 1957a) observed essentially no irritation when electrical-grade silicone fluid was tested undiluted, although slight pain and conjunctivitis, which subsided in 24 h, were noted when the electrical-grade silicone fluid was instilled as a 10% solution in propylene glycol. Treated and untreated electrical-grade fluid instilled as a single dose or daily for 5 days produced conjunctival irritation that was slow to heal; the irritation was more severe following repeated exposure (Dow Corning Corp. 1957b).

Dow Corning Corp. (1959) reported very slight but definite conjunctival irritation in another repeated-dose study using rabbits, but details were not available.

Dow Corning Corp. (1968) stated that Dimethicone at 10% and 29% in trade formulations produced essentially no irritation. Slight conjunctivitis or iritis was noted with 35%, but lesions had cleared in 24 h.

Dow Corning Corp. (1970) stated that Dimethicone (as XF-1-3753) produced a very slight conjunctival reponse in a rabbit that subsided within 24 h.

Dow Corning Corp. (1972b) stated that Dimethicone, as a 50% aqueous dispersion (XEF-4-3561), produced slight conjunctivitis in rabbits at 1 h; the conjunctivitis cleared by 24 h.

Dow Corning Corp. (1975) stated that Dimethicone (as XF 2-1075) produced essentially no response when tested in rinsed and unrinsed rabbit eyes.

Hazleton Labs (1975) reported that although Dimethicone (50% in SM2080) was a mild irritant to rabbit eyes following a 2- or 4-s rinsing, it was a severe irritant to unrinsed eyes.

CTFA (1977c) reported that Dimethicone produced a conjunctival reaction when instilled into one conjunctival sac of each of three rabbits. The total score was 4.7 (maximum 110). It was considered a "minimal irritant."

Dow Corning Corp. (1977, 1978a, 1978b) tested three heat-transfer fluids (containing Dimethicone) on six rabbits. The protocol used was not reported but the conjunctiva, cornea, and iris were observed 24 h, 48 h, 72 h, and 7 days after exposure. Two fluids produced no reaction (Dow Corning Corp. 1978a, 1978b), the third produced conjunctival redness in all rabbits and conjunctival chemosis in two rabbits at the 24-h observation (Dow Corning Corp. 1977). The chemosis had cleared by 48 h, whereas the redness persisted through the 72-h scoring, but cleared by day 7. The cornea and iris were not affected.

The Bushy Run Research Center (1984) reported that a 0.1-ml dose of a trade mixture (15% Dimethicone) produced moderate corneal injury, iritis, and conjunctival irritation in all of the six rabbits. A 0.01-ml dose produced moderate conjunctival irritation in all rabbits and moderate iritis in two. A 0.005-ml dose produced minor to moderate conjunctival irritation in all rabbits that cleared in five of six rabbits by 72 h.

Hazleton France (1989) reported that Dimethicone (a major component of trade mixture) was a slight irritant when instilled into one eye of six rabbits followed by a 72-h observation period.

Springborn Labs (1991) instilled 0.1 ml of a trade mixture (containing >90% Dimethicone) into one eye of each of six rabbits, followed by a 7-day observation period. The authors concluded that Dimethicone was a nonirritant based on the European Commission evaluation criteria.

Five 35% aqueous emulsions tested separately produced slight conjunctivitis in rabbits that cleared within 2 days with no corneal damage, although one emulsion produced "immediate and painful irritation" when first instilled (Dow Corning Corp. 1950).

Methicone

Three undiluted methicone oils were each instilled (0.1 ml) into one conjunctival sac of each of two albino rabbits (sex, species, body weights were not given). The contralateral eye served as the control. One dosed eye was rinsed 20 s after exposure with tap water for one min; the other dosed eye was not rinsed. Eyes were examined by a hand slit lamp at 1 and 4 h, and

at 1, 2, and 3 days. None of the three oils produced corneal injury; DF 1040 produced minimal congestion of the iris at 1 h; and all produced mild conjunctival redness that lasted up to 2 days (Dupont De Nemours & Co. 1966).

Vinyldimethicone

A substance identified as "vinyl dimethylsiloxy-terminated polydimethylsiloxane" (CAS no. 68083-19-2) was instilled (0.1 ml undiluted) into the lower conjunctival sac of one eye of six New Zealand rabbits. Eyes were scored for 7 days using the Draize scale. Minor conjunctivitis was noted; the conjunctivitis cleared within 1 to 2 days. The maximum mean score was 6.0 (Myers and Ballantyne 1993).

REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY

Oral

Dimethicone

The Food and Drug Research Labs (1966) tested Dimethicone-containing fluids in oral studies to investigate possible atrophic changes in rat seminal vesicles. The test material was administered directly into the stomach of 10 male Sprague-Dawley rats at a dose of 3.3 ml/kg/day for 6 days. A control group received saline. Feed and water were available ad libitum. Rats were killed at the end of dosing and necropsy was performed. Final body weight and the weight of the seminal vesicles were measured. A Dimethicone sample (TX-158F) produced a significant reduction in the average seminal vesicle to body weight ratio but not in absolute organ weight. Two other Dimethicone samples had no adverse effect.

Atlas Chemical Industries (1970) reported a study in which a medical grade antifoam compound (93% Dimethicone) was given orally to pregnant Wistar rats on gestational days (GDs) 6 to 15 at doses of 0.38, 1.20, and 3.80 g/kg/day. The highest dose was selected to represent 70 times the recommended clinical dose for the treatment of intestinal gas and 1000 times that recommended to treat peptic ulcers. A control group received tap water. Rats were examined by laparotomy on GD 20 at which time fetuses were removed from the uterus. Dams were killed and the ovaries were examined for corpora lutea. The authors concluded that Dimethicone at any dose did not induce significant differences in fetal viability at laparotomy, resorptions, average weight, and gross external, soft tissue, and skeletal anomalies.

