Safety Assessment of Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride) as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: May 10, 2019
Panel Date: June 6-7, 2019

The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst, Ivan Boyer, Ph.D., former CIR Toxicologist, and Jinqiu Zhu, Ph.D., Toxicologist.

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Memorandum

To: CIR Expert Panel Members and Liaisons

From: Wilbur Johnson, Jr.
Senior Scientific Analyst

Date: May 10, 2019

Subject: Draft Final Report on Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride)

The Draft Final Report on Polyaminopropyl Biguanide is now ready for review by the Expert Panel; this report was tabled at the December 2017 Expert Panel meeting. At that meeting, the Panel received a commitment from the cosmetics industry for the completion of a 100-person human repeated insult patch test (HRIPT) of a product containing Polyaminopropyl Biguanide. This commitment was made in response to the one of the data needs listed in the Tentative Report (insufficient data conclusion) issued at the September 2017 Panel. Updates have been given to the Panel at several meetings (June and December 2018) since the report was first tabled.

The reason for the insufficient data conclusion that was issued at the September 2017 Panel meeting was two-fold:

1. HRIPT on Polyaminopropyl Biguanide involving a diverse population (i.e., with a range of Fitzpatrick skin types) of 100 subjects tested with a dose of 1000 µg/cm^2 (and recommend to test at 500 µg/cm^2 as well), and
2. Consumer use data on pump and propellant hair sprays, for use in determining the extent of exposure to Polyaminopropyl Biguanide during product use.

To date, CIR has received the results of the HRIPT (*polyam062019data1*), in which 108 subjects were tested with 0.2% Polyaminopropyl Biguanide (in distilled water; 750 µg/cm^2), but it has not received consumer use data on pump and propellant hair sprays (a remaining insufficiency confirmed by the Panel at the December 2018 meeting). A revised no-expected-sensitization-induction-level (NESIL; memorandum and worksheet included: *polyam062019data2 and polyam062019data3*, respectively) that is based on this HRIPT was also provided. Because a revised NESIL has been provided, the QRA worksheet with the NESIL that was received initially (*polyam062019data4*) is also included so that the Panel can compare the differences. These data are attached for the Panel's review.

The attached Draft Final Report (*polyam062019rep*) has been updated to include the new HRIPT and updated NESIL that were provided by industry, as well as 2019 VCRP data (*polyam062019fda*); these data are highlighted in the report. (There were no significant changes in frequency of use.) Additionally, comments that were received from the Council prior to the June 2018 (*polyam062019pcpc1*) and December 2018 Panel meetings (*polyam062019pcpc2*) are attached and have been addressed.

Also included in this package for your review are the CIR report history (*polyam062019hist*), flow chart (*polyam062019flow*), literature search strategy (*polyam062019strat*), ingredient data profile (*polyam062019prof*), and minutes from prior Panel meetings (*polyam062019min*).

After consideration of the Draft Final Report, and consideration of the data that were submitted as well as the data need that has not been fulfilled, the Panel should determine whether a Final Report with an insufficient data conclusion should be issued at this meeting. The Panel may also consider issuing a split conclusion, based on the data received. (In that case, a revised Tentative Report should be issued for public comment.) It should be noted that if a Final Report with an insufficient data conclusion is issued at this meeting, interested parties will have 2 years to satisfactorily fill the data gap before the conclusion is categorized as "Use Not Supported by the Data and Information Submitted to the CIR."

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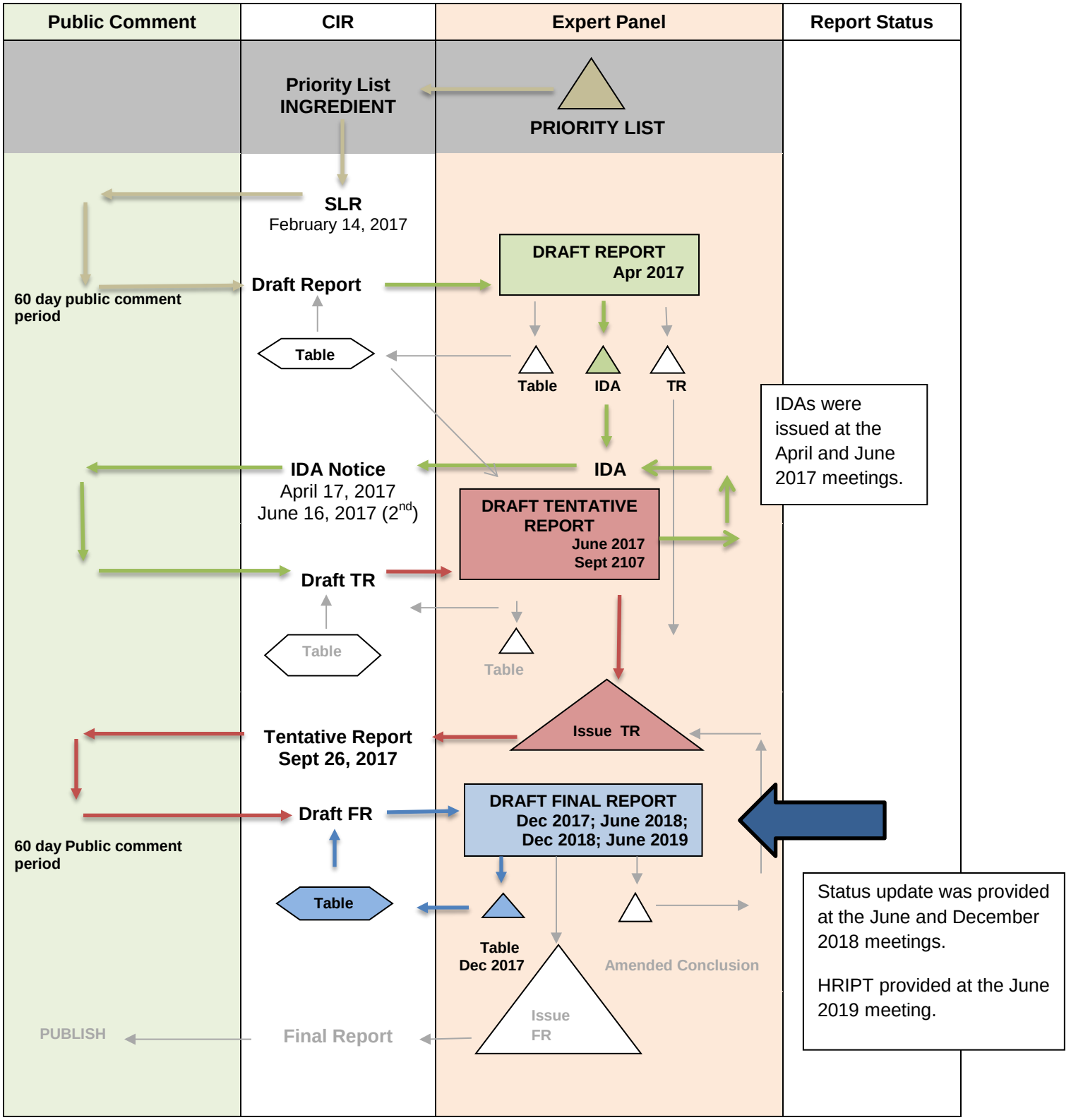
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Polyaminopropyl Biguanide (i.e., polyhexamethylene biguanide hydrochloride)

MEETING June 2019



CIR History of:

Poloyaminopropyl Biguanide

A Scientific Literature Review (SLR) on Polyaminopropyl Biguanide was issued on February 13, 2017.

Draft Report, Teams/Panel: April 10-11, 2017

The following ingredient data that were submitted by the Council have been added to the Draft Report: Use concentration data, Supplier comments on the identity of Polyaminopropyl Biguanide, and a Cosmetics Europe Dossier on the safety of Polyaminopropyl Biguanide. Comments that were received from the Council (*polyam042017pcpc*) have also been incorporated.

An Insufficient Data Announcement (IDA) with the following data requests was issued:

(1) Skin sensitization data to determine the no-effect-level (i.e., threshold) for Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride)-induced sensitization
(2) Data needed to evaluate anaphylactic reactions to Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride) in case studies
(3) Data from Korean studies on lung injury/mortalities attributable to exposure to a disinfectant (polyhexamethylene guanidine phosphate) used in humidifiers

Draft Tentative Report, Teams/Panel: June 12-13, 2017

In response to the IDA that was issued, the following data were received from the Council: (1) Data summaries from the Cosmetics Europe Consortium (relating to skin sensitization potential) and (2) Human repeated insult patch test (HRIPT) on a neck cream containing 0.2% Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride). The studies summarized in the Cosmetics Europe Consortium data submission are not new data, and were included in the Draft Report that was reviewed at the April 2017 Panel meeting.

Regarding item #2 of the IDA, the primary references (in published literature) for the 2 case studies (referenced in Draft Tentative Report) relating to anaphylactic reactions to the hospital disinfectant Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride) after surgical wound exposure were received. Regarding item #3 of the IDA, the 3 Korean studies relating to (polyhexamethylene guanidine phosphate/polyhexamethylene guanidine inhalation exposure-related lung injury/mortalities previously provided by the Council are summarized in the report text (enclosed in borders).

An Insufficient Data Announcement (IDA) with the following data requests was issued at the June 12-13, 2017 Expert Panel meeting:

- Calculation of a margin of safety (MOS) for Polyaminopropyl Biguanide inhalation exposure, using exposure data from the short-term (28 days) rat inhalation toxicity study and current use concentration data on Polyaminopropyl Biguanide in hair sprays, both included in the CIR safety assessment.
- Further clarification of urticaria reactions reported in SCCS reports on Polyaminopropyl Biguanide.
- Raw data sheets (i.e., individual scores during induction and challenge phases) on subjects evaluated in the HRIPT on a product containing 0.2% Polyaminopropyl Biguanide, that was provided by the Council.
- A dermal sensitization quantitative risk assessment (QRA) for Polyaminopropyl Biguanide.

Additionally, industry is encouraged to provide any available HRIPT data that can yield a more refined no-expected-sensitization- induction-level (NESIL); the current NESIL, at 25µg/cm^2, is likely to be overly conservative for use in the QRA.

Furthermore, at the meeting, the Council informed the Panel that they will provide CIR with a corrected HRIPT summary and a corrected concentration of use table.

Draft Tentative Report, Teams/Panel: September 11-12, 2017

Responses to the IDA were received. The MOS calculation for Polyaminopropyl Biguanide inhalation was completed by the CIR staff, and is included under the Risk Assessment Subheading in the Short-Term Toxicity Studies section of the report. Given the Panel's concern relating to contact urticaria, the 3 case reports in the published literature that have been identified as relevant

to an evaluation of contact urticaria potential (Kautz et al., 2010; Creytens et al., 2014; Goossens, 2016) have been placed under the Contact Urticaria subheading in the section on Case Reports. Because the raw data sheets from the HRIPT on a product containing 0.2% Polyaminopropyl Biguanide were included in a previous Council data submission, this study is available for the Panel's further evaluation. More recent use concentration data were received from the Council, and these data are also available for the Panel's evaluation . A corrected summary of the HRIPT on a leave-on product containing 0.5% Polyaminopropyl Biguanide (previously provided by the Council) was also received. It was determined that the product tested in this study was actually a leave-on product that contained 0.1% Polyaminopropyl Biguanide, and the corrected HRIPT summary is available for the Panel's evaluation.

To date, a dermal sensitization QRA has not been received from the Council, and the same is true for any additional available HRIPT data that can yield a more refined NESIL.

Comments relating to the inhalation toxicity of polyhexamethylene guanidine phosphate (PHMG) that were received from Women's Voices For The Earth (WVE) are available for the Panel's evaluation. In these comments, the "discrepancy of professional opinion" with respect to how similar PHMG and Polyaminopropyl Biguanide are was noted and CIR was made aware of the following 3 publications: a review article on PHMG-induced lung toxicity (Kim et al., 2016**)** and 2 inhalation risk assessments on PHMG (Lee et al., 2012; Lee et al., 2013).

The Panel issued a tentative report with a conclusion stating that the available data are insufficient to make a determination that Polyaminopropyl Biguanide is safe under the intended conditions of use in cosmetic formulations. The data that are needed to complete the safety assessment of this ingredient are:

- HRIPT on Polyaminopropyl Biguanide involving a diverse population (i.e., with a range of Fitzpatrick skin types) of 100 subjects tested with a dose of 1,000 μg/cm^2 (and recommend to test at 500 μg/cm^2 as well)
- Consumer use data on pump and propellant hair sprays, for use in estimating the extent of exposure to Polyaminopropyl Biguanide during spray product use

In response to a previous IDA, a spray model and a no observed adverse effect concentration (NOAEC) were used to calculate a margin of safety (MOS). MOS values for both pump hair sprays and propellant hair sprays were calculated. In reviewing this risk assessment, the Panel noted that the exposure scenario (e.g., sprayed over 6 hours) in one of the underlying experimental studies was not representative of pump and propellant hair spray product use. Thereby, consumer use data on these product types are needed to determine a dose, if the safe use of this ingredient is to be determined for products that are intended to be sprayed. However, this ingredient might not actually be in use in products that are intended to be sprayed. Indeed, one supplier submitted a comment that their company would not consider using this ingredient in such applications.

A quantitative risk assessment (QRA) yielded a no expected sensitization induction level (NESIL) of 1000 μg/cm^2, which theoretically supports the use of this ingredient at concentrations of ≤ 0.1%. However, the Panel noted that the HRIPT study utilized to support this NESIL may not be adequately diverse, and suggested that an HRIPT (> 100 subjects) on a more diverse study population at a dose of 500 and 1,000 μg/cm^2 is needed to derive an acceptable NESIL.

The Panel noted the contact urticaria potential of Polyaminopropyl Biguanide, but determined that this would not be an issue in relation to cosmetic product applications after considering that contact urticaria was observed under the conditions of burn dressings on severely damaged skin. It was also determined that the skin irritation potential of Polyaminopropyl Biguanide at cosmetic use concentrations is not a concern, based on the studies in the assessment.

Draft Final Report, Teams/Panel: December 4-5, 2017

Comments that were received from the Council on October 23, 2017 have been addressed. To date, CIR has not received the data that the Panel needs (stated in report Discussion) in order to arrive at a conclusion on the safety of Polyaminopropyl Biguanide in cosmetic products.

The draft final report was tabled in response to a commitment from the cosmetics industry to complete a 100-person human repeated insult patch test of a product containing Polyaminopropyl Biguanide. The task force that will be overseeing this project is being formed, and the Panel will receive ongoing updates relating to this project. The Panel requested that a progress report be given at the March 2018 Panel meeting. Statements relating to the Panel's

discussion on Polyaminopropyl Biguanide and the data that are needed for completion of this safety assessment are included below.