Siddiqui (1994) fed an antifoam compound (food-grade Dimethicone) to time-mated New Zealand white rabbits at concentrations of 0%, 0.5%, 1.0%, and 2.5% on GDs 6 to 19. Females were observed daily for clinical signs of toxicity. On gravid day 29, confirmed-pregnant females (20 to 22 per group) were evaluated for gestational outcome. Each live fetus was examined for external, visceral, and skeletal malformations. No overt signs of toxicity in the dams, and no statistically significant differences in feed consumption were observed between treated and control rabbits. No adverse effects were noted in mean maternal body weight or liver weight. The incidence of resorptions among the total fetal population was not altered by feeding the antifoam compound. Male and female pup weights were not affected by the maternal treatment. No significant treatment related adverse effects in the incidence of external, visceral, or skeletal abnormalities were observed.

Dermal

Dimethicone

Kennedy et al. (1976) applied 200 mg/kg Dimethicone (medical grade fluid, 350 cs; suspended in either corn oil or sesame oil in a 1:5 ratio) to the shaved backs of groups of 15 pregnant rabbits on GDs 6 to 18. Other groups received subcutaneous injections of 20, 200, or 1000 mg/kg Dimethicone (diluted in sesame oil, or undiluted at the highest dose). Vehicle control groups were treated with corn oil or sesame oil. Litters were delivered by cesarean section on day 29. The uterus and other genital organs of each dam were inspected. Implantation sites and live and dead pups were counted. Live pups were incubated for 24 h and then killed. Dead pups and two thirds of those killed were cleared and stained for skeletal examination. The remaining pups were necropsied. The investigators considered that the vehicles, corn, and sesame oil had an effect on the incidence of resorptions. No treatment-related fetal abnormalities were found. The incidence of talipes varus in the 200-mg/kg group was at or above the upper limit for historical controls, but the abnormality was not detected at the 1000 mg/kg dose.

Following the same protocol, these authors applied Dimethicone (225 fluid, 10 cs) suspended in corn oil (1:5) (200 mg/kg) to the shaven backs of groups of 15 pregnant rabbits on GDs 6 to 18. Treatment did not affect maternal body weight, weight gains, number of implantation or resorption sites, or viable fetuses. Umbilical hernia was noted in one pup each of the treated and control group; one treated pup had talipes varus. No other abnormalities were observed and 24-h survival was comparable between treated and control pups (Kennedy et al. 1976).

In a study by an unknown author, retrieved from the National Technical Information Service (NTIS 1987a), motor oil containing an unspecified amount of Dimethicone was applied undiluted to the shaved backs of the parental (P_1) and first (F_1) generation of Sprague-Dawley rats, 7 days a week for an 8 week premating period, 3-week mating period, and throughout gestation and lactation. Doses applied were 0.1, 0.4, and 1.5 ml/kg. Twenty pregnant P_1 females from each dose group underwent natural parturition; the remaining 20 were killed on GD 13 and the uteri content was examined for implants. A single male and female were selected from each F_1 litter to produce the F_2 generation; dermal treatment began one day after weaning. All F_1 females were allowed a natural parturition. P_1 and F_1 males were killed at the end of mating. F_2 rats were not treated and were killed at weaning.

No statistically significant difference was detected in the mortality or survival rates in F_1 litters on day 0 (parturition). However, mortality after day 0 was significantly decreased in the

0.4- and 1.5-ml/kg groups. In contrast, mortality in the F_2 litter was significantly increased in the 0.4-ml/kg group on day 0. Body weights and weight gains were significantly reduced in adult F_1 male rats of the 1.5-ml/kg group beginning on week 7 and continuing throughout the mating period. Absolute testes weight was also significantly reduced in these males, but the relative testes to body weight ratio was not significantly different from controls.

Gestating dam body weights were significantly increased in the 0.1- and 0.4-ml/kg group compared to sham controls. No significant differences were noted in F_1 or F_2 litter body weight or body weight gains. External appearance and microscopic features of the F_1 and F_2 skeletal systems were comparable to controls. Mild dermal irritation was observed in P_1 and F_1 rats. Mild epidermal acanthosis was observed in P_1 and F_1 rats of the 1.5-ml/kg group. According to the authors, the motor oil did not induce any significant alterations in the reproductive performance of either the P_1 or F_1 generation (NTIS 1987a).

In a study by an unknown author, retrieved from the National Technical Information Service (NTIS 1987b), motor oil containing an unknown concentration of Dimethicone was applied undiluted (1.5 ml/kg) to the shaved back of 20 timed-pregnant Sprague-Dawley rats on GDs 6 to 15. A sham-control was maintained. No deaths occurred during the study. Mean dam and litter body weight, pup viability, incidence of external, soft tissue, and skeletal abnormalities were comparable between treated and control animals.

GENOTOXICITY

Dimethicone

Mutagenicity studies done on Dimethicone are summarized in Table 4. Dimethicone, tested pure or in a trade mixture, was not mutagenic in either in vitro studies using bacterial or mammalian cells, or in vivo studies using mammalian systems.

CARCINOGENICITY

Oral

Dimethicone

Cutler et al. (1974) fed an antifoam compound containing 91% Dimethicone at 0.25% and 2.5% to groups of 100 outbred mice (50 of each sex) for 76 weeks. Another group received a single subcutaneous injection of the test material (0.2 ml) into the left flank. Silicone exposure was calculated to be 520 and 5200 mg/kg/day for the 0.25% and 2.5% oral dose groups, respectively, and 201 mg for the subcutaneous injection group. A control group for the oral-dose study was fed untreated feed and a control group for the injection study received an injection of liquid paraffin. Mice were killed at 80 weeks and necropsied.

Microscopic examination was done on any organ that appeared abnormal and sections from the lungs, heart, stomach, small intestine, spleen, liver, and kidneys from 20 mice of each group were examined. The liver, kidneys, spleen, and perirenal fat of five mice that had been subcutaneously injected were analyzed for silicon. Ten mice of the 2.5% oral dose group were analyzed for whole-body silicon content.

Survival to week 80 was significantly ($p < 0.05$) less than controls for female mice fed 2.5% silicone (however, four had died from cage flooding, and the parameter was not significant when these deaths were excluded) and male mice injected with silicone (however, mice had been killed after the appearance of subcutaneous fibromas). A significantly greater percentage of males injected with silicone developed injection site cysts, had hair loss; a smaller proportion had silicone deposits in the urinary bladder.

Males of the 0.25% diet group had increased incidence of superficial ulceration of the stomach and females of this group had an increased incidence of lymphoid hyperplasia. Neither change was noted in the 2.5% diet group and thus was not considered treatment related. A reduced incidence of uterine atrophy was noted in the females of the 2.5% dietary group. No increase in the number of malignant or benign neoplasms was observed in mice that received silicone in the feed or by injection, compared to controls. In some instances, the incidence of certain benign neoplasms was lower in dosed mice, compared to controls. Analysis of tissue failed to detect silicone in samples obtained from orally dosed or subcutaneously injected mice (Cutler et al. 1974).

Dermal

Dimethicone

In a study by an unknown author, retrieved from the National Technical Information Service (NTIS 1987c), a motor oil containing an unspecified amount of Dimethicone was applied undiluted (50 μl) to the shaved skin of 50 male C3H/HeN mice, twice weekly for life. The sites were not covered and the test material was not mechanically spread after its application. A sham-control group had 120 male mice. The study was terminated when the survival rate for each group reached $\leq$10%. Mice were necropsied, and tissue samples of the application site and stomach were prepared for microscopic examination.

Five control mice died accidentally during the study and were excluded from statistical analysis. The median life span was 79.5 weeks for treated mice and 79.0 weeks for control mice. Mean time-to-death and mortality rates were comparable between treated and control mice. At certain observations, treated mice had significantly greater mean body weight and body weight gains compared to control mice. The differences were not considered treatment related or of biological significance. The final effective number (number of mice alive at week 60 plus the number of dead mice with neoplasms prior to week 60) was 44 treated mice and 91 control mice.

No application site dermal neoplasms were microscopically confirmed in treated or control mice. Ulceration at the application site was observed in 8.0% of treated mice compared to 2.6% of control mice. One treated mouse had a palpable skin mass at the application site during week 65, which regressed by week 67. Epidermal hyperplasia at the application site was more evident

TABLE 4
Genotoxicity testing on Dimethicone

Test	Protocol and Dimethicone dose*	Results	Reference
Bacterial cell			
Ames assay: *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538	Dimethicone (pure) tested at 33.3, 100, 333.3, 1000, 3333.3, and 10000 μg/plate ± S9	Negative	SRI International 1980
Ames assay: *S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	Dimethicone (fluid at 100 and 1000 cs) tested at 0.5, 5, 100, and 500 μg/plate ± S9	Negative	Dow Corning Corp 1978c
Ames assay: *S. typhimurium* TA98, TA100, TA1535, TA1537	Dimethicone mixture (unknown conc) tested at 50, 158, 500, 1580, and 5000 μg/plate ± S9	Negative	NTIS 1988
S. typhimurium TA98, TA100, TA1535, TA1537, TA 1538	Trade mixture (to contain >90% Dimethicone) tested at 1, 5, 10, 50, 100 μl/plate ± S9	Negative	Hazleton France 1988b
S. typhimurium TA98, TA100, TA1535, TA1537 and *Escherchia coli* WP2	Surfactant containing 3 wt.% Dimethicone was tested in ethanol at 100, 333, 1000, 3333, and 5000 μg/plate ± S9	Negative	Microbiological Associates 1994
Bacterial reverse mutation: *S. typhimurium* TA98, TA100, TA1535, TA1537 and *E. coli* WP2	Ethanol extractions of CU-7439 (<0.1% Dimethicone) tested at 312.5, 625, 1250, 2500, and 5000 μg/plate ± S9	Negative	Dow Corning Corp 1989e
Bacterial reverse mutation	X2-5169 (10% Dimethicone)	Negative	Dow Corning Corp 1986a
Bacterial reverse mutation	X2-3379 (28% Dimethicone)	Negative	Dow Corning Corp 1990a
Bacterial reverse mutation	X3-9626 (49% Dimethicone)	Negative	Dow Corning Corp 1986b
Bacterial reverse mutation	X2-3320 (59% Dimethicone)	Negative	Dow Corning Corp 1990b
Bacterial reverse mutation	Q7-2159A gel (79% Dimethicone)	Negative	Dow Corning Corp 1986c
Bacterial reverse mutation	Q7-2867	Negative	Dow Corning Corp 1990c
Mammalian cell line			
BALB/C-3T3 mouse cell transformation assay	Q7-2159A gel (79% Dimethicone) tested at 500, 1000, and 2000 μg/ml ± S9	Negative	Dow Corning Corp 1986d
BALB/C-3T3 mouse cell transformation assay	Q7-2167/68 gel (79% Dimethicone) tested at 1250, 2500, 5000, and 10000 μg/ml ± S9	Negative	Dow Corning Corp 1989f
Chinese hamster ovary (CHO) chromosome aberration assay	Q7-2167/68 gel (79% Dimethicone) tested at 625, 1250, 2500, 5000, and 10000 μg/ml ± S9	Negative	Dow Corning Corp 1989g
CHO/HGPRT forward mutation assay	Q7-2159A gel (79% Dimethicone) tested at 31.3, 62.5, 125, 250, 500, and 1000 μg/ml ± S9	Negative	Dow Corning Corp 1986e
CHO/HGPRT forward mutation assay	Q7-2167/68 gel (79% Dimethicone) tested at 312.5, 625, 1250, 2500, 5000, and 10000 μg/ml ± S9	Negative	Dow Corning Corp 1989h