In response to a previous IDA, a spray model and a no observed adverse effect concentration (NOAEC) were used to calculate a margin of safety (MOS). MOS values for both pump hair sprays and propellant hair sprays were calculated. In reviewing this risk assessment, the Panel noted that the exposure scenario (e.g., sprayed over 6 hours) in one of the underlying experimental studies was not representative of pump and propellant hair spray product use. Thereby, consumer use data on these product types are needed to determine a dose, if the safe use of this ingredient is to be determined for products that are intended to be sprayed. However, this ingredient might not actually be in use in products that are intended to be sprayed. Indeed, one supplier submitted a comment that their company would not consider using this ingredient in such applications.

A quantitative risk assessment (QRA) yielded a no expected sensitization induction level (NESIL) of 1000 μg/cm^2, which theoretically supports the use of this ingredient at concentrations of ≤ 0.1%. However, the Panel noted that the HRIPT study utilized to support this NESIL may not be adequately diverse, and suggested that an HRIPT (> 100 subjects) on a more diverse study population at a dose of 500 and 1000 μg/cm^2 is needed to derive an acceptable NESIL.

A letter expressing concern about the inhalation toxicity potential of Polyaminopropyl Biguanide was received from Women's Voices for the Earth (WVE) prior to this Panel meeting. According to this communication, the results of an internet search yielded a number of cosmetic products whereby inhalation is a route of exposure. These products were not identified specifically in 2017 FDA Voluntary Cosmetic Registration Program (VCRP) data on Polyaminopropyl Biguanide, however, CIR indicated in the use table that some of the product types reported to the VCRP may be sprays or powders, but it is not known if they are sprays or powders. The CIR Executive Director will develop an appropriate response to WVE's concerns.

Draft Final Report, Teams/Panel: June 4-5, 2018

The draft final report has been updated to include 2018 FDA VCRP data. Comments on the draft final report that were received from the Council on November 27, 2017 will be addressed.

The Panel tabled the draft final report, pending receipt of the following data that are needed for completion of this safety assessment:

• Human repeated insult patch test (HRIPT) on Polyaminopropyl Biguanide involving a diverse population (i.e., one with a range of Fitzpatrick skin types) of 100 subjects tested with doses of 500 μg/cm2 and of 1,000 μg/cm2
• Consumer use data on pump and propellant hair sprays, for use in determining the extent of exposure to Polyaminopropyl Biguanide during product use

The decision to table the safety assessment was based on an oral commitment from the Personal Care Products Council (at this meeting) to provide these data. The expectation is that the data will be made available this winter or early in 2019.

The following rationale for requesting the HRIPT was stated in the announcement of the September 2017 Panel meeting results, and, as determined by the Panel, remains valid: The QRA for contact dermatitis with Polyaminopropyl Biguanide in cosmetics yielded a no expected sensitization induction level (NESIL) of 1,000 μg/cm2, which supports the use of this ingredient at concentrations of ≤ 0.1%. Among the human data that were used to derive the NESIL was an HRIPT involving 26 subjects tested with 1% Polyaminopropyl Biguanide at a dose of 1,000 μg/cm2, the highest non-sensitizing dose in relation to all of the HRIPT data that were considered. The Panel noted the small subject population in this HRIPT (≥ 100 subjects usually preferred). Furthermore, in an HRIPT on a neck cream containing 0.2% Polyaminopropyl Biguanide (dose = 100 μg/cm2) that involved more than 100 subjects, faint, pink reactions were observed at various times during challenge or during induction and the skin types evaluated were not sufficiently diverse. Based on these observations, the Panel suggested that the NESIL of 1,000 μg/cm2 may not be correct and determined that an HRIPT (100 subjects) on Polyaminopropyl Biguanide at doses of 500 and 1,000 μg/cm2 is needed.

Similarly, the following rationale for requesting consumer use data was also announced previously and, as determined by the Panel, remains valid: The ConsExpo Web Spray Model (used to estimate the inhalation exposure concentrations of Polyaminopropyl Biguanide) and a no observed adverse effect concentration (NOAEC) (from a 28-day inhalation study in which rats were exposed, nose only, to Polyaminopropyl Biguanide in an aerosolized water solution (6 h/day, 5 days/week)) were used in the margin of safety (MOS) calculations. MOS values for pump hair sprays (MOS = 11) and propellant hair sprays (MOS = 200) were calculated. Exposure concentrations that would yield an MOS of 100 for propellant and pump hair sprays were also calculated. After reviewing this risk assessment, the Panel noted that the exposure scenario in the 28-day inhalation study is not representative of pump and propellant hair spray product use and determined that consumer use data on these product types are needed. Furthermore, at this meeting, the Panel emphasized their concern over multiple exposures (as well as the duration of exposure) to cosmetic products containing Polyaminopropyl Biguanide daily, whereby inhalation is a potential route of exposure. Also, in the absence of consumer use data, the Panel speculated that brief inhalation exposure to these products would not be a major concern. The Panel agreed that the consumer use data would be needed in order to accurately calculate an inhalation MOS (using the exposure dose).

Draft Final Report, Teams/Panel: December 3-4, 2018

The Draft Final Report has been updated to include a published case report (Jaque and DeKoven, 2017) as well as the following published data on Polyaminopropyl Biguanide (from Chowdhury et al. 2018): absorption, distribution and excretion; short-term oral toxicity; and carcinogenicity + mode of action for tumor formation. Additionally, comments on the Draft Final Report that were received from the Council on May 30, 2018 have been addressed.

To date, CIR has not received any updates regarding the status of the HRIPT or the availability of consumer use data on pump and propellant hair sprays.

The draft final report on Polyaminopropyl Biguanide was tabled at the June 2018 meeting, pending the completion and subsequent availability of the human repeated insult patch test (HRIPT) that the Council agreed to provide. However, an additional data insufficiency determined by the Panel remained:

- Consumer use data on pump and propellant hair sprays, for use in determining the extent of exposure to Polyaminopropyl Biguanide during product use

Thus, a strategy memo was issued at this meeting, to provide the Panel with an opportunity to review, in detail, the exposure parameters that are associated with pump and propellant spray use with this ingredient. Upon completion of this review, the Panel confirmed that the consumer use data are yet insufficient to accurately calculate an inhalation margin of safety.

Draft Final Report, Teams/Panel: June 6-7, 2019

To date, CIR has received the results of an HRIPT in which 108 subjects were tested with 0.2% Polyaminopropyl Biguanide (in distilled water), but has not received consumer use data on pump and propellant hair sprays. A revised no expected sensitization induction level (NESIL; worksheet and memorandum included that is based on this HRIPT was also provided.

Polyaminopropyl Biguanide Data Profile for April 8-9, 2019 Panel - Wilbur Johnson

			Dermal Penetration			Nail Penetration	Penetration Enhancement	ADME					Acute Toxicity			Short-Term Toxicity	Sub-Chronic Toxicity	Chronic Toxicity	DART		Genotoxicity	Carcinogenicity	Other Relevant Studies		Dermal Irritation*	Dermal Sensitization*/ Phototoxicity*		Ocular Irritation *		Clinical Studies	Case Reports		Epidemiology Studies
			In Vivo -Animal	In Vitro-Human	In Vivo-Human	In Vitro-Human	In Vitro-Animal	In Vitro-Human Dermal	Animal-Dermal	Animal-Oral	Animal-IV	Human-Oral	Animal-Dermal	Animal-Oral	Animal-Inhalation	Animal	Animal	Animal	In Vitro	In Vivo	In Vitro/In Vivo	In Vivo/In Vivo	In Vitro	In Vivo-Animal	Animal/Human	Animal	Human	In Vitro	Animal/Human	Human-Dermal/Oral	Human-Dermal	Human-Oral	Human
Polyaminopropyl Biguanide				**X**						**X**			**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X/X**	**X/X**			**X/X**	**X/X**	**X/X**		**X/X**	X/0	X		

X = data; 0 = no data*

[Polyaminopropyl Biguanide (11/09/2016 & 11/14/2016; Updated on 3/08/2019)

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	FEMA	ECETOC
Polyaminopropyl Biguanide	133029-32-0 32289-58-0	1/1	18/162	3/126	3/11	No	Yes	No Dossier	No	No	No	No	No	No	No	No	No	No
Polyhexamethylene Biguanide	28757-47-3	1/1	8/84	13/370	4/99	no	Yes	No Dossier	No	No	Yes	Yes	1/19	1/4	0/2	No	No	No

Search Strategy

[*document search strategy used for SciFinder, PubMed, and Toxnet*]

[*identify total # of hits /# hits that were useful or examined for usefulness*]

LINKS

InfoBase (self-reminder that this info has been accessed; not a public website) - http://www.personalcarecouncil.org/science-safety/line-infobase
ScfFinder (usually a combined search for all ingredients in report; list # of this/# useful) - https://scifinder.cas.org/scifinder
PubMed (usually a combined search for all ingredients in report; list # of this/# useful) - http://www.ncbi.nlm.nih.gov/pubmed
Toxnet databases (usually a combined search for all ingredients in report; list # of this/# useful) – https://toxnet.nlm.nih.gov/ (includes Toxline; HSDB; ChemIDPlus; DAR; IRIS; CCRIS; CPDB; GENE-TOX)

FDA databases – http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm (CFR); then,
list of all databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm; then,
http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true (EAFUS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm (GRAS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm (SCOGS database);
http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives (indirect food additives list);
http://www.fda.gov/Drugs/InformationOnDrugs/default.htm (drug approvals and database);
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf (OTC ingredient list);
http://www.accessdata.fda.gov/scripts/cder/iig/ (inactive ingredients approved for drugs)

EU (European Union); check CosIng (cosmetic ingredient database) for restrictions and SCCS (Scientific Committee for Consumer Safety) opinions - http://ec.europa.eu/growth/tools-databases/cosing/
ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
OECD SIDS documents (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/
NTIS (National Technical Information Service) - http://www.ntis.gov/
NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/ (FAO);
FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
Web – perform general search; may find technical data sheets, published reports, etc
ECETOC (European Center for Ecotoxicology and Toxicology Database) - http://www.ecetoc.org/

Day 1 of the April 10-11, 2017 CIR Expert Panel Meeting – Dr. Belsito's Team

Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride)

DR. BELSITO: Okay; okey doke. So, then, we're moving on to polyaminopropyl biguanide. There's a lot of data there. I wonder if it all comes from use, in pills, and

(inaudible). So this is our first time we're looking at this preservative. I think it's important to look at because Europe is going to regulate it, and we should be on board too. So, the original opinion was a limit of.3, and then, I think, there were some people who wanted to get rid of it completely, but the SCCS came in with a revised opinion in Europe; I'm talking about a.1. There's been some confusion about its name. The ingredient is polyaminopropyl biguanide, correct, Bart?

DR. HELDRETH: Yes.

DR. BELSITO: That's the cosmetic ingredient; and the chemical is polyhexamethylene biguanide?

DR. HELDRETH: Yes; the hydrochloride salt.

DR. BELSITO: Right, hydrochloride salt; but it's the same thing. So, we've been asked to look at all that data and decide where we are with it. There was a ton of data on this, and I don't know if we just want to go through our comments on the report first. But on page 11, Wilbur, at the bottom of the page, the paragraph, what is wINCI monograph?

DR. HELDRETH: So, that is the council provides info base that we used to look through the dictionary, but there's also a publicly available one that anybody can get access to if they pay the fee, and that's called wINCI.

DR. LIEBLER: I thought it was a typo when I struck it out.

MR. ANSELL: No, wINCI, like Wikipedia.

DR. LIEBLER: So, we need to save the wINCI, okay; I can see that.

DR. BELSITO: And then I had a question for everyone about the impurities on PDF, page 12; any of those jump out to you? I mean, there are a lot of things like hexans and things, cyanos?

GROUP: No.

DR. KLAASSEN: In regard to the chemistry here in the -- way in the beginning, it talks about this problem in South Korea and it says --

DR. BELSITO: What page are you on, Curt?

DR. KLAASSEN: Actually, the absolute first page, kind of the preface, the memoranda --

DR. SNYDER: The memo from Wilbur.

DR. LIEBLER: He's looking at the memo from Wilbur?

DR. KLAASSEN: Yeah; and it says in here that this compound that we're looking at is the hydrochloride, and then it says that the phosphates are different chemicals. How true is that? I mean, yes it is; but, biologically are they that different?

DR. HELDRETH: That was, actually, our point was to put that question to all of you. That data on the phosphate was submitted to us in regard to this report. We weren't sure of the relevance of it; so, Wilbur was posing that question to you all to decide if that data was useful for looking at the hydrochloride salt.

DR. KLAASSEN: I would think that it would be; that's why I'm bringing it up.

DR. LIEBLER: Right; I agree. I mean, the chemical biological driver here is going to be the organic piece, and either the chloride or phosphate, just, you know, counter anions in salts; and so, I would think that unless there's some unanticipated difference in the absorption or distribution of these molecules -- which I don't think there would be -- because they disassociate -- then I think that the data from the PHMG phosphate should be considered in our report.

DR. KLAASSEN: And the scientific significance of this phosphate in Korea is huge in that it's been added to water vapor-type things, and there've been a number of children died from it in the last couple of years; and, in fact, there is a toxicologist that's in prison right now because someone interpreted what he wrote in a manuscript as different from what he really said.

Nobody can get him out of prison; so, I think as people look at this -- not that it's identical as far as -- but I think we need to put this story in here because somebody's going to look at this and -- like we're not aware of it.

DR. BELSITO: What happened? This guy was interpreted as advocating that this material be added to water?

DR. KLAASSEN: Well, no. It had been --

DR. BELSITO: Because it's used as like a pool and - -

DR. SNYDER: Bactericide.

DR. BELSITO: Yeah, bactericide to replace percelphates that people are allergic to; Babaquel is, I think, the trade name.

DR. KLAASSEN: And this was added -- I don't know the whole story here. I wrote a letter for him to try to help to get him out of prison -- but in South Korea, they were adding it, you know, like you have for children, a vaporizer?

DR. BELSITO: Oh, yeah, a steam vaporizer for like asthma, or whatever.

DR. KLAASSEN: Yeah; something like that; and they were putting this chemical in there and children were dying; and then they had people testify and things, and somehow since he had published something and he said, you know, under these conditions, well they didn't -- the court doesn't understand science, and meanwhile he's sitting in prison -- I don't know the whole story. But, I mean, it has gone so far that there have been numerous children that have died.

DR. LIEBLER: I'd like to see the papers. I haven't seen those; but it doesn't make much sense because this molecule is not going to be volatile unless it somehow gets into droplets that are -- I don't know --

DR. BOYER: Like a vaporizer.

DR. LIEBLER: Yeah, but, so, I'd like to see the --

DR. KLAASSEN: Yeah; no; I agree.

DR. LIEBLER: -- because I'm not sure if we'd be able to draw a conclusion that this substance, per se, is

(inaudible); I'd like to look at the data.

DR. KLAASSEN: That's all I'm saying is I think we should look at this because someone else might look at it through those eyes, and if we didn't mention it -- and maybe you know more about than I do.

DR. BOYER: No, I don't; but it could, I'm speculating, I'm imaging it's these cool midst vaporizers that basically aerosolize the water, so you're not getting that kind of, just deletion of high heat.

DR. BELSITO: Right; I see, sort of more aggressive at forming midst droplets, yeah.

DR. BOYER: Right.

DR. LIEBLER: Well, I think the argument that these are chemically dissimilar doesn't wash; and so, we should consider the data on this as well as part of this report.

DR. JOHNSON: One question that I have, are you saying that polyhexamethylene guanidine and polyaminopropyl biguanide are one in the same, because that name is slightly different?

DR. BELSITO: Chemically, not.

DR. JOHNSON: Not?

DR. BELSITO: The problem is this polyaminopropyl biguanide is the inky, right; and it's chemically wrong, but it's the inky name, so it's what we have. So, but the name of this phosphate is what it is, apparently; and so it is -- even though it has a different name than the inky name, it's the same structure, except for the counter anion.

DR. JOHNSON: So polyhexamethylene guanide and polyhexamethylene biguanide are, from a biological standpoint, they are the same?

DR. LIEBLER: Right.

DR. BELSITO: They are. I mean, that's the introduction; so, it's the dictionary misnamed this chemical; and this is what the chemical structure really should be called, but that's not what we're going to call it because it's not what it's called in the dictionary.

DR. JOHNSON: Yeah, I was just -- the guanidine versus the biguanide, but

they're basically the same?

DR. BELSITO: Yeah.

DR. JOHNSON: Okay.

DR. LIEBLER: Yeah, I would like to see the papers, and I would like to see the identity of that, of the compound that's implicated in this apparent toxicology confirmed.

DR. BELSITO: Okay.

DR. ANSELL: Yeah, one of the papers says that the disinfected views were actually a combination of a variety of materials. Two of the other papers said something different; but we do think the three papers should be --

DR. LIEBLER: Yeah, I agree.

DR. BELSITO: But if the reports are that iffy about exactly what was in the materials, I think we could mention it and not spend a lot of time; and then dismiss it, and say these reports, you know, add nothing. Let's look at them.

DR. LIEBLER: Let's just see the papers before we draw any conclusions.

DR. KLAASSEN: Right. I don't think it probably will affect the conclusion --

DR. BELSITO: Right.

DR. KLAASSEN: -- what I was suggesting, there probably needs to be a short paragraph about this.

DR. BELSITO: Okay; so, on page 17 of the PDF under carcinogenicity studies there's a dermal that shocked me at first, but I guess it's a non-genotoxic mechanism because if it was genotox, it would automatically be banned in Europe. So, I was wondering what you thought about this, Paul?

DR. SNYDER: Yeah; I read through that pretty carefully, and it's all at near maximum tolerated doses and it has (inaudible) toxicity and secondary changes, so I don't think it's --

DR. BELSITO: Relevant?

DR. SNYDER: -- yeah, I think we've captured it appropriately.

DR. JOHNSON: Which study is this; I'm sorry.

DR. BELSITO: The dermal carcinogenicity study on page 17. I don't think we need to delete it, but we will need for Paul to suggest some comments in the discussion as to why. There is further information later on, obviously, in the genotox section that this affect is not genotoxic. We need an explanation as to why we thought it happened and why it doesn't bother us using this material in cosmetics. So, Paul, you'll think about?

DR. SNYDER: Yes.

DR. ANSELL: Yeah; that study is discussed in the dossier.

DR. BELSITO: Yeah; okay. So, then on other relevant study effects on lung cells. This is going to be coming up under the respiratory boilerplate and the large letter we got from Missoula, Montana -- I forget what is the - -

DR. LIEBLER: WVE.

DR. BELSITO: -- the Women's for --

DR. SNYDER: Women's Voices for the Earth.

DR. BELSITO: Right. Going down to the last paragraph on page 17, effects on lung cells and reactive oxygen generation, and F-count could be activation. It's used in aerosol products, and you don't necessarily have to get down to the alveoli and begin activating all those immune substances, which could go along with the vaporizers and the Korean issues, which I wasn't even aware of until now.

DR. SNYDER: I have a question. Why did the SEC revise their acceptable level in 2016 from.3 to.1?

DR. BELSITO: We're going to discuss that under sensitization. We don't have a noel for sensitization.

DR. SNYDER: Okay; so, it was all sensitization; it wasn't anything else?

DR. BELSITO: I think so.

DR. SNYDER: That's what I was worried about; okay. I had a sensitization question mark.

DR. BELSITO: My understanding was that they, actually, there was a movement to ban it because of the carcinogenicity study, and then the SEC has, actually, if you

read the entire report, you see they actually talk about the importance of biocides; and then they went through all the data, they looked at it pretty thoroughly, and they came up with the conclusion that the issue is sensitization.

DR. SNYDER: And they banned it in the spray -- aerosol use.

DR. BELSITO: I don't think so.

DR. SNYDER: I thought it was -- was it banned in aerosol use in cosmetics, and.1 percent for all other uses, or is that (inaudible)?

DR. BELSITO: I think we'll have to look up the year. It's in the report.

DR. JOHNSON: They expressed the need for inhalation toxicity data.

DR. BELSITO: Okay; so maybe they --

DR. JOHNSON: The evaluation (inaudible).

DR. BELSITO: Maybe that's what it is. So, it could be based upon this too. I didn't --

DR. JOHNSON: Well, also, they completed two additional skin penetration studies; you know, one at 0.3 percent and one at 0.1 percent, and seemed as though they were leaning in the direction of 0.1 percent based upon skin penetration data.

DR. BELSITO: I got the sense from my read of it -- and we'll get to it when we talk about sensitization. So, what they did is they sensitized people at 2 percent; and then they took those people who were sensitized and they tested them; and at.5 percent they still got a significant number of people reacting strongly; and then at.1 percent they had, I think, two people with very weak reactions; and they said, okay, if we take sensitized people and we can barely elicit a reaction at.1 percent, then.1 percent should be okay not to induce new sensitization. But we do not have a shown level at which you cannot induce new sensitization. So, that will be a question moving forward. First of all, you know, if we go safe as used, it's up to.5 in this country, right?

DR. SNYDER: Yes.

DR. BELSITO: So, I mean, that's going to be a rather high dose; and then if we don't go safe as used, where do we go?

DR. ANSELL: We actually don't think it is.5. We think that report was 20 percent active.

DR. SNYDER: So, it's.1?

DR. ANSELL: Yes.

DR. SNYDER: So, it's 20 percent applied
(inaudible)?

DR. ANSELL: Yeah; when we get to that level of detail.

DR. BELSITO: Okay; when we get there. So, we're dealing with lung right now. I need some comments.

DR. LIEBLER: Yeah. I thought I was going to comment on your question about effect on lung cells; so, we're back to the bottom of PDF 17. So, this is another one of these studies that I hate when they show up in our reports because basically you take some cultured cells, you dump some chemical on them, and then you measure something that there is a assay for and you, you know, the NF-kappa B is the major transcriptional regulator for a whole battery of genes involved in inflammation.

DR. JOHNSON: (Inaudible)

DR. LIEBLER: And there are many things, many, many things -- that trigger activation of the NF-B, and of kappa B, and its downstream genes. And, I think, you know this is 10 to 80 mg/ml of this material on lung cells. You know, I haven't looked at that paper; but, you know, I'm not sure that I would draw any significant inference from it. I mean, I think, it's -- if the conclusion is that this compound induces inflammatory responses by the NF-B signaling pathway, well, just about everything that causes inflammation activates this pathway. So, that's not news; and whether that says that this compound is uniquely toxic or pro-inflammatory, I think, is way too much for stretch based on just one experiment like that.

DR. BELSITO: And I'm just concerned when we clear the rescuable part that this type of inflammatory response will occur if it gets in the epiglottis; if it gets in the upper airway; if it gets in the lower airway, but not the alveoli; and how do we say, okay, I mean -- we can't -- in the aerosols -- and then that gets back to I didn't catch that in the SEC report, I concentrated mainly on the skin part, and skimmed the rest; but if the SECS is still asking for

respiratory data, then how do we clear its aerosol uses because we don't have inhalation toxicity here?

DR. LIEBLER: Right.

DR. BELSITO: This is what we have.

DR. LIEBLER: I would think that if we have a question about respiratory, we need respiratory data. Particularly, in light of this Korean thing; if there's an issue there that we can attach to this chemical. So, but I don't think this study that's cited here on the 85 part anion cells really sheds much light one way or another.

DR. BELSITO: Okay. So, I think that looking at -- I mean, we probably won't clear this at this meeting -- we need all of the data on the Korean studies, and --

DR. LIEBLER: Right.

DR. BELSITO: -- we need to go out and probably try to get some inhalation data on this.

DR. SNYDER: We have some.

DR. JOHNSON: Acute-A, no long term.

DR. SNYDER: Table 8 and 9 is --

DR. BELSITO: But we don't have anything long term, right?

DR. LIEBLER: I understand. I'm just trying to see how long --

DR. BELSITO: Four weeks, no?

DR. JOHNSON: Yeah; just acute and short term toxicity information, tox data.

DR. KLAASSEN: When they did this four-hour exposure, they did have dark red lungs for observing the

(inaudible) which doesn't -- which shows something can go on there; not a very high concentration.

DR. LIEBLER: Well, these are all at near 20 percent.

DR. KLAASSEN: Yeah.

DR. JOHNSON: Did you want the comments relating to the effect on lung cells to be addressed in the discussion?

DR. BELSITO: I don't think we're even there yet, Wilbur. Let's wait for the discussion once we get through all our other points. I think that a lot of that is going to depend upon what we see in the Korean study and if we can get any additional inhalation data because -- what was the longest we had again?

DR. LIEBLER: What I was looking at here -- looks like --

DR. BELSITO: Four weeks, no?

DR. LIEBLER: I don't believe we have that.

DR. KLAASSEN: Inhalation?

DR. LIEBLER: 28 days.

DR. KLAASSEN: Yeah; there is a 28 days in which they determine a no-observed adverse effect concentration of.025 mg/m2.

DR. BELSITO: To bring some area of expertise, but it sounds like a fairly high amount, no?

DR. SNYDER: Yeah; and it looks like it was eliciting irritation to because there was (inaudible), and that's typical upper respiratory response to irritation over a period of time.

DR. BELSITO: So, we know that a very high amount used in an aerosol product could over the long term create issues; but we don't know, even a low (inaudible), which is a problem, no?

DR. SNYDER: Well, this was a 20 percent (inaudible) solution and they targeted the paradynamic size to a rescuable size too, so; and if our formulations aren't rescuable, so, I think, it's going to be complicated.

DR. BELSITO: But, again, my point is that, you know, we're talking about an inflammatory response. It doesn't really need to get down to the (inaudible). We're not talking about something that's going to get absorbed and go through the system. We're talking about something that would cause an inflammatory response in the airway.

DR. SNYDER: So, this was in the larynx region; so - -

DR. BELSITO: Yeah.

DR. ANSELL: Also, not certain -- I only see one generic listing for an aerosol

application and the use concentration is 0.0002.

DR. SNYDER: I have the max spray use as.27.

DR. ANSELL: Yeah, per pump. All good questions.

DR. SNYDER: Yeah; so, I think we just have to flesh it out a little more.

DR. BELSITO: Okay; moving along. So, for respiratory we need the -- I wish I was as (inaudible) with you Dan in how to deal with these comments here. Okay, so, we want the Korean studies, and if there's any other inhalation data out there, would be nice. Anything else, there; and then at some point, we'll have to deal with it in the discussion.

DR. SNYDER: Yeah, we'll have to probably get --

DR. BELSITO: And we have 0.27 in a pump spray, right?

DR. SNYDER: Yes;.5 percent for all others.

DR. BELSITO: Right; okay. So, then we have a dermal study with a non-genotoxic affect. Do we need to ask Ivan to look at margins of exposure because of that --

DR. SNYDER: No, I think we can explain --

DR. BELSITO: -- or do we mention it at all in the discussions?

DR. SNYDER: -- well, I think we have to because if you read it, it appears to be this affect, but it was due to the persistent side of toxicity, it had nothing to do with the chemical's effect on endothelial cells.

DR. BELSITO: Okay; so we don't need --

DR. SNYDER: No. We'll just make sure we have wording in there to address it.

DR. BELSITO: Okay. You'll work on that wording with Tom Slaga?

DR. SNYDER: Yes. And we did get sensitization data, 20 percent in the oil in wave 2.

DR. BELSITO: We got a lot of sensitization data, but, you know, we don't have a noel for sensitization. You know, we know that it sensitizes at 2 percent. That's the lowest concentration; and then we know that if you take up people who are sensitized and you take then back and you patch test them, you can get reactions down to.1 percent. So, or.2 elicitation; can be listed as concentration beginning at.2, I believe. So, I mean, I think that's the basis as to why the Europeans went at.1. They say, okay, you can sensitize at 2 percent; you can elicit at.2; and so, let's go to.1 because everyone agrees that you sensitize at a concentration higher than you elicit. But, we don't have -- I mean, it's not like we used to seeing at Riffen where we have nestles and HRIPTs, and we have part, you know, EC3's and we have hard data that are then confirmed in an HRIPT; we just have data that sensitizes and then we call back a bunch of patients to patch test. I think it's okay, but it's not very scientifically robust.

DR. ANSELL: I think when you look at the dossier there's going to be more relevance. They do have a conclusion that 1 percent did not induce.

DR. BELSITO: I didn't see that -- in the dossier? What page?

DR. ANSELL: It's page 79 of the PDF.

DR. SNYDER: Under what?

DR. BELSITO: It's the SCCS opinion that was added to this.

DR. ANSELL: No; this is the submission to the SCC. This is the cosmetic dossier --

DR. BELSITO: Okay.

DR. ANSELL: -- that was provided. I think this was a way to --

DR. BELSITO: Yeah, I do know. Oh, it's wave 2?

DR. ANSELL: I'm not too sure?

DR. BELSITO: Yeah; it's in the actual one, here.

DR. LIEBLER: Page 79.

DR. BELSITO: Skin and mucus membrane irritation sensitization.

DR. ANSELL: So, it's the summary of reliable tox data.