(Continued on next page)

TABLE 4
Genotoxicity testing on Dimethicone *(Continued)*

Test	Protocol and Dimethicone dose*	Results	Reference
Mammalian system			
Micronucleus test using Swiss/Webster mice	Ten mice (5 of each sex) received a single intraperitoneal injection of an extract of Q7-2159A gel (79% Dimethicone) in tissue culture fluid (dose 5 g/kg)—peripheral blood samples were taken at 24, 48, and 72 h post dosing. Micronuclei per 1000 polychromatic erythrocytes counted	Negative	Dow Corning Corp 1986f
Micronucleus test using CD-1 mice	Groups of 10 mice (5 of each sex) received a single intraperitoneal injection of an extract of Q7-2167/68 gel (79% Dimethicone) in ethanol (sterile water dilutions of the ethanol extract were made to obtain doses** of 1.25, 2.0, and 2.5 g/kg)—peripheral blood samples were taken at 24, 48, and 72 h post dosing. Micronuclei counted	Negative	Dow Corning Corp 1989i

*All studies used CAS no. 63148-62-9 to identify dimethyl silicones and siloxanes except for SRI International (1980), which used CAS no. 9006-65-9; all studies maintained appropriate positive- and negative-control groups; S9 activation prepared from an adult male rat liver; HGPRT (hypoxanthine guanine phosphoribosyl transferase) locus.

**Linear dimethylsiloxane at doses of 0.005, 0.008, and 0.01 g/kg; dimethyl cyclics at 0.01 to 0.02 g/kg.

in treated mice (17/50) than in control mice (1/115), suggesting to the author slight dermal irritation (NTIS 1987c).

CLINICAL ASSESSMENT OF SAFETY

Oral

Dimethicone

Bio-Research Labs (1985a) tested 350 cs Dimethicone fluid as a food additive. In a preliminary study, six men received the additive as 1% of the diet for 5 days (15 g), followed by a 2-day "washout" period. Subjects then received the additive as 2% of the diet for another 5 days (30 g), followed by another washout period. Blood, urine, and fecal samples were collected to assess absorption of selected nutrients. No anal leakage or major GI disturbances were reported. An increased frequency of bowel movements was reported. No changes in protein, carbohydrates, or vitamin A, D, or E were observed.

Bio-Research Labs (1985b) conducted a subsequent study in which seven male subjects received the additive in ascending doses of 2%, 3%, 4%, and 5% of the diet by weight for five consecutive 3-day periods. After this phase of the study, a bolus dose was given. One subject was withdrawn due to inability to produce a fecal specimen until day 6. Three subjects were placed on control diets on day 10 after 3 days at the 3% dose because they experienced anal leakage. Another subject experienced leakage after the first day on the 4% diet; the next day (day 11), this subject, as well as the remaining two subjects, were all placed on the control diet. On day 14, all subjects received a bolus dose of 30 g of the additive (equal to the 2% daily intake dose) and the control diet was continued for another two days. No anal leakage was observed following the bolus.

Subjects experienced flatulence during the study but no other significant discomfort. An increase in the frequency of bowel movements was noted. No significant changes in vitamin K absorption, as estimated by serum prothrombin time and partial thromboplastin time values, were observed. A decrease in mean platelet count was noted following introduction of the test material, but the count returned to baseline values post study. An increase in the percentage of neutrophil count, accompanied by a decrease in the percentage of lymphocyte count with a slight decease in total white blood cell count, was observed post study. Post study mean SGOT, SGPT, and BUN were decreased 14% to 16% from prestudy values. Post study mean values for alkaline phosphatase increased 8%, and total serum bilirubin

increased 54% (this increase was almost entirely accounted for by one subject). Weight loss of 2.7 to 5 kg was observed in three subjects. The significance of the clinical findings was not known (Bio-Research Labs 1985b).

Dermal Irritation

Dimethicone

Dimethicone, applied in a 24-h occlusive patch to the forearm, produced no irritation in 54 men (CTFA 1981).

Dermal Sensitization

Dimethicone

Hill Top Research (1984) conducted a repeated-insult patch test (RIPT) with a solution containing 5.0% *w/v* active Dimethicone in cyclomethicone. During induction, 10 24-h patches containing 0.3 ml of the test material were applied to the same site on the arm of 103 Caucasian subjects. Twenty subjects were withdrawn before study termination due to noncompliance unrelated to the test material. Subjects were challenged at an unexposed site. Sites were scored on a scale of 0 to 5. Patch application was either terminated or moved to another site if any reaction >1 was observed. The protocol was followed except for isolated instances of site scorings being conducted later than prescribed. Reactions were all ≤1. The investigators concluded that the test substance was neither an irritant nor a sensitizer.

Therapeutic

Dimethicone

Johnson (1976) tested a cream consisting of 2.5% Dimethicone in a hydrophilic base as an alternative to steroid creams in the treatment of allergic contact dermatitis. The cream contained no pharmacologically active ingredient. Participants included 56 patients with cutaneous disease considered "likely to respond" to an inactive cream, as well as 19 patients who were considered "not likely to respond." The panel consisted of 47 males and 28 females ranging in age from less than 2 years to 78 years old. Patients (or their parents/caregivers) were instructed to apply the cream to the affected area(s) four times per day for 14 days as well as after the affected areas had been washed. Panelists were instructed to avoid other therapy for the cutaneous disease.