DR. BELSITO: So, it says that in guinea pig maximization Buehler, threshold concentration for induction to sensitization in guinea pigs is demonstrated to be above 1 percent. But, I didn't see that data.

DR. SNYDER: Above 1 percent, what does that mean?

DR. BELSITO: That means it was 2 percent; but it doesn't say that they did 1

percent and it was negative.

DR. SNYDER: Right; and it was negative, exactly.

DR. BELSITO: I didn't read that as that. The only data I saw was that they did 2 percent, it was positive; and 2 percent is above 1 percent, but, you know, I mean, it's like - -

DR. SNYDER: Well, I mean, we can take the same approach they did, simply the maximum concentration is.5 percent, so we're not anywhere below that, so.

DR. BELSITO: I don't think.5 is safe.

DR. JOHNSON: It's actually 0.2, now.

DR. ANSELL: I think the use of concentration is.1.

DR. JOHNSON: 0.2 is the highest; I mean, based upon what Carol gave us today.

DR. ANSELL: I think what Carol gave you was that the --

DR. HELDRETH: 20 percent of the.5?

DR. ANSELL: --.5 was 20 percent active; so, that would be a fifth; it'll be.1.

DR. JOHNSON: But she had some ranges that, you know, based upon that calculation --

DR. ANSELL: Okay; well, I mean, this is the first time. These are all good questions.

DR. BELSITO: Well, here's what was on our table today, and there's an eye lotion at.2. And, you know, that's a question that's going to come up repeatedly that's so very confusing with these things that aren't supplied at 100 percent, and what are these concentrations we're getting? Are they concentrations of the active, or are they concentrations of the cold product? And then there will be another question I will pose tomorrow, Jay, and this really concerns me and so as does a lot of patch testing. So, when -- if this chemical -- there is a chemical; I'm forgetting which one it is. I think it's the polyurethane sitters supplied in methylisothiazolinone as a preservative in what's given to the manufacturer to make. Do they have to label methylisothiazolinone, or are they labelling only the active? Do you know the answer to that question?

DR. ANSELL: For the raw material, or for the finished (inaudible)?

DR. BELSITO: The raw material comes to them and they're buying chemical X, but chemical X has BHA in it as an antioxidant and methylisothiazolinone is little known as a preservative. Do they have to label the BHA and the methylisothiazolinone?

DR. ANSELL: They don't have to as long as it is not used, as long as it's not effective. If they put into their concentration of the preservative, then it would appear there. But non-functional additives that would come in that way are not required to be labeled.

DR. BELSITO: So, the answer is no; they wouldn't have to necessarily label them.

DR. ANSELL: No; they wouldn't have to.

DR. BELSITO: That's what I thought. Okay; back to this. So, I'm okay going with point one; I'm not okay going with point 2; and even that point one is a rather non- scientific. It's out of the approach that Europe is taking with what's called the minimal elicitation threshold 10 for nickel and chromium and other things that they've restricted. They take people who were sensitized; they bring them back; they patch test them; and they look at how low can you and still have 10 percent of that sensitive population reacting; and at that level, we think it's okay in the general population. I mean, to use that theory, I guess.1 is fine, but I don't see a no-affect level for sensitivity; and I don't think we can fudge this one and say when formulated to be nonsensitizing because it's not going to be added to anything else that we can't control that would cause issues.

DR. SNYDER: I have a moderate to strong sensitizer as low as.2 percent, and so that's not a very big difference to.1 percent. So, I think we need to see if there's any additional data out there. We can see if we have a no-affect level for sensitization.

DR. BELSITO: It would certainly be nice. I mean, again, this is the first time we're looking. We're already asking for some additional inhalation studies or data; we're asking to look at the Korean reports; and I think we can ask for additional sensitization data that would indicate a level which it does not in desensitization.

DR. SNYDER: I think, let's ask, and then we'll know. I think we'll be more scientifically sound than just arbitrarily saying.

DR. ANSELL: Right.

DR. BELSITO: Okay. So, it's no longer used at.3 in eye products. It's been corrected. It's now.2. So, we know that 20 percent can be irritating, and.04 percent is not irritating around the eye, but we don't have anything in between. So, do we want to ask for additional ocular irritation studies at the reported concentration of.2? I mean, we didn't used to ask for them because they're done in animals, but now, you know, there are OCD guidelines for in vitro ocular irritations, so I don't see why we have any concerns about asking for them.

DR. LIEBLER: Yeah, I think even if we had the animal model irritation data at the use concentration, we would probably be able to roll that into a stronger weight of evidence; so, I think we should ask for it.

DR. BELSITO: Okay.

DR. SNYDER: So, I think that probably goes along with the lung things. I think the lung thing is all irritation too. So, we want to --

DR. BELSITO: Now, but if you say the lung thing is all non-exposure of irritation from induced inflammatory side effects, you're right.

DR. SNYDER: I think it's all related irritation. So, I think --

DR. LIEBLER: There are a lot of toxic chemicals that are not what you would think of as inflammatory chemicals that can activate NF-kappa B. I mean, I just remember, and Curt does too, I'm sure, at the SOT meeting there was like an NF-kappa B activation era in the mid-nineties where every kap- toxic chemical that got thrown into any kind of model, it was just a new thing you could measure. So, this study reminded me of that.

DR. SNYDER: It's that there's no biological context?

DR. LIEBLER: Right. I think it's just an observation at this point, but we do have inhalation data that suggests that it is irritating. So, how can we obviate the irritation ocular in the lungs? So, we would probably want to know at what point what concentration we

DR. BELSITO: Mm-hmm; okay.

DR. LIEBLER: -- we don't foresee those affects, so we put those together.

DR. BELSITO: Yeah. So, then, I just wanted to make a comment about, you know, that all of the patch testing studies were done in Europe where this is -- now with Jay's comment, it may not have been used at such a different concentration -- but it may have also, so, none of those patch test study data are coming out of the U.S. Was anyone bothered by the anaphylactic issues with use on damaged skin? I could not get those reports or read them. Can you tell us more about those, Wilbur?

DR. JOHNSON: What page?

DR. BELSITO: Page 20 of the --

DR. SNYDER: Under case reports.

DR. BELSITO: -- two case reports, surgical wound dressing,.2 percent polyaminopropyl biguanide deaths from severe anaphylactic reactions.

DR. JOHNSON: Actually, those studies were in the SCCS report and, I think, that was an unpublished study; but that's, you know, basically all the information that I was able to capture from the SCCS report.

DR. SNYDER: A hospital disinfectant would have lots of other things in it that could be an issue. I'm not certain about the wipes.

DR. BELSITO: That's what I mean, but, you know, it's there looking like it was the biguanide that caused that.

DR. SNYDER: I think we look at those and say that they just have a table that listed everything that was in there and said, any of these were potential.

DR. LIEBLER: One of the references is cited as this NECNAS --

DR. JOHNSON: Yes, I'm sorry, not the SCCS, but the NECNAS report, yes.

DR. LIEBLER: And then there are two publications -- third reference is 35 and 36, that you cite for those. The two cases of anaphylaxis and then the paragraph right after it that also refers to anaphylaxis.

DR. BELSITO: Yeah, it's a German -- that I couldn't access and Columbia Library doesn't subscribe to Allergy either, so I couldn't look at either of those reports.

DR. JOHNSON: If that report is that important then we could, you know, perhaps have that special ordered.

DR. BELSITO: If it's in German, then you'll have to get it translated; but I just don't like the idea of us just - - first of all, you know, as I tell my students, you can read something in an article and you can say that they quoted the paper and that's what they thought the paper said, but unless you actually got the paper and read it, that's not what you report. So, we've, you know, limited polyethylene -- well, I call them burn patients because of renal damage -- I mean, is this an issue where we need to consider -- of course, then we got rid of that -- but, I mean, is this an issue where we need to consider limiting the use of this chemical on individuals who have, you know, severely damaged skin? I don't no.

DR. SNYDER: You want wait for Matt?

DR. LIEBLER: So, we should get copies of both papers, 35 and 36. So, one is in this Swiss journal -- and I wouldn't be surprised if there's an English version of it -- and then the other's an Allergy study; so, that shouldn't be an issue.

DR. BELSITO: Yeah; I know. Okay, so far in the discussion, we're going to have the respiratory boilerplate which is going to have to deal with the inflammatory findings in the lung; we're going to have to deal with the sensitization issue and, hopefully, have that resolved by data that we're going to ask for along with respiratory data.

DR. JOHNSON: Any concentration limit for sensitization?

DR. BELSITO: We're not even going with a conclusion here, Wilbur.

DR. JOHNSON: Oh, no, I don't mean -- I'm just saying with respect to the sensitization data --

DR. BELSITO: Whatever concentration industry wants us to approve up to.

DR. JOHNSON: Okay.

DR. BELSITO: I mean, you know, they need to give us a no-affect level, or a level that they want to use that doesn't have enough (inaudible).

DR. SNYDER: Right now it's.2, based it on eye lotion.

DR. BELSITO: Yeah, right now it's.2. So, if that eye lotion wants.2, they better show us data on.2; --

DR. JOHNSON: Okay.

DR. BELSITO: -- and, particularly, if they want.2, they'd better show us data on the ocular irritation on.2. We want the references 35, 36 on the anaphylaxis. So, we're going insufficient. We would like additional inhalation data at use concentrations; we'd like sensitization at whatever concentration of use they want to use; ocular irritation at whatever concentration they want to use; and we want to review references 35 and 36 in the current report.

DR. SNYDER: So, what dermal absorption data did we have?

DR. JOHNSON: It's in the table on skin penetration.

DR. LIEBLER: Yeah, there are a number of animal studies that doesn't appear to be not very significant to our --

DR. SNYDER: I wouldn't expect it to be. It's a 4,000 molecular weight on average.

DR. LIEBLER: Okay.

DR. BELSITO: So, anything else -- inhalation, sensitization, ocular irritation, and get us references, 35 and 36? And so far in the discussion, we're going to be talking about, obviously, inhalation sensitization; but we're going to also talk about the generous.

DR. JOHNSON: Are there any concerns relating to reproductive and developmental toxicity?

DR. BELSITO: I didn't have any, Paul?

DR. SNYDER: No; I didn't see any. Did you have anything specific in mind, Wilbur?

DR. JOHNSON: Yeah. I know there was a teratogenicity study involving rats and the chemical was classified as teratogenic at an intraperitoneal dose of 10 mg/kg per day.

DR. BELSITO: You okay with that?

DR. LIEBLER: Yeah, that's fine. (Inaudible).

DR. BELSITO: Okay; anything else?

DR. KLAASSEN: Not to be the devil's advocate -- how do we know Tulcid isn't teratogenic?

DR. SNYDER: Well, we have other studies; there a number of studies in Table

12, right?

SPEAKER: Mm-hmm.

DR. JOHNSON: And that value was also a no-observed adverse effect level in mice?

DR. KLAASSEN: Right.

DR. JOHNSON: 10 mg/kg per day?

DR. KLAASSEN: Okay; fine; now we're okay.

DR. SNYDER: Any of them are oral?

DR. JOHNSON: That's why I'm looking. I thought they were all dietary.

DR. LIEBLER: I think the other thing is the IP administration. I think this material doesn't get absorbed very well, if much at all.

DR. SNYDER: No; probably had a raise in pertinetis.

DR. BELSITO: Okay; so, to repeat, so insufficient, we want inhalation data, and then we also want the Korean studies that talked about these tests; we want sensitization on ocular irritation on concentration of use; and we want to review the two reports on anaphylaxis, the current references 35, 36. Anything else?

DR. HELDRETH: I have one thing -- what we had brought up about the identity of the polyhexamethylene guanidine phosphate that's in the Korean papers, do we want to have some further clarification that is really the biguanide and it's not some mono-guanide?

DR. LIEBLER: That's one of the things I'd like to review when I see those papers.

DR. HELDRETH: Because looking through those papers, they all just say polyhexamethlyne guanide phosphate; and even tracking down through the references that they cite, can't find anything that gives you a structure or tells you the CAT's number or anything to verify that they really meant the biguanide.

DR. LIEBLER: So, you could have the guanide, I guess.

DR. HELDRETH: And that was our major rationale, not so much the phosphate salt issue, but that we weren't sure that this really is the ingredient under review.

DR. LIEBLER: Well, we should review the papers and we'll take a look at that, and if that issue can't be resolved, we'll just need to consider that when we consider the importance of those reports to our conclusion, so; but let's see the papers anyway.

DR. KLAASSEN: We could also contact the author.

DR. LIEBLER: Yeah; right; because these are very recent publications.

DR. KLAASSEN: Yeah; these are recent papers.

DR. LIEBLER: Contact the author. I hope it's not the guy in jail.

DR. SNYDER: I hope he doesn't use his one phone call.

DR. KLAASSEN: Rather keep his phone call for his wife.

DR. LIEBLER: (Inaudible).

DR. BELSITO: Oh, God.

DR. KLAASSEN: They've had their fair amount of troubles this year.

DR. JOHNSON: One last question, Dr. Belsito, you said the discussion should have some language relating to the tumor formation that was observed --

DR. BELSITO: Right.

DR. JOHNSON: -- and why we're --

DR. SNYDER: Why we're not concerned; I can insert something in there for you.

DR. JOHNSON: Okay.

DR. KLAASSEN: I mean, if you have a bile side, you're going to expect some toxicities, by definition.

DR. BELSITO: Let me make sure I save this so I don't --

DR. KLAASSEN: In fact, this is pesticide is the reason why there's a fair amount of data.

Day 1 of the April 10-11, 2017 CIR Expert Panel Meeting – Dr. Marks' Team

Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride)

DR. MARKS: So this is a first review of the polyaminopropyl biguanide. And we don't have to ask if ingredients are okay since there's a solo ingredient, so it's okay. But Wilbur, I'll ask you to clarify the chemical names in a minute perhaps. So, Tom, Ron, and Ron, that might be part of what you're asking. Do you have needs for this single ingredient? And this is the first time we've reviewed it.

DR. SLAGA: To me, there's sufficient data.

DR. HILL: I think so too actually.

DR. MARKS: Sufficient. Ron Shank, you're looking with a smirk, I can see. I have okay, but I would set a limit based on sensitization.

DR. SHANK: Well, a limit but, there's data there.

DR. MARKS: Sufficient data. Well, I'm not sure on the sensitization.

DR. SHANK: No.

DR. MARKS: Oh, you want to hear what I say?

DR. SHANK: No, I want to know, you want to set a limit on what chemical?

DR. MARKS: Oh yeah, well that gets into what chemical. The polyaminopropyl biguanide. And you're not quite sure which chemical this is.

DR. SHANK: Well, I found this very hard to read.

DR. MARKS: Okay.

DR. SHANK: And it's not the writer's fault. Let me explain. If understand this correctly, the title compound is polyaminopropyl biguanide. But that's not the chemical that's being used. But that's the name that's being used. Really? Okay? Now let me go farther. You read the search, how it was searched, and both compounds were searched. So what am I reading here? It says will use only the name polyaminopropyl biguanide. No matter what it is. So are all of the data for the PHMB? But it's not called that. It's called PAPB. So I think either we should table this until the dictionary is corrected. But then, all of that labeling and history, the wrong compounds. I think this is very confusing. And I really don't know what I'm reading. On the other hand, dermal penetration of whatever it is, seems to be small. And what stays on the skin seems to be in the epidermis. And it's not a reservoir for circulation. So it's probably okay. But I don't know what it is. Sorry.

DR. MARKS: No, you don't have to apologize. That was my first comment. Wilbur, clarify the chemical names. So you suggest tabling it. Til we clarify what chemical we're really dealing with. Is that? Will you be able to do that Wilbur?

DR. HELDRETH: I can clarify it now.

DR. MARKS: Oh, you can.

DR. GILL: And I would just add that the issue about tabling it, this was added by the panel as a priority, because it is a preservative. And the concern that the European decision might impact that. So if Bart can clarify it for you.

DR. HELDRETH: All right. Much of what Dr. Shank presumed is correct. This ingredient, the ingredient name is polyaminopropyl biguanide. But if you use that as a chemical name, none of that is in the ingredient. And, my understanding, talking with the INCI Committee, and there interaction with the suppliers, nobody's ever been using the chemical polyaminopropyl biguanide as an ingredient. In every case it's been polyhexalmethylene biguanide hydrochloride. And so it's that one ingredient that we're reviewing. And that's the chemical that whoever included tox data on in the report. polyhexalmethylene biguanide hydrochloride. It's right there at the beginning of the chemistry section.

DR. SHANK: Okay. So can the title be changed? So it says polyaminopropyl biguanide parentheses?

DR. HELDRETH: Sure

DR. SHANK: And the other one? Or the other way around? And then explain it in the introduction, as you did, very nicely. But then, everything in the report is referred to, not everything, but a lot of the report, refers to a polyaminopropyl biguanide. But it ain't that.

DR. HELDRETH: I agree. It's extremely confusing. What we've been trying to

do, over the past couple of years, at least, is try to only use the INCI name throughout our documents. And stick with just that one. Instead of using other technical names, or trade names. But just use that strictly. And much still to do on that. I push that we stick with that process and just use the INCI name throughout the report. We can certainly make a title change and put more introductory language in the report, and make those changes. But it is truthful that it's all this PHMB HCL. Is all we're really looking at.

DR. GILL: Is there a plan to change that name?

DR. HELDRETH: I have not heard that there's a plan to change that name. You do have to remember that part of the rationale for not changing a name in the INCI dictionary is because other countries use older versions of our dictionary and if you go and change those names in a country that has very difficult registration systems for bringing a new ingredient, you may severely impact their ability to do business in that country. So making a change on an ingredient like this, that's quite old, and in significant use numbers, could have a profound effect. So, the INCI folks did help us out by making the monograph of the definition in the dictionary more clear that it's just specifically this ingredient. So, if I had to guess, I wouldn't suspect that the name is going to change anytime soon.

DR. MARKS: And again, the chemical name is polyhexal methyl biguanide

DR. HELDRETH: polyhexalmethylene

DR. MARKS: Methylene. Okay.

DR. HELDRETH: Kind of a weird way of saying hexane.

DR. MARKS: Yeah

DR. HELDRETH: But, hexal methyene biguanide hydrochloride. Is our understanding is, from the suppliers, that it's always hydrochloride.

DR. SHANK: Then I would suggest having the title polyamino propyl biguanide. And then in parentheses the hexylmene biguanide.

DR. HELDRETH: We can do that.

MR. JOHNSON: If I might just add, if you look at PDG page 18, under cytotoxicity. The section titled Cytotoxicity and Antimicrobial Activity. Polyhexalmethylene biguanide and polyaminopropyl biguanide are compared. I think that's the only instance in which you actually have data on polyaminopropyl biguanide.

DR. MARKS: Now I'm confused. When you say you have data on both. I thought they were the same.

DR. HELDRETH: So what Wilbur's trying to say here is that, in the paragraph on cytoxicity, the authors are comparing the toxicities of the chemical names.

DR. MARKS: Okay

DR. HELDRETH: Polyaminopropyl biguanide and polyhexalmethylene biguanide. Only the polyhexalmethylene biguanide though is an ingredient. So herein Wilbur laid out those instances where they use the chemical, polyaminopropyl biguanide by calling it PABP. Give it a little bit different of a moniker so that it's as less confusing as can be.

DR. MARKS. Yeah. So, can we say then all the tox data we have in this report is on polyhexalmethylene biguanide, aka INCI name polyaminopropyl biguanide? Because I think, Ron Shank, that was your initial concern is, what were we testing when we read this data.

DR. HELDRETH: That is true except for this instance where they compare.

DR. MARKS: Except for the instance, okay. Okay. With that in mind, now that we've clarified the chemical names. And unless Lillian or Wilma, you have any concerns, I like the title. It includes both names in it. Then the introduction would also clarify that.

DR. BERGFELD: And your discussion perhaps.

DR. MARKS: Yeah, and discussion. But I think right up front, it hopefully will minimize the confusion that could occur. So, with that in mind, as I recall now, we had a fair amount of discussion since Tom. Tom, you were fine with the safety of this?

DR. SLAGA: I didn't say that. It's a very toxic chemical.

DR. MARKS: Oh, I know. It's an irritant and a sensitizer.

DR. SLAGA: You don't get cancer, but you have three feet going up in the air.

(laughter)

DR. MARKS: So now we'll come to the next. Now that we've clarified what the ingredient is we're really looking at here. Now the question is concerns.

DR. EISENMANN: Well, speaking up, if I give you updated concentrations of use. I'll look more careful, talk to the company that had the highest concentrations reported. And they were reporting a concentration of 20% solution. So 0.1% is the maximum that company is using. I have one company still reporting 0.2% in an eye lotion. And that's now the highest concentration. So it's gotten to be more consistent with the European conclusion.

DR. HILL: So they said 0.5%, but really only 20% of that was the ingredient?

DR. EISENMANN: Correct. So I gave you updated concentration of use information this morning.

DR. MARKS: SO what is the highest now?

DR. EISENMANN: 0.2

DR. MARKS: Okay, so we go from 0.1 to 0.2. Is the highest concentration?

DR. EISENMANN: Went from 0.5 to 0.2.

DR. MARKS: Yes.

DR. EISENMANN: And the European limit it 0.1

MR. JOHNSON: Is that official now, Carol?

DR. EISENMANN: Yes. Well, unless I hear something else changes. But I confirmed the 0.2 so.

MR. JOHNSON: I mean the European limit

DR. EISENMANN: Oh, the opinion. No, the opinion's not. They're still working on it.

MR. JOHNSON: Okay.

DR. EISENMANN: The counter period is over. They have not finalized it yet.

MR. JOHNSON: All right.

DR. MARKS: Well concerning sensitization there it a Bueller testing which set a sensitization threshold of 1%. There's an HRIPT that showed no irritation at 2% but it could sensitize at the concentration. But that's ten times higher than the use concentration and 0.2 is below the Bueller threshold at 1%. So I thought it was okay with that. But I can't speak to these limbs going up in the air, Tom.

DR. SLAGA: Well those are high doses.

DR. MARKS: High doses, okay. So, Ron, Ron, and Tom. A tentative report with a conclusion of? Or do we have insufficient data? Is it safe or not safe?

DR. SHANK: It has a broad toxicity profile. And you can argue dosage, which is a good argument. I don't understand the molecular weight. Ranges from less than 500 to more than 1,000. That's quite a range.

DR. HILL: It's a polymer, so what you have to get is the nature of hexalmethylene diamide. So that in itself is a complex substance when you actually have a bottle of that. Because the simplest form it can take is sort of a cage like structure where you have multiple interconnected six member rings with three nitrogens in it. So then if you take that and react it with anything, stuff comes apart, rearranges and so forth. And so when you do that, which is what they're doing here. And they're reacting it with a compound that is also a mixture, which is the sodium dicyanamide, which is also a mixture. The equilibrium, that's a nice little figure in there, those are very different compounds. Then you're getting a complex mixture with a range of molecular weights. And in fact, while we're on the subject, where it says impurities. If you read those compounds that are listed before you get to the trace metals, those are really the monomers and dimers that you would expect to get in the process of doing that chemistry. So I guess you could regard them as impurities, but I don't. I regard those as just part and parcel to this polymeric substance. Because on the low end, with the 500 molecular weight, that's probably dimers, maybe trimers, but I think dimers with the calculation. So you've got a complex mixture and it's been tested however and evaluated as such. And the only ambiguity in here is the place where you've got a poly, the propyl, where you've got two amides on the end and just three carbons in between instead of six. That would be giving us a very different substance. So the issue there is any toxicology studies that were actually done on that propyl, in the middle, we should ditch those. They shouldn't even be used for read across here. Because I don't think they relate.

DR. HELDRETH: We only have one in there and it's for comparison.

DR. HILL: Okay. As long as we're very explicitly clear, because of the confusion and nomenclature, then it would be bad to take it out, it would be better to leave it in.

But I just want to make sure everyone is clear in reading that. What the story is because of this name mess-up. Which as far as I can tell is just because somebody put the brackets on the wrong place in the polymer and named it.

DR. HELDRETH: I think that's the case, but unfortunately there is actual, the chemical name.

DR. HILL: I know. I know. I got that. And it's good that we pointed that out in the context.

DR. HELDRETH: There was some global confusion about this. I mean, you'll notice even in the SCCS report, it's got CAS numbers that will take you to polyaminopropyl biguanide, the chemical name, as well.

DR. HILL: But as far as staying on the skin, these guanide residues are what amounts to a permanent positive charge. Comparable to a quot. PKs are up around 12.5, 13. So they're always going to have a positive charge. That means for them to get through this intact skin, except when we have something like a mucous membrane, is not easy. So that's the good news in terms of surface type applications. Now, inhale a little into the nasal passages, put it on mucous membranes, that's a different story.

DR. MARKS: They get through the skin to sensitize.

DR. HILL: Yes. I would say they get into the skin.

DR. MARKS: So, Ron Shank, do you have needs? So it's either a tentative report with a conclusion

DR. SHANK: I don't have needs. The dermal penetration is very small, so. Dermal application is okay. Wilbur asked should we include the Korean data, where this was used as a preservative in some spray.

DR. HELDRETH: Using a humidifier.

DR. SHANK: Korean study where humans were exposed to

DR. HELDRETH: It's a humidifier additive.

DR. SHANK: Humidifier additives. And developed lung injury. So I would say it should not be used, there was no concentration given, that I can remember.

DR. HELDRETH: Part of our rationale for proposing, is this relevant or not, is again, with more nomenclature issues. In all three of the publications that were provided, they use the term polyhexalmethylene guanide phosphate. Which would suggest not the biguanide, but a monoguanide polymer. Now that may just be a nomenclature issue, and they really meant the biguanide. But, looking through all three papers, and chasing down the citations that are in those papers, there's no way to make that clear. So we don't know if they're talking about the same chemical or not. And that's why whoever put this in a memo to you, are these relevant, we don't know.

DR. HILL: Although I don't know how you get a polymer if they only had one group on there. Effectively that's what you're seeing anyway. Starting with the hexalmethylene diamide. I get your point though. I guess what I'm saying is, you're not starting with something that has a guanide already on it. You're reacting an amine with the cyanamide. Generating the guanide while in situ in such a way that you're getting polymers. And then the interesting thing is, cyanamines on the other end.

DR. MARKS: Ron, so how, would the inhalation

DR. SHANK: Presumably having this as a disinfectant in a humidifier, the exposure would be over a significant amount of time. Whereas used in an aerosol, cosmetic aerosol, would be very short exposure. But that's a lot of unknowns. So, topical application seems to be all right. But I don't know about aerosol products. So if we can't really have the information, I guess the way out is to say that's insufficient for products that can be inhaled. So they'd have to provide inhalation data.

DR. MARKS: So I guess the question then in my mind, that would be a way of handling this, and obviously in the discussion, you have to point out the chemical difference there. But we could either put a insufficient data announcement and then ask for, or we could do a tentative report, safe for topical, insufficient for inhaled products. And I think it just depends on how we want to handle it. Do we want to press forward with a tentative report? Or do want to just, usually when we ask for more data we do an insufficient data announcement.

DR. SHANK: Safe for dermal application of an inhalation product?

DR. MARKS: No, no. I thought you said safe for topical.
DR. SHANK: Only
DR. MARKS: Yes
DR. SHANK: Not inhalation
DR. MARKS: Yeah. Insufficient for inhalation.
DR. SHANK: Yes
DR. MARKS: If I wasn't clear, that's what I meant.
DR. SHANK: Okay
DR. MARKS: But, do you want to do this as an insufficient data announcement pointing out for insufficient? Yes.
DR. GILL: Well if part of it is insufficient, since this is the first time, it will be an insufficient data announcement.
DR. MARKS: Okay.
MR. JOHNSON: I'd just like to add that the safety assessment does contain acute and a short term inhalation toxicity data.
DR. SHANK: Sorry, where is that?
DR. HILL: But it's only acute and short term. That's the bothersome thing there.
MR. JOHNSON: Okay.
DR. HILL: So sensitization, that's probably, I guess you'd pick that up. But since this is being put out there as having carcinogenic effects, if you don't have chronic, I think you're missing something. In my humble opinion. I don't know what these guys think.
DR. MARKS: I just lost, damn.
DR. HILL: Of course that insufficiency is consistent with the European's take on this. Which is they think there's not enough information to make them comfortable for safety in spray products, is what it says, what I got.
DR. SHANK: Okay, the animal inhalation toxicity data, say what the exposure concentration was in milligrams per cubic meter. But nothing about the aerodynamic properties. If that information is available it should be stated.
MR. JOHNSON: It wasn't stated. These data are taken from the SCCS report. And that specific information is not included.
DR. MARKS: Okay. So tomorrow, I presume we're gonna, I will second an insufficient data announcement for this ingredient.
DR. SHANK: Well, what do we do with the inhalation data that's in there? If we ask for inhalation data and we already have it?
DR. MARKS: But not for chronic is what I understood. There was acute and sub-acute, but not chronic.
DR. SHANK: 28 days inhalation.
DR. MARKS: That's enough for you? Ron?
DR. SHANK: Yes. Yes.
DR. EISENMANN: In the dossier that we got later, it does give the particle size.
DR. SHANK: And what was it?
DR. EISENMANN: 0.32 to 1.3 micrometers.
DR. SHANK: Okay
DR. EISENMANN: And, depends on the concentration, so the 0.257 milligram per meter cube is 0.48 to 5.06. And the 2.47, the highest concentration was 0.67 to 1.67.
DR. SHANK: Point, zero point?
DR. EISENMANN: Yes.
DR. SHANK: Respirable?
DR. EISENMANN: mm hmm
DR. SHANK: For 28 days.
DR. MARKS: You feel comfortable?
DR. HILL: You wouldn't see any carcinogenic effects.
DR. SHANK: No carcinogenic, but you would get the lung injury. Presumably. So. That would have to be in the discussion. To counter the Korean data.
DR. MARKS: So, how do you want to move forward, Ron? You would put

tentative report? Or an insufficient? It sound like you said we have enough inhalation data now to come to a conclusion.