The cutaneous disease characterized by dryness, roughness, scaling, and cracking of the skin were either cleared or improved by the therapy (46 of the 56 "likely responders"). Symptomatic relief and lessened discomfort was noted in some of the 19 "unlikely responders." The nonactive cream was considered a viable alternative in the treatment of cutaneous disease that did not require steroid therapy (Johnson 1976).

SUMMARY

Dimethicone is a fluid mixture of fully methylated linear siloxane polymers end-blocked with trimethylsiloxy units. Methicone is a linear monomethyl polysiloxane. The other dimethicones and methicones covered in this review are siloxane polymers of Dimethicone and Methicone. Most of the data reviewed in this report are studies of Dimethicone.

Almost all of the 20 ingredients function as conditioning agents in cosmetic formulations. FDA reported seven of the ingredients used in 1998 in a total of 1884 formulations; CTFA reported 10 uses. The highest current concentration of use was 15%.

Dimethicone has both food and over-the-counter topical drug use. Its use in foods is limited by molecular weight.

Clinical and animal absorption studies generally reported that Dimethicone was not absorbed following oral or dermal exposure, although some absorption was seen in humans following ingestion of a Dimethicone sample containing low-molecular-weight polymers.

Dimethicone, Methicone, and Vinyldimethicone were not acutely toxic following oral exposure. Mice and rats were dosed for 90 days with up to 10% Dimethicone without adverse effect. Changes in body weight or spleen weight were observed in some rat studies. Anal leakage was noted when Dimethicone fluids of low viscosity were used. Bile deposits in the Kupffer and hepatic cells were observed in dogs dosed with 3 g/kg/day for 6 months.

The dermal LD_{50} for Dimethicone was >2 g/kg in rats and rabbits. The dermal LD_{50} for Methicone was >20 ml/kg in rabbits. The dermal LD_{50} for Vinyldimethicone was >16 ml/kg in rabbits. No adverse reactions were found in rabbits following short-term dermal dosing with 6% to 79% Dimethicone. Adverse effects were noted with a hand cream formulation containing 1% Dimethicone (the other components of the cream were not disclosed).

Only limited inhalation toxicity data were available. A "200 fluid" did produce adverse effects in one study. Methicone and Vinyldimethicone were negative in acute exposure studies using rats. Hexyl Methicone did produce toxic effects in Fischer F344/N rats—the LC_{50} was 1.8 mg/L.

Most dermal irritation studies using rabbits classified Dimethicone as a minimal irritant. Studies that scored reactions according to the Draize scale reported PIIs of ≤2.8 (with test samples containing 5% to 100% Dimethicone).

Dimethicone (tested undiluted and at 79%) was not a sensitizer in four assays using mice and guinea pigs. It was not a sensitizer at 5.0% in a clinical RIPT using 83 panelists. Vinyldimethicone was not irritating to rabbits following a 4-h exposure.

Most ocular irritation studies using rabbits classified Dimethicone as a mild to minimal irritant. The most common finding was a conjunctival reaction. However, a few studies reported severe reactions. Similar to Dimethicone, Methicone and Vinyldimethicone also produced conjunctival reactions.

Dimethicone was tested in numerous oral-dose (using rats) and dermal-dose (using rats, rabbits, monkeys) reproductive and developmental toxicity studies. In a few studies, treated males had significantly decreased body weight and/or decreased testes or seminal vesicles weights.

No treatment-related adverse findings were noted in dosed pregnant females or fetuses.

Dimethicone was negative in all mutagenicity assays. It was negative in both an oral (tested at 91%) and dermal (tested an unknown concentration) dose carcinogenicity assay using mice.

DISCUSSION

The CIR Expert Panel considered it unlikely that any of these polymers would be significantly absorbed into the skin due to the large molecular weight of these polymers. Inhalation exposure, however, was of concern given the limited inhalation toxicity findings in the report. It was noted, however, that only a few of these ingredients are used in aerosol formulations and at a very low concentration. In addition, the Panel was informed that particles from cosmetic formulations containing these ingredients would not likely be inhaled. In particular, it was stated that expected particle sizes would primarily be in the range of 60 to 80 microns, and less than 1% would be under 10 microns, which is an upper limit for respirable particles. The Panel expects that the manufacture process for cosmetic formulations in which these ingredients are found and which may be inhaled would continue to produce particle size distributions that are not significantly respirable.

Overall, the safety test data in the report support the safety of these ingredients at the concentrations that they are known to be used in cosmetic formulations. Accordingly, the CIR Expert Panel was of the opinion that Stearoxy Dimethicone, Dimethicone, Methicone, Amino Bispropyl Dimethicone, Aminopropyl Dimethicone, Amodimethicone, Amodimethicone Hydroxystearate, Behenoxy Dimethicone, C24–28 Alkyl Methicone, C30–45 Alkyl Methicone, C30–45 Alkyl Dimethicone, Cetearyl Methicone, Cetyl Dimethicone, Dimethoxysilyl Ethylenediaminopropyl Dimethicone, Hexyl Methicone, Hydroxypropyldimethicone, Stearamidopropyl Dimethicone, Stearyl Dimethicone, Stearyl Methicone, and Vinyldimethicone may be used safely in cosmetic formulations.

CONCLUSION

Based on the available data, the CIR Panel concludes that Stearoxy Dimethicone, Dimethicone, Methicone, Amino Bispropyl Dimethicone, Aminopropyl Dimethicone, Amodimethicone, Amodimethicone Hydroxystearate, Behenoxy Dimethicone, C24–28 Alkyl Methicone, C30–45 Alkyl Methicone, C30-45 Alkyl Dimethicone, Cetearyl Methicone, Cetyl Dimethicone, Dimethoxysilyl Ethylenediaminopropyl Dimethicone, Hexyl Methicone, Hydroxypropyldimethicone, Stearamidopropyl Dimethicone, Stearyl Dimethicone, Stearyl Methicone, and Vinyldimethicone are safe as used in cosmetic products.