DR. SHANK: Yes. Tentative.

DR. MARKS: Tentative report. And the conclusion is? Safe?

DR. SHANK: Safe.

DR. MARKS: No restrictions?

DR. SHANK: Well, concentration.

DR. MARKS: Yes. The 0.2%, which is the use concentration. So we don't have to put that in the conclusion.

DR. SHANK: Okay.

DR. HILL: But, what do we have in spray products? Do we know whether there's a pump hairspray that could be used every day for years and years and years?

DR. BERGFELD: Body lotion with 0.2.

DR. SHANK: The use in sprays says it's not, it may be sprays and it may not.

DR. HILL: That's what I thought it said.

DR. BERGFELD: The concentration (inaudible)

DR. SHANK: 0.5%

DR. BERGFELD: So 0.5 is not (inaudible)

DR. HILL: Yeah. It's the 0.2.

DR. HILL: 0.5 in sprays right now?

DR. BERGFELD: Correct.

MR. JOHNSON: In hair sprays it's up to 0.004% in aerosol sprays. And 0.052% in pump sprays.

DR. MARKS: Okay. So I'll be, for our team, I'll be seconding presumably a motion that's issue a tentative report with a safe conclusion. And from a discussion point of view, we'll include the chemical and INCI name in both the abstract, the introduction and the discussion to clarify the nomenclature. Does that summarize it, do you think?

DR. SLAGA: Great.

DR. MARKS: Oh, title. Yes. Thank you. I have to include the title there, thank you. Somehow I deleted all my notes and I had to go back.

DR. HILL: I'm sorry. I've got a question. I'm looking at the use table. And it has hairsprays, pump spray, up to 0.27%. Is that a mistake?

MR. JOHNSON: We received new data this morning

DR. HILL: But that's not there anymore?

DR. EISENMANN: That was one of the concentrations that they were reporting concentration of the mixture rather than

DR. HILL: Okay. So divide by five.

DR. MARKS: Okay. Wilbur.

MR. JOHNSON: Are there any concerns relating to reproductive and development of toxicity? Genotoxicity or carcinogenicity that would need to be addressed in the discussion?

DR. MARKS: I didn't hear any comments from Ron, Ron, or Tom. Specifically do you have any concerns

DR. SLAGA: No

DR. SHANK: The in vitro utegenicity assays really aren't valid because it's antimicrobial. So those in vitro studies usually are complicated by cytotoxicity. And the reproductions, developmental changes we're seeing only at very high doses.

DR. MARKS: Okay. Good. That answers that, Wilbur.

MR. JOHNSON: Yes. Thank you.

DR. MARKS: No, thank Ron Shank. Okay. Any other comments? Well we managed to stretch this one ingredient out to a robust discussion. Okay. Well I think for all of us because of the nomenclature issue.

Day 2 of the April 10-11, 2017 CIR Expert Panel Meeting – Full Panel

Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride)

Moving onto the next one, which is a preservative, Dr. Belsito, the polyaminopropyl biguanide, I guess it's pronounced?

DR. BELSITO: Yeah. Interest pointing it's the INCI name, but it's not the chemical name. But we will stay with the INCI name. I really had asked that this be moved up as a priority ingredient, because it's increasingly being used as preservatives. And the EU is rapidly moving. And has actually set out a revised opinion to limit this to.1 percent in preservatives. So I was very interested in the U.S. getting their opinion in about this. So, having said that, we looked at this, and the issue is, I had two issues with this. First of all, we know that at two percent, it induces sensitization. And in those individuals in whom it induces sensitization at two percent, that sensitization can be elicited in patch testing down to.1 percent in a very small number of individuals. Very weak reactions. What we don't have is a no effect level for sensitization. Wilbur was kind enough to send me over, and I was trying to --. So we know there's a hazard. We don't know how to assess the risk of the hazard. I asked Wilbur to send me the Gerbrick article, and it simply states, that there was a positive LLNA. And that there was a positive guinea pig maximization in the 4 biguanide. What it doesn't give me is an EC3 value. It gives me any sense for how potentially sensitizing this is. Nor is there a reference in there specifically. So, I think the positive LLNA exists somewhere maybe in P&G's files. Or one of the other company files of the co-authors on this paper that included, I believe, David Basketer, who was with Unilever at the time. So, someplace out there, there must be an LLNA. But it is not in the published literature. I spent over a half hour trying to search for it. So, at this point, I'm not comfortable signing off on this at any concentration, even.1, without knowing the sensitization capacity of this material. And the second issue, minor, but still there, were the reports of anaphylaxis when this was used in wound dressings. And I was wondering if this is an issue similar to the pegs, where it's simply, you know, damaged skin and severely damaged skin. Or what was going on. And it was a late request, late Saturday night, I think, to Lillian, to get those reports. Those two reports I've not yet had a chance to review. So, I think it's insufficient for a no effect level for sensitization. And I would like to review the two papers that talked about anaphylactic reactions in wound dressings.

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

DR. BERGFELD: Announcement.

DR. BELSITO: Yes.

DR. BERGFELD: Yeah. It's a new one.

DR. MARKS: Very interesting Don. I had a little bit of a different take. But certainly our team can support that. I was somewhat reassured by the sensitization data in this report. That, if I interpreted things correctly, the Bueller sensitization threshold is one percent.

DR. BELSITO: But we didn't see that data. It's just --

DR. MARKS: Yeah.

DR. BELSITO: -- summarized in the SCCS opinion.

DR. MARKS: Okay. Yeah. Any rate. So, I'll second that insufficient data announcement.

DR. BELSITO: There was one final request. I believe it came from Dan. And that had to with inhalation studies. Some Korean studies. Do you want to comment on that?

DR. LIEBLER: Well, only that --

DR. BELSITO: Or to Curt?

DR. LIEBLER: -- there was a question about, in the memo, about whether we wanted to see that. That the council had brought this up. And Curt commented on these studies as being an important significant tox problem in Korea. And, you know, I felt that we needed to see this to verify, if possible, that the chemical substance studied there was the same as what we're evaluating. So there's -- it's not entirely clear that's the case. And then to evaluate the toxicology, and figure out to what extent that's relevant to our assessment. If Curt has further comment.

DR. SHANK: I think it's relevant. It should be in the report.

DR. BERGFELD: Curt, do you want make a comment?

DR. KLAASSEN: Yeah. For those that don't know, there had been a number of children that died in Korea in the last few years from humidifiers in the homes. And, they'd been adding a similar compound. And that's what we're trying to figure out. If it is exactly the same or not. But, if it is or not, it should be included in here, so people know the story. It's kind of a national disaster in South Korea at the present time in the last couple of years. In fact, a relatively well known toxicologist is sitting in prison now as a result of this.

DR. BERGFELD: Well, I believe that the whole panel agrees that we can wait and do an insufficient data announcement to make sure that we have everything. Does anyone else want to comment?

DR. SHANK: Yes.

DR. MARKS: Yes.

DR. BERGFELD: Go ahead.

DR. MARKS: No. Do you want to?

DR. BERGELD: Ron was first.

DR. MARKS: Okay. Ron was first?

DR. BERGELD: Mm-hmm.

DR. MARKS: He hit the button before I did.

DR. BERGFELD: You did. You did.

DR. MARKS: Yeah. I think. Go ahead Ron. You're probably going to say the same thing I did.

DR. SHANK: You have to be quick. I'd like to change the name of the document. And in parenthesis add, what is it?

(Polyhexamethylene biguanide hydrochloride). Because that's actually what we're reviewing. And we're not reviewing the amino propyl biguanide. But that has to stay in the title because that's the name in the dictionary. But I think the title should clearly show that what we're reviewing chemically is the hexamethylene compound.

DR. BERGFELD: Jim.

DR. LIEBLER: I agree.

DR. MARKS: Good. Because I was going to say the same thing Ron, at your request. Because I remember yesterday, Dr. Shank said, this is a confusing paper to read because the different names. And so not only include the chemical and INCI name in the title. But, actually throughout the report in the abstract in the introduction and also in the discussion. So it's clear that we're dealing with a chemical. PHMB hydrochloride.

DR. HILL: Particularly important, because there is a polyaminopropyl biguanide that has a separate identity. A three carbon instead of six carbon-bridge.

DR. BERGFELD: Okay. I'm going back. Dr. Belsito, do you want to list the request that your --?

DR. BELSITO: So what we need, the data need is for threshold for induction of sensitization. And then the additional requests are for the papers that exist on the anaphylactic reactions to wound dressings. And the papers that deal with these reactions in Korea.

DR. BERGFELD: Okay.

DR. BELSITO: The respiratory reactions. That data is out there, so it's not in data request. It's a request that we actually see the hard documents.

DR. BERGFELD: All right. Beth.

DR. JONAS: Yes. I just wanted to make sure and to just clarify that the ingredient of concern in Korea, is actually a different ingredient. I want to make sure everybody's aware of that. And that's on the record. And the other per your data request, we have requested the LLNA data. And hope to get it. Of course, we're still in that 60 day combat period, and so our members still have time to respond.

DR. BELSITO: Right.

DR. BERGFELD: Thank you.

DR. BELSITO: I mean, it exists someplace, because it's in Gerbrick's paper.

DR. JONAS: It's out there somewhere.

DR. BELSITO: It's just not published.

DR. JONAS: Yes.

DR. BERGFELD: So, it seems reasonable that this would come to the June meeting then.

DR. BELSITO: Do we have time?

DR. BERGFELD: I don't know. I'm asking.

DR. JONAS: We always request it. It's just whether people will provide the information.

DR. EISENMANN: I've requested it, but, you know, I'm a little concerned that it didn't show up in the European dossier. So, whether or not it's an internal study that was done a long time ago, and they have concerns about it. And that's why they didn't --. I don't know. So, I'm trying to get an answer one way or another. Either get the study or --.

DR. BELSITO: From Frank? Or from whom?

DR. EISENMANN: From one of those companies. Yes.

DR. BELSITO: Well, I mean, but Frank was the first author on this paper. Frank Gerbrick. So, I mean, he's been with P&G forever. So.

DR. EISENMANN: As far as I understand, no, it's not from Frank.

DR. BELSITO: Okay. But he should know where he got that information for the paper. He's an author.

DR. EISENMANN: Well, no we've gotten who we're supposed to be asking.

DR. BELSITO: I see.

DR. EISENMANN: We've asked them.

DR. BELSITO: Okay.

DR. EISENMANN: But so far, they have not come up with it. And so I either want them to come up with a study. Or the reason why they're not coming up with a study.

DR. BELSITO: I see. Okay.

DR. BERGFELD: All right. Well, we'll try for June, and we'll see how that goes. All right. Thank you.

Day 1 of the June 12-13, 2017 CIR Expert Panel Meeting – Dr. Belsito's Team

So now the next one, polyaminopropyl biguanide. So this is an up and coming cosmetic preservative and at the April meeting we issued an insufficient data announcement with the following request. Skin sensitization data to determine a no effect level for polyaminopropyl biguanide. Data needed to evaluate the anaphylactic reactions to this in case studies and data from the Korean papers on lung injury mortality as attributable to material that we were not certain whether it was structurally related to a polyaminopropyl which is actually polyhexamethylene guanidine that we are reviewing.

So we got the Korean data including some last minute handouts because of copy right laws that could not be sent to us. We got a lot of data on in the report and then some additional data in wave 2 on HRIPT and what we didn't really get was a lot of data on the anaphylactic reactions.

MR. JOHNSON: Just the two case reports.

DR. BELSITO: Right.

MR. JOHNSON: That were provided, yes.

DR. BELSITO: So I guess the first question is the deaths, the lung disease, pulmonary disease linked to this material in humidifiers. Where are we with that? We have got all the information. It's not my area of expertise.

DR. LIEBLER: Well, I think that was determined that that was another substance that the ingredient that we are reviewing is not one of the substances that was present in the humidifier solution and that the focus on that was -- and I just got these papers or this paper. But my understanding is that the focus was on another ingredient that was superficially structurally related. In fact I actually have a little bit of language for the draft discussion on that. But it's a different substance.

DR. BELSITO: Do you want to share your language with us?

DR. LIEBLER: Yes, sure. So this regards PDF page and it is the, let's see, one, two, three, four, fifth

paragraph regarding the issue of inhalation exposure. And the final sentence is the relevance of the finding to polyaminopropyl biguanide as a cosmetic ingredient will be determined after these studies. And I just struck that sentence and I substitute the panel noted that these structures are significantly different particularly in the biguanide in the cosmetic ingredient versus guanidine in the inhaled toxicant. The toxicity of the guanidine compound was considered not to be relevant to the assessment of the polyaminopropyl biguanide.

DR. BELSITO: So you've deleted the last sentence.

DR. LIEBLER: Right.

DR. BELSITO: In that paragraph.

DR. LIEBLER: The last sentence of that paragraph.

DR. BELSITO: And you've word smithed it to point out that it's a different chemical.

DR. LIEBLER: Correct.

DR. BELSITO: Okay. So who is reporting on this?

DR. LIEBLER: Jim.

DR. BELSITO: Jim. But if they don't point that out I will refer to you to word smith.

DR. LIEBLER: Sure. Yes.

DR. BELSITO: Okay. The anaphylactic issue. I don't know what to make of this personally because what you're finding is is that this is increasingly being used in particularly in eye medications and contact lens solutions and things like that and there have not been any reports of, you know, significant urticarial reactions to them. You know, I'm not even sure that it warrants a damage skim at this point unless we want to actually ask for specific information like we did with PEG's.

DR. LIEBLER: You know, assessing a case report like this is definitely outside of my own expertise. One thing that occurred to me is that the guanidine compound that was apparently the source of the trouble with the inhalers in South Korea is chemically somewhat similar to the biguanide that we are analyzing and its always possible that that compound, the

guanidine could be a contaminant of a, of the ingredient that we are evaluating. Depending on how the, you know, the material was generated and how it was purified or whether it was purified, et cetera. And I don't know if that could be related to the effect and this was simply a potential chemical explanation for what they were seeing but I'm not sure that clinically you could accept the conclusion, Don, of what's reported in this report?