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2021 VCRP Frequency of Use Data - Methicones

Ingredient Name	Category Code & Description	CPIS count
Amino Bispropyl Dimethicone; Total Uses: 1		
Amino Bispropyl Dimethicone	05I - Other Hair Preparations	1
Aminopropyl Dimethicone; Total Uses: 35		
Aminopropyl Dimethicone	05A - Hair Conditioner	5
Aminopropyl Dimethicone	05F - Shampoos (Non-Coloring)	2
Aminopropyl Dimethicone	05G - Tonics, Dressings, and Other Hair Grooming Aids	5
Aminopropyl Dimethicone	05I - Other Hair Preparations	5
Aminopropyl Dimethicone	06C - Hair Rinses (Coloring)	1
Aminopropyl Dimethicone	07C - Foundations	2
Aminopropyl Dimethicone	07F - Makeup Bases	1
Aminopropyl Dimethicone	12C - Face and Neck (Exc Shave)	5
Aminopropyl Dimethicone	12F - Moisturizing	9
Amodimethicone; Total Uses: 641		
Amodimethicone	01C - Other Baby Products	2
Amodimethicone	03C - Eye Shadow	8
Amodimethicone	03G - Other Eye Makeup Preparations	2
Amodimethicone	05A - Hair Conditioner	301
Amodimethicone	05B - Hair Spray (Aerosol Fixatives)	2
Amodimethicone	05C - Hair Straighteners	12
Amodimethicone	05E - Rinses (Non-Coloring)	12
Amodimethicone	05F - Shampoos (Non-Coloring)	64
Amodimethicone	05G - Tonics, Dressings, and Other Hair Grooming Aids	79
Amodimethicone	05H - Wave Sets	1
Amodimethicone	05I - Other Hair Preparations	83

Amodimethicone	06A - Hair Dyes and Colors (All Types Requiring Caution Statements and Patch Tests)	10
Amodimethicone	06C - Hair Rinses (Coloring)	7
Amodimethicone	06D - Hair Shampoos (Coloring)	3
Amodimethicone	06E - Hair Color Sprays (Aerosol)	7
Amodimethicone	06G - Hair Bleaches	1
Amodimethicone	06H - Other Hair Coloring Preparation	9
Amodimethicone	07B - Face Powders	3
Amodimethicone	07C - Foundations	1
Amodimethicone	07E - Lipstick	2
Amodimethicone	07F - Makeup Bases	3
Amodimethicone	07I - Other Makeup Preparations	4
Amodimethicone	10A - Bath Soaps and Detergents	5
Amodimethicone	11B - Beard Softeners	1
Amodimethicone	12C - Face and Neck (Exc Shave)	8
Amodimethicone	12D - Body and Hand (Exc Shave)	1
Amodimethicone	12F - Moisturizing	3
Amodimethicone	12G - Night	2
Amodimethicone	12J - Other Skin Care Preps	5
Behenoxy Dimethicone; Total Uses: 1		
Behenoxy Dimethicone	07E - Lipstick	1
C20-24 Alkyl Dimethicone; Total Uses: 34		
C20-24 Alkyl Dimethicone	03B - Eyeliner	1
C20-24 Alkyl Dimethicone	03C - Eye Shadow	1
C20-24 Alkyl Dimethicone	03D - Eye Lotion	1
C20-24 Alkyl Dimethicone	07E - Lipstick	23
C20-24 Alkyl Dimethicone	07F - Makeup Bases	1
C20-24 Alkyl Dimethicone	12C - Face and Neck (Exc Shave)	4

C20-24 Alkyl Dimethicone	12F - Moisturizing	2
C20-24 Alkyl Dimethicone	12G - Night	1
C24-28 Alkyl Methicone; Total Uses: 3		
C24-28 Alkyl Methicone	07C - Foundations	3
C26-28 Alkyl Dimethicone; Total Uses: 5		
C26-28 Alkyl Dimethicone	03C - Eye Shadow	5
C30-45 Alkyl Dimethicone; Total Uses: 51		
C30-45 Alkyl Dimethicone	03A - Eyebrow Pencil	1
C30-45 Alkyl Dimethicone	03C - Eye Shadow	1
C30-45 Alkyl Dimethicone	03D - Eye Lotion	1
C30-45 Alkyl Dimethicone	03F - Mascara	1
C30-45 Alkyl Dimethicone	05A - Hair Conditioner	3
C30-45 Alkyl Dimethicone	07A - Blushers (All Types)	2
C30-45 Alkyl Dimethicone	07E - Lipstick	35
C30-45 Alkyl Dimethicone	07I - Other Makeup Preparations	4
C30-45 Alkyl Dimethicone	12C - Face and Neck (Exc Shave)	2
C30-45 Alkyl Dimethicone	12F - Moisturizing	1
C30-45 Alkyl Methicone; Total Uses: 51		
C30-45 Alkyl Methicone	03A - Eyebrow Pencil	3
C30-45 Alkyl Methicone	03B - Eyeliner	2
C30-45 Alkyl Methicone	03D - Eye Lotion	2
C30-45 Alkyl Methicone	03E - Eye Makeup Remover	1
C30-45 Alkyl Methicone	03F - Mascara	1
C30-45 Alkyl Methicone	05G - Tonics, Dressings, and Other Hair Grooming Aids	2
C30-45 Alkyl Methicone	07A - Blushers (All Types)	1
C30-45 Alkyl Methicone	07C - Foundations	1
C30-45 Alkyl Methicone	07E - Lipstick	8
C30-45 Alkyl Methicone	07F - Makeup Bases	1
C30-45 Alkyl Methicone	07I - Other Makeup Preparations	1