DR. BELSITO: Yes, I mean --

DR. LIEBLER: That the anaphylaxis is due to this compound?

DR. BELSITO: Yes, I mean it doesn't say what else is in the compound and we know that chlorhexidine is a frequently used, you know, hospital disinfectant and has been reported to cause anaphylaxis. I mean, the FDA just recently put out an announcement on that so, you know, I'm not overwhelmed by the data. I guess the question becomes, you know, how do, you know, we explain it. I mean, if you look at the, so if you look at the reports here, okay, first guy its angioedema and pruritus after using a wet wipe and he's patch test negative but he's prick test positive but there's no control. There are a lot of things you can prick into the skin that aren't IgE mediated that cause you to develop a wheel and flair. So that I can't make a lot of sense of.

And then the next guy has contact dermatitis and we will talk about that. And then the two cases of severe anaphylaxis that were reported after a hospital disinfectant and they don't give you any other information, you know, as to why they believe that its polyaminopropyl biguanide. And again, the same thing with the grade three anaphylaxis with a using a new brand of wet toilet paper. So I'm not -- the literature is out there. I think we need to or I can go into it further and craft some language for the discussion as to why it, you know, the conclusions that they were due to this material are not appropriate. But it is there and it is from cosmetic use. Its --

DR. LIEBLER: And they attribute it to this disinfectant called lavasept which the text of this article or this report simply says it contains polyhexanide biguanide and polyethylene glycol and (inaudible) lactate. So in this little two pager that Wilbur just gave us, I'm just reading this for the first time but the patient case one, patient under anesthesia with bupivacaine presented an anaphylactic shock while the medullary cavity of the femur was being washed with lavasept. Now I don't know if anything else about this situation would be potentially able to cause anaphylaxis and again I ask my clinician colleagues about that because I have no idea.

DR. SNYDER: The one question I had was that there, in this introduction it says that urticarial reactions to lavasept appear to be rare but have been reported to the Swiss Center of Pharmacovigilance. So do we have access to that data to see if there, that there are urticarial reactions that are above? Because this seems to be an expansion that not only urticarial reactions but then these two case reports on anaphylaxis.

DR. LIEBLER: Both of these patients were under general anesthesia.

DR. KLAASSEN: Yes, right. I mean, thank goodness they were I guess.

DR. LIEBLER: I mean, it sounds like they were using this stuff by the gallon.

DR. KLAASSEN: Inside of the body.

DR. LIEBLER: Yes. Right.

DR. BELSITO: And, I mean, they are coming to the conclusion only because of the structural relationship of the biguanide to chlorhexidine which is known to cause urticarial reactions. You know, on the other hand we have approved chlorhexidine for use in cosmetic products.

DR. SNYDER: But and then it also does go to the in context that this damaged skin.

DR. BELSITO: Right. Mucosal. I mean, more than damaged skin.

DR. KLAASSEN: Right. This was inside the body.

DR. BELSITO: Yes.

DR. LIEBLER: They were pouring it on the bone.

DR. KLAASSEN: Yes, both cases.

DR. LIEBLER: Right.

DR. KLAASSEN: Like an IV administration.

DR. LIEBLER: So I don't know, I mean, maybe you can consider those factors in crafting some language here but it just seems like the exposures are so dissimilar. The only thing that gives me any pause is, you know, anaphylaxis, you know, I understand in some cases

can be caused by exposure to a very small amount of a substance so you can't rule out the possibility that a small amount could present a risk to the right person. But it seems like the overall safety profile of this stuff doesn't point you in that direction at all.

DR. BELSITO: Yes, I mean, the first patient was, you know, clearly multi allergenic individual, you know, cat dander, grass, cereals, corn, hazel, birch, walnut were IgE, you know, were all positive. His skin prick tests were negative to everything. It was his intradermal that was positive at a 1 to 10 dilution or ten to the minus four micrograms per ML of polyhexanide.

And the same thing with the other, I mean, if this were even on damaged skin, okay, you know, skin prick test is where you're putting it, you know, you're not even scratching the skin. You're putting it down underneath the epidermis and then the intradermals were positive. I mean, that, I mean, if this were an allergic reaction the skin prick test should have been positive. You know, particularly since they are claiming the intradermal reaction occurred at such a low dose. I mean, the studies just don't make sense to me.

DR. LIEBLER: Um-hum.

MR. JOHNSON: I have one question. The chemical structure is on page two and my question is is this the chemical structure for polyaminopropyl biguanide or polyhexamethylene biguanide hydrochloride?

DR. BELSITO: Dan?

DR. LIEBLER: Which one?

DR. BELSITO: The top one is chlorohexidine. The bottom one is polyhexanide. Is that the chemical we are looking at?

DR. LIEBLER: I am paging down to the table in our report, hang on just a moment.

MR. JOHNSON: And I'm saying that because according to the dictionary polyaminopropyl biguanide is not the cosmetic ingredient for polyhexamethylene biguanide hydrochloride. It's actually the cosmetic ingredient.

DR. BELSITO: Right.

DR. HELDRETH: Yes, they've drawn hexamethylene. It even says hexamethylene in the name below the structure on that page.

DR. LIEBLER: Yes, the structure is the same.

MR. JOHNSON: So that means polyhexamethylene biguanide --

DR. BELSITO: That's what we are looking at.

MR. JOHNSON: Right, okay. Thank you.

DR. LIEBLER: Yes. Speaking of structures, I would suggest going back to the Korean vaporizer episode, the bottom of PDF page 38 the bottom where you say the chemistry of PHMG which is the abbreviation, the acronym for the ingredient implicated in that toxicity. I suggest you actually show the structure there just to show that it's different.

DR. KLAASSEN: Yes, I agree.

MR. JOHNSON: What page are we on?

DR. LIEBLER: PDF 38 at the bottom, very last sentence. So right around there you could, you know, put figure X and show the structure of PHMG. You've already got the structure of the other one elsewhere in the report but it would be clear that they are different.

DR. KLAASSEN: Preferably put both of them there.

DR. LIEBLER: Yes you could put them both their just side by side.

DR. KLAASSEN: So us dummies don't have to go back and compare it.

DR. LIEBLER: Right. Right.

DR. KLAASSEN: On the computer it's not so easy to do.

DR. BELSITO: So where would you do that, Don? So beginning in 2006 that's the paragraph you are talking about?

DR. LIEBLER: Yes. Somewhere around that paragraph. But the two structures are ingredient.

DR. BELSITO: So maybe right after the third sentence which says these disinfectants contain put a comma which is chemically dissimilar, see figure whatever.

DR. LIEBLER: Sure, yes.

DR. BELSITO: So that last line, Wilbur, on page 38 where it says dodecyl

dimethyl ammonium chloride comma which is chemically dissimilar to the material under review and then see figure.

DR. LIEBLER: Also I would say chemically it's similar.

DR. BELSITO: Which is --

DR. LIEBLER: But its --

DR. BELSITO: -- toxicologically?

DR. LIEBLER: Right. Yes. And I, that's why I have that other line in the discussion to explain the dissimilarity is significant enough. I mean, chemically they're similar but they're dissimilar enough to have different biological effects.

DR. BELSITO: Which is so then we can just say which is not the material under review and deal with that in the discussion and --

DR. LIEBLER: Exactly.

DR. BELSITO: And so which is not the material under review see figure.

DR. LIEBLER: Yes, so you could edit the last line of that paragraph on PDF 38, the chemistry of PHMG comma and I will put it into mine, Wilbur, which is not the material under review.

DR. BELSITO: Okay.

DR. LIEBLER: Is similar, right.

DR. BELSITO: Okay. So where are we with the anaphylaxis?

MS. BURNETT: Chlorhexidine.

DR. BELSITO: Yes. Yes. The FDA has recently put out an announcement on chlorhexidine. Right. So I guess we are going to note those in the discussion, state that what? The negative skin prick testing and positive intradermal testing is a little bit unusual for an IgE mediated process? That -- the other reports were uncontrolled?

DR. LIEBLER: And damaged skin.

DR. BELSITO: And could be damaged skin but then are we saying that it should be used on damaged skin? I mean, you know, because we also can't say it can't be used on mucosal surfaces because right now its biggest use are eye drops. And Europe has said now they are allowing it to point three, is that right? It was point.

MR. JOHNSON: No point one.

DR. BELSITO: It was point one. But I thought they just upped it to point three now at the recent --

MR. JOHNSON: No its 0.1, I mean, they've lowered it to 0.1 in the final monogram.

DR. BELSITO: All right. I thought they upped it.

MR. JOHNSON: It was 0.3 and they lowered it to 0.1.

DR. LIEBLER: PDF 30 --

DR. BELSITO: Yes, I see it.

DR. LIEBLER: Third paragraph.

DR. BELSITO: So they said unsafe at point three and they have now said safe at point one. Right. Okay. I mean, but we have this in our reports, I think we need to address it. I --

DR. KLAASSEN: Well, I think the point that this wasn't placed on the skin but it was placed in essence on the bone and on the gut, you know, while they were doing surgery. I mean, that's, I don't know how relevant that is to in fact I don't think it's relevant at all to dermatology.

DR. BELSITO: Well, except one case report was following the use of a wet wipe. So a male patient with a history of angioedema and pruritus after using a wet wipe.

DR. KLAASSEN: Maybe we can be asking for more data.

DR. BELSITO: And then a female patient after using a wet wipe. I mean, its 14, 17 and 38 are the references, right? I thought I looked at those. Let me make sure they may have been ones I couldn't get, I don't know. 14, 17, -- it was 14, 17.

DR. SNYDER: 14, 17 and 38.

DR. BELSITO: Yes so NICNAS I didn't see obviously.

DR. LIEBLER: Did we get 14?

DR. BELSITO: 14 is from contact dermatitis.

DR. LIEBLER: Right. Did we get that?
DR. BELSITO: And I don't know that I could get allergy --
DR. LIEBLER: Okay.
MR. JOHNSON: From the Korean studies and the anaphylactic reaction report.
DR. BELSITO: But they are 14, 17 and 38 all dealt with anaphylaxis.
DR. LIEBLER: Is contact urticaria syndrome or urticaria syndrome anaphylaxis?
DR. BELSITO: It can result in anaphylaxis, yes, latex is a good example.
DR. LIEBLER: But as in described in that reference. I just, I mean, I honestly if I was reading contact dermatitis I would be lucky to just know it's right side up.
DR. BELSITO: Right.
DR. LIEBLER: So I defer to you guys to tell me if it, if this is relevant.
DR. BELSITO: Let me get to the Columbia website. E -resources. So while I'm trying to get that data from the Columbia library here's an issue that I have with this material. First of all, Wilbur, with the new data that we have on the HRIPT, you've misstated the dose because it was a dilution so in that HRIPT at the new data we got on wave two, the NESIL, the dose that did not create an issue was let me pop this up. Was a point, you stated it was 125 micrograms per square centimeter. That's not true. Or, I'm sorry --
MR. JOHNSON: 0.125 micrograms or, I mean, milligrams per square centimeter.
DR. BELSITO: But in the report it was not correct. Where are we? So many comments on this.
DR. SNYDER: It says summary of an HRIPT (inaudible) point five percent --
DR. BELSITO: Yes so this is wave two.
DR. SNYDER: Yes, page seven of the wave two documents.
DR. BELSITO: Right. But in Wilbur's summary he says that a dose sensitivity of 25 milligrams per centimeter squared in the summary. If that were to come into the report its actually 125 micrograms per centimeter squared.
DR. SNYDER: Okay.
MR. JOHNSON: Now see I'm looking at PDF page 8. The actual data.
DR. BELSITO: I'm looking at wave two.
MR. JOHNSON: Yes, these are the wave two data --
DR. BELSITO: Yes, the actual data is correct. But your summary of it at the beginning in your letter dated June
is incorrect.
MR. JOHNSON: Okay.
DR. BELSITO: So if you were to take your summary and put it into the text it would be incorrect because if you were looking at what you summarized for the human sensitization data you would think that the results of the HRIPT were negative at 25 milligrams per centimeter squared.
MR. JOHNSON: Yes.
DR. BELSITO: You said the product point one gram under two by two centimeter occlusive patch was applied for at a dose density of 25 milligrams per centimeters squared. That was not the, the does density was 250 micrograms per centimeter. 125 micrographs per centimeter squared.
MR. JOHNSON: Well, I'm looking at the --
DR. BELSITO: I'm looking at your introduction, Wilbur.
MR. JOHNSON: Yes. I'm looking at the actual data.
DR. BELSITO: I'm looking at the actual data too.
Mr. JOHNSON: Okay.
Mr. BELSITO: I'm just saying your conclusion of the actual data in your letter of June 2 is incorrect.
MR. JOHNSON: Okay.
DR. BELSITO: So you need to correct that because it should not hopefully if you cut and paste what you summarized as the dermal irritation sensitization that value will be wrong.

MR. JOHNSON: Okay.

DR. BELSITO: And I point that out only because very interestingly since we last looked at this I had a woman with severe eyelid dermatitis who I tested to her CVS saline solution for sensitive eyes which contains.0003 percent of the material under polyaminopropyl biguanide. The other constituents were boric acid, potassium chloride, sodium chloride and EDTA. She had a three plus reaction to the cleansing solution and I have no explanation other than polyaminopropyl biguanide. I just got the material. She is clear using contact lens solutions without it and doesn't want to come back in for confirmatory patch testing.

I point that out only because I think that this is a preservative where we have to use the QRA and not just simply say safe as used. Because just to point out that for instance if this, if we assume that the NESIL for this is 125 micrograms per centimeter squared I couldn't exactly find one in the RIFM database that's the same. Isoeugenol is 250 micrograms per centimeter squared and it ranges from point 01 in lip products and point 02 percent in intimate wipes up to 1.25 percent rinse off products.

So I think this is a conclusion that we need to craft like we did the cocamidopropyl betaine solution and the stearamidopropyl conclusions that we don't endorse the QRA but you need to use some type of approach to what you are using. Otherwise I think this will end up being the next methylisothiazolinone on the market. I'm very concerned about it and I think and we are losing so many preservatives that I don't want to see this one lost.

DR. ANSELL: Yes, we would support the inclusion of that in the I don't know the discussion or somewhere in the report.

DR. BELSITO: Yes.

DR. ANSELL: That safe when formulated based on a QRA similar language.

DR. BELSITO: Or some other --

DR. ANSELL: Yes.