C30-45 Alkyl Methicone	08G - Other Manicuring Preparations	1
C30-45 Alkyl Methicone	12B - Depilatories	21
C30-45 Alkyl Methicone	12D - Body and Hand (Exc Shave)	1
C30-45 Alkyl Methicone	12F - Moisturizing	3
C30-45 Alkyl Methicone	12J - Other Skin Care Preps	1
C30-45 Alkyl Methicone	13A- Suntan Gels, Creams, and Liquids	1
Caprylyl Methicone; Total Uses: 183		
Caprylyl Methicone	03B - Eyeliner	7
Caprylyl Methicone	03C - Eye Shadow	31
Caprylyl Methicone	03D - Eye Lotion	1
Caprylyl Methicone	03G - Other Eye Makeup Preparations	11
Caprylyl Methicone	05A - Hair Conditioner	1
Caprylyl Methicone	05B - Hair Spray (Aerosol Fixatives)	3
Caprylyl Methicone	05F - Shampoos (Non-Coloring)	1
Caprylyl Methicone	05G - Tonics, Dressings, and Other Hair Grooming Aids	3
Caprylyl Methicone	05I - Other Hair Preparations	2
Caprylyl Methicone	07B - Face Powders	6
Caprylyl Methicone	07C- Foundations	8
Caprylyl Methicone	07E - Lipstick	20
Caprylyl Methicone	07F - Makeup Bases	2
Caprylyl Methicone	07H - Makeup Fixatives	3
Caprylyl Methicone	07I - Other Makeup Preparations	9
Caprylyl Methicone	08C - Nail Creams and Lotions	1
Caprylyl Methicone	11G - Other Shaving Preparation Products	1
Caprylyl Methicone	12A - Cleansing	1

Caprylyl Methicone	12C - Face and Neck (Exc Shave)	22
Caprylyl Methicone	12D -Body and Hand (Exc Shave)	7
Caprylyl Methicone	12F - Moisturizing	27
Caprylyl Methicone	12G - Night	8
Caprylyl Methicone	12J - Other Skin Care Preps	6
Caprylyl Methicone	13A - Suntan Gels, Creams, and Liquids	2
Cetearyl Methicone; Total Uses: 9		
Cetearyl Methicone	01B - Baby Lotions, Oils, Powders, and Creams	1
Cetearyl Methicone	03D - Eye Lotion	1
Cetearyl Methicone	12C - Face and Neck (Exc Shave)	2
Cetearyl Methicone	12F - Moisturizing	4
Cetearyl Methicone	12J - Other Skin Care Preps	1
Cetyl Dimethicone; Total Uses: 87		
Cetyl Dimethicone	03B - Eyeliner	2
Cetyl Dimethicone	03C - Eye Shadow	18
Cetyl Dimethicone	03D - Eye Lotion	1
Cetyl Dimethicone	03F- Mascara	2
Cetyl Dimethicone	03G - Other Eye Makeup Preparations	8
Cetyl Dimethicone	05A - Hair Conditioner	1
Cetyl Dimethicone	05G - Tonics, Dressings, and Other Hair Grooming Aids	2
Cetyl Dimethicone	07A - Blushers (All Types)	7
Cetyl Dimethicone	07B - Face Powders	3
Cetyl Dimethicone	07C - Foundations	13
Cetyl Dimethicone	07E - Lipstick	10
Cetyl Dimethicone	07I - Other Makeup Preparations	2
Cetyl Dimethicone	12A - Cleansing	2
Cetyl Dimethicone	12C - Face and Neck (Exc Shave)	4

Cetyl Dimethicone	12D - Body and Hand (Exc Shave)	1
Cetyl Dimethicone	12F - Moisturizing	8
Cetyl Dimethicone	12G - Night	1
Cetyl Dimethicone	12H - Paste Masks (Mud Packs)	1
Cetyl Dimethicone	13A - Suntan Gels, Creams, and Liquids	1
Dimethicone; Total Uses: 7656		
Dimethicone	01B - Baby Lotions, Oils, Powders, and Creams	20
Dimethicone	01C - Other Baby Products	1
Dimethicone	02A - Bath Oils, Tablets, and Salts	2
Dimethicone	02D - Other Bath Preparations	3
Dimethicone	03A - Eyebrow Pencil	20
Dimethicone	03B - Eyeliner	105
Dimethicone	03C - Eye Shadow	744
Dimethicone	03D - Eye Lotion	101
Dimethicone	03E - Eye Makeup Remover	4
Dimethicone	03F - Mascara	50
Dimethicone	03G - Other Eye Makeup Preparations	122
Dimethicone	04B - Perfumes	1
Dimethicone	04E- Other Fragrance Preparation	32
Dimethicone	05A - Hair Conditioner	362
Dimethicone	05B - Hair Spray (Aerosol Fixatives)	13
Dimethicone	05C - Hair Straighteners	9
Dimethicone	05E - Rinses (Non-Coloring)	19
Dimethicone	05F - Shampoos (Non-Coloring)	152
Dimethicone	05G - Tonics, Dressings, and Other Hair Grooming Aids	153
Dimethicone	05H- Wave Sets	4