DR. BELSITO: -- toxicological approach to where it's used and how it's used. Now just an across the board statement of -- I just throw that tout. I'm just trying to get to the contact dermatitis for the urticaria. I can't get allergy here. So I don't know if you have that report, Wilbur? Its Columbia Library doesn't prescribe to it.

MR. JOHNSON: Which number is it in the reference manual?

DR. BELSITO: I don't know. Can someone tell me the contact dermatitis one is 38 or 14?

DR. LIEBLER: Let me look here. 14.

MR. JOHNSON: 14.

DR. BELSITO: No, the allergy one is 38. Isn't it? Wilbur needs to get the non-contact dermatitis.

DR. BERGFELD: 38 is allergy.

DR. BELSITO: Yes. So 38.

DR. HELDRETH: For Wilbur's summary where he had the megs per cubic centimeter dose density I'm looking at the

data and I see where he got it from. I think they have called two things in the raw data dose density. Whereas one of them is intended to mean the density of the entire amount of formulation that was applied.

DR. BELSITO: Right.

DR. HELDRETH: So I think that's where the error came into there.

MR. JOHNSON: It was in the report 0.125 value relates to polyaminopropyl biguanide.

DR. HELDRETH: Yes.

DR. KLAASSEN: I mean, the last sentence of the sensitization paragraph actually is eight references in regard to human skin sensitization. And they say that begins at 0.2 percent active ingredient. That's pretty important.

DR. BERGFELD: Was that skin?

DR. KLAASSEN: Yes.

DR. BERGFELD: Not rabbit?

DR. KLAASSEN: Humans. The last sentence, it's on page 37. There's a sensitization paragraph.

DR. BELSITO: So what was the article on anaphylaxis from contact derm? What volume, what was the reference?

MR. JOHNSON: Let's see, so there's reference 38.

DR. BELSITO: No reference 38 was allergy this is reference 14.

DR. LIEBLER: Yes it's a volume 71 so year 2014.

DR. BELSITO: Yes.

DR. LIEBLER: Volume 71 issue 5, page 307.

DR. BELSITO: Yes, here it is okay. So this is a report that came out of Holland. How do I reverse this here? Hey Dan, I just flipped this whole thing sideways. How do I get it back up? Okay.

MR. JOHNSON: Oh yes, I have it right here. What's his email address? Okay. Let me attach this to you and send this to you.

DR. BELSITO: Okay.

MR. JOHNSON: I have the Creighton's publication, we are going to send it to you.

DR. BELSITO: The allergy one?

MR. JOHNSON: Yes, the Creighton.

DR. BELSITO: I have it.

MR. JOHNSON: You have that one?

DR. BELSITO: Yes. It's the allergy one I need, Wilbur. I don't have access. I have access to contact derm.

MR. JOHNSON: 38. Oh, okay, 38.

DR. BELSITO: Right. So basically this was a 39 year old woman and she did have strong immediate positive prick test to the wipes and to the ingredients. So these were prick tests after 15 minutes and then they did a flow assisted basophil activation test which I don't believe is FDA approved and it was positive to polyaminopropyl biguanide. And that test was positive, was performed in three healthy controls who had been exposed but not, did not develop symptoms and was negative. But that was the basophil activation test. And it doesn't look like they did any controls for the skin prick testing on polyaminopropyl biguanide.

MR. JOHNSON: But this is it.

DR. BELSITO: So they didn't do positive controls, so they said the problem was cleared by not using wet wipes with polyaminopropyl biguanide. And then if you go into contact dermatitis since I was searching for this there's a review of contact urticaria with polyaminopropyl biguanide. I don't know that, if you saw that, Wilbur?

MR. JOHNSON: Which one is that?

DR. BELSITO: I'm just popping it up again because I was just thrown out of the library for being a bad student. It says contact urticarial syndrome by polyaminopropyl biguanide wipes. This is another reference from 2000, wait a minute, is this the same one? Yes. Sorry, it's the same one. There is an article in 2016 polyhexamethylene biguanide and wound care products are non-negligible cause of peri-ulcer dermatitis. So that gets us to some damaged skin that probably should be brought in and then the one that I was referring to is a 2016 cosmetic components causing contact urticarial, a review and update and I suspect it's by N. Gussen (phonetic) so it probably just adds polyaminopropyl biguanide to the list of materials. I'll pop it up now, see if it's even relevant to review. But it would be nice to look at that one done in sterile wound care.

Yes basically just ads, just to review adding her finding that it can cause contact urticaria there is no additional data there. So I don't know it doesn't really seem to be an issue. There have been a couple of case reports not conclusively documented. One used only basophil analysis in controls not skin prick testing. So I'm not sure where to go with the urticarial issue.

DR. KLAASSEN: This reference number 31 from the title it says the biocide polyhexamethylene biguanide remains an uncommon contact allergen, recent multi center surveillance data and contact dermatitis.

DR. BELSITO: Yes, I agree.

DR. KLAASSEN: That might be a useful reference.

DR. BELSITO: But that's for contact dermatitis and I think part of the issue is and the reason why I wanted this brought forth is that as the number of cosmetic preservatives gets

limited in Europe, you know, they are now limiting, further limiting parabens, they've banned methyl dibromogluerteral (phonetic) nitride. They've essentially banned methylisothiazolinone except in the MCMI mixture. This material is going to get increasingly used. It's not a common sensitizer because it's not been a common preservative until recently. But you're seeing it coming into more and more cosmetic products.

And I think that it's just like methylisothiazolinone. When we reviewed it in 2005 not only did we have the HRIPT data wrong but we weren't thinking of how these materials are used and we said across the board 100 parts per million. Well 100 parts per million wasn't an issue for, you know, wash off products but when you started putting it in baby wipes it caused this huge epidemic. I would hate to see this material get banned in Europe because we got it wrong and it caused epidemics. I mean, if they do the QRA I think it will be fine or some other means of risk assessment for contact dermatitis.

But that doesn't address the urticaria angioedema issue which is extraordinary rarely reported and I don't think, I would like to see the allergy paper but and N. Gussen is a wonderful researcher but, I mean, the skin prick tests were not controlled in the basophil activation tests as far as I know are not FDA approved or scientifically approved by any regulatory body to be used as a surrogate so the fact that three negative controls were negative with the basophil activation test doesn't, I mean, I would have liked to see them skin pricked tested with the material. Did you send the allergy paper, Wilbur?

MR. JOHNSON: Well, actually I don't have that but I can order it and it can be here by tomorrow morning if not before the end of the day.

DR. BELSITO: Okay. Let me try one other avenue to get into Columbia Library on that. I might be able to get it. What's the reference for the allergy paper which is 38?

MR. JOHNSON: That's, yes, that's --

DR. ANSELL: 2010.

MR. JOHNSON: Yes. Volume 65 issue 8.

DR. BELSITO: Okay. Who is the author?

MR. JOHNSON: Kautz, that's K-a-u-t-z and Schumann, that's S-c-h-u-m-a-n-n.

DR. BELSITO: No results. Oh, I misspelled it. It would help if I spelled correctly, huh. Allergy --

DR. LIEBLER: Vanderbilt versus Columbia.

DR. BELSITO: Allergy and clinical immunology is what I'm getting.

MR. JOHNSON: Its number eight. Issue eight.

DR. BELSITO: It's just allergy, right?

DR. LIEBLER: Yes, I've got it.

MR. JOHNSON: Just allergy. Angioedema and oh that's not the right word. 1068 I'm looking for --

DR. BELSITO: Keeps shunting me to allergy and clinical immunology.

DR. LIEBLER: Here we go. I've got the reference.

DR. SNYDER: Email it to everybody.

DR. LIEBLER: I am going to download it. Okay.

DR. SNYDER: And, Scott, he is going to email it.

DR. BELSITO: Yes, I keep getting shunted back over to allergy and clinical immunology where it doesn't exist. I thought I had it. And you have the NICNAS data reference --

MR. JOHNSON: Yes, sir.

DR. BELSITO: You're sending that to me?

MR. JOHNSON: Yes.

DR. BELSITO: And you're going to send me the allergy paper.

DR. LIEBLER: Here it comes. It has been sent.

DR. BELSITO: Okay. So, I mean, I think I will see if I can draft something to address the urticaria issues and I'm fine with safe as used when formulated to be non- sensitizing and then in the discussion, you know, state that they can use various ways of assessing sensitizing capacity QRA or other similar methodologies.

DR. LIEBLER: Okay, I'm good with that.

DR. BELSITO: I got it. Thank you, Dan.

DR. LIEBLER: Sure.

DR. BELSITO: And you'll send me the NICNAS, the other?

MR. JOHNSON: Yes.

DR. BELSITO: Okay. Anything else on polyaminopropyl biguanide? Now that I've lost my page. Oh yes, so Ron Shanks comment and I understand where he is coming from but this is not polyaminopropyl biguanide. It's actually polyhexamethylene biguanide. Putting that in parenthesis has throughout this document made it extremely, extremely confusing for me to understand what you're saying. And in some places I actually think that you got it wrong by using the comment twice and I was just wondering could we do something like polyaminopropyl biguanide, I mean, it's not trademarked, that's not the trademarked name but could we come up with some super script INCI instead of putting in parenthesis polyhexamethylene biguanide because when I was reading it it's like which one are you talking about here, you know, I mean, is it the material we are reviewing, is it the material that is, you know, the actual polyaminopropyl biguanide?

DR. LIEBLER: Well, you've got the convention that we use in our reports of capitalizing the names of the INCI names of the ingredients we review. So and you clearly state in the second paragraph or the first paragraph of the introduction, the discrepancy between the actual the INCI name and the correct chemical name and what you have been doing is putting the correct chemical name in parentheses after the INCI name but you could simply state right up front that the INCI name is what it is, its capitalized throughout the report and that refers to this chemical substance as shown in table one and leave it at that. And then not have to drag the parenthesis and then the long chemical, correct chemical name in throughout the report.

DR. BELSITO: Yes.

DR. LIEBLER: And maybe that would satisfy Ron and --

DR. BELSITO: I mean, I agree we need to distinguish but for instance, I mean, it just results in screw ups. On page 38 where you described cytotoxicity, Wilbur.

MR. JOHNSON: Yes.

DR. BELSITO: Basically you say however the last paragraph or the last sentence in the paragraph, however, concentrations greater than point 25 percent polyaminopropyl biguanide were highly cytotoxic to cells of both cell lines after 24 hours. When compared directly polyaminopropyl biguanide consistently resulted in significantly higher survival rates than polyhexamethylene biguanide. And irrespective of the concentration so it really starts getting, you know, very, very confusing there because, you know, polyhexamethylene biguanide is what we are reviewing and so then you should put in parenthesis before that polyaminopropyl, you know, biguanide parenthesis polyhexamethylene. I mean, it was just, it was mind blowing for me to try and read and take a pause each time and decide, okay, what are we comparing? So I like Dan's idea of throughout the text when its capitalized and bold it's the material we are reviewing and when it's not capitalized and not bold its actually polyaminopropyl biguanide.

DR. LIEBLER: Yes, I mean, I don't, I don't even think bold is necessary. It's capitalized according to our convention in the reports. We don't really need to add the bold. You just say in the first paragraph in the introduction the capitalized name is the INCI name and that's the name we would use to refer to this substance. The correct chemical name is blah, blah, blah and you put that in the first paragraph and its done and it's also in table one. And then that takes care of it.

DR. BELSITO: Okay. Okay, yes. We will see what Ron says about that. Then on PDF page 28 I again I thought that it was like really too exhaustive going through the INCI name and yada, yada, yada. I essentially got rid of with that first paragraph in the introduction accordingly and just dropped the whole thing. I thought it was just too much. I think that, you know, indeed the cosmetic -- indeed the chemical polyaminopropyl biguanide is not a cosmetic ingredient. In this report when capitalized polyaminopropyl biguanide refers to the cosmetic ingredient which is actually polyhexanide hexamethylene, whatever. Get rid of all of that and then the whole thing about the SCCCS, I don't think we need to define to the world what the SCCCS is. So the following paragraph I got rid of the whole thing, I mean, you can tell us what their opinion was but you don't need to tell us what they were incorporated to do or what their mission is.

Then I had a question for Paul some place. So it was with the hepatic and the hemangio sarcomas in the so on page 41 of the PDF under the carcinogenicity oh that's where I

noted it on the summary but it's in the carcinogenicity section. What did you think of those studies?

DR. SNYDER: Yes, that's all secondary to cytotoxicity's so that's not, it's not relevant to the --

DR. BELSITO: Is it even important enough that we bring it up in discussion?

DR. SNYDER: Well, I think we should bring it up because it is data. But I think I thought it was appropriate when we discussed this before that it's related to --

MR. JOHNSON: It's in the discussion.

DR. SNYDER: Yes. It's in the discussion.

DR. BELSITO: You're happy with that?

DR. SNYDER: Yes, yes.

DR. BELSITO: And then on page 42 if of the PDF I think and this is in the summary that you have it backwards, Wilbur, because I thought the polyaminopropyl biguanide cosmetic consistently you said resulted in a higher survival rate that is less cytotoxicity than the polyaminopropyl biguanide. Oh. What you didn't, what you got wrong is you added polyhexamethylene biguanide to the first polyaminopropyl biguanide so it should simply say this is on page 42 PDF the second paragraph. Polyaminopropyl biguanide, get rid of polyhexamethylene consistently results in significantly higher survival rate, less cytotoxicity than polyaminopropyl biguanide in parenthesis polyhexamethylene biguanide irrespective of the concentrations because if the cosmetic material was more cytotoxic than the polyaminopropyl biguanide.

DR. LIEBLER: So, Wilbur, I have added at the first paragraph of the discussion to simplify and it and to explain we are just using the INCI name to refer to this ingredient.

MR. JOHNSON: Sure. Now what about the conclusion which will you just have polyaminopropyl biguanide in the conclusion?

DR. LIEBLER: Correct.

MR. JOHNSON: Okay.

DR. LIEBLER: Again because the conclusion will refer to the INCI name of the ingredient.

DR. KLAASSEN: In regard to the topic of epigenetic effects on page 36, we have two or three paragraphs, two paragraphs there. I don't think they should be called epigenetic effects. There's kind only one sentence in that, in those two paragraphs that really have to do with what we now called epigenetic effects. And that is the DNA methylation and modification of DNA basis. I guess in fact it goes on and this is really I don't know what we should call this or where we should place it. It's really kind of talking about what kind of molecular effects of --

DR. LIEBLER: Its cytotoxicity.

DR. KLAASSEN: Okay.

DR. LIEBLER: It is, I mean, there is some mechanistic aspects to it but basically its cytotoxicity studies so.

DR. KLAASSEN: But we shouldn't call it epigenetic effects.

DR. LIEBLER: No. You're right, Curt, because that connotes a very specific, it