Dimethicone	05I - Other Hair Preparations	126
Dimethicone	06A - Hair Dyes and Colors (All Types Requiring Caution Statements and Patch Tests)	177
Dimethicone	06B - Hair Tints	3
Dimethicone	06C - Hair Rinses (Coloring)	12
Dimethicone	06G Hair Bleaches	2
Dimethicone	06H - Other Hair Coloring Preparation	7
Dimethicone	07A - Blushers (All Types)	209
Dimethicone	07B - Face Powders	217
Dimethicone	07C - Foundations	255
Dimethicone	07D - Leg and Body Paints	5
Dimethicone	07E - Lipstick	390
Dimethicone	07F - Makeup Bases	48
Dimethicone	07G - Rouges	40
Dimethicone	07H - Makeup Fixatives	9
Dimethicone	07I - Other Makeup Preparations	158
Dimethicone	08A - Basecoats and Undercoats	20
Dimethicone	08B - Cuticle Softeners	2
Dimethicone	08C - Nail Creams and Lotions	3
Dimethicone	08E - Nail Polish and Enamel	119
Dimethicone	08F - Nail Polish and Enamel Removers	2
Dimethicone	08G - Other Manicuring Preparations	26
Dimethicone	09C - Other Oral Hygiene Products	2
Dimethicone	10A - Bath Soaps and Detergents	11
Dimethicone	10B - Deodorants (Underarm)	5
Dimethicone	10E - Other Personal Cleanliness Products	19

Dimethicone	11A - Aftershave Lotion	38
Dimethicone	11B - Beard Softeners	2
Dimethicone	11D - Preshave Lotions (All Types)	1
Dimethicone	11E - Shaving Cream	6
Dimethicone	11G - Other Shaving Preparation Products	11
Dimethicone	12A - Cleansing	72
Dimethicone	12B - Depilatories	1
Dimethicone	12C - Face and Neck (Exc Shave)	622
Dimethicone	12D - Body and Hand (Exc Shave)	484
Dimethicone	12E - Foot Powders and Sprays	1
Dimethicone	12F - Moisturizing	2148
Dimethicone	12G - Night	163
Dimethicone	12H - Paste Masks (Mud Packs)	71
Dimethicone	12I - Skin Fresheners	8
Dimethicone	12J - Other Skin Care Preps	186
Dimethicone	13A - Suntan Gels, Creams, and Liquids	23
Dimethicone	13B - Indoor Tanning Preparations	20
Dimethicone	13C - Other Suntan Preparations	15
Methicone; Total Uses: 579		
Methicone	02A - Bath Oils, Tablets, and Salts	1
Methicone	03A - Eyebrow Pencil	1
Methicone	03B - Eyeliner	14
Methicone	03C - Eye Shadow	88
Methicone	03D - Eye Lotion	3
Methicone	03F - Mascara	6
Methicone	03G - Other Eye Makeup Preparations	14

Methicone	04C - Powders (Dusting and Talcum, Excluding Aftershave Talc)	1
Methicone	05A -Hair Conditioner	3
Methicone	05C - Hair Straighteners	5
Methicone	05F - Shampoos (Non-Coloring)	1
Methicone	06H - Other Hair Coloring Preparation	3
Methicone	07A - Blushers (All Types)	50
Methicone	07B -Face Powders	30
Methicone	07C - Foundations	45
Methicone	07E - Lipstick	232
Methicone	07F - Makeup Bases	3
Methicone	07G - Rouges	24
Methicone	07H - Makeup Fixatives	1
Methicone	07I - Other Makeup Preparations	29
Methicone	08A - Basecoats and Undercoats	2
Methicone	08E - Nail Polish and Enamel	8
Methicone	08G - Other Manicuring Preparations	1
Methicone	10A - Bath Soaps and Detergents	3
Methicone	12C - Face and Neck (Exc Shave)	6
Methicone	12F - Moisturizing	4
Methicone	12J - Other Skin Care Preps	1
Stearoxy Dimethicone; Total Uses: 18		
Stearoxy Dimethicone	03C - Eye Shadow	2
Stearoxy Dimethicone	03F - Mascara	1
Stearoxy Dimethicone	07A - Blushers (All Types)	1
Stearoxy Dimethicone	12A - Cleansing	1
Stearoxy Dimethicone	12C - Face and Neck (Exc Shave)	2
Stearoxy Dimethicone	12D - Body and Hand (Exc Shave)	6

Stearoxy Dimethicone	12F - Moisturizing	4
Stearoxy Dimethicone	12J - Other Skin Care Preps	1
Stearyl Dimethicone; Total Uses: 79		
Stearyl Dimethicone	03A - Eyebrow Pencil	2
Stearyl Dimethicone	03B - Eyeliner	3
Stearyl Dimethicone	03C -Eye Shadow	12
Stearyl Dimethicone	03G - Other Eye Makeup Preparations	1
Stearyl Dimethicone	04E - Other Fragrance Preparation	1
Stearyl Dimethicone	05A - Hair Conditioner	1
Stearyl Dimethicone	05G - Tonics, Dressings, and Other Hair Grooming Aids	1
Stearyl Dimethicone	05I - Other Hair Preparations	2
Stearyl Dimethicone	07A - Blushers (All Types)	16
Stearyl Dimethicone	07B - Face Powders	1
Stearyl Dimethicone	07C - Foundations	4
Stearyl Dimethicone	07E - Lipstick	5
Stearyl Dimethicone	07G - Rouges	1
Stearyl Dimethicone	07I - Other Makeup Preparations	2
Stearyl Dimethicone	12C - Face and Neck (Exc Shave)	6
Stearyl Dimethicone	12D - Body and Hand (Exc Shave)	8
Stearyl Dimethicone	12F - Moisturizing	5
Stearyl Dimethicone	12G - Night	2
Stearyl Dimethicone	12J - Other Skin Care Preps	3
Stearyl Dimethicone	13A - Suntan Gels, Creams, and Liquids	3
Stearyl Methicone; Total Uses: 1		
Stearyl Methicone	07I - Other Makeup Preparations	1
Vinyl Dimethicone; Total Uses: 8		
Vinyl Dimethicone	12C - Face and Neck (Exc Shave)	1
Vinyl Dimethicone	12D - Body and Hand (Exc Shave)	2

Vinyl Dimethicone	12F - Moisturizing	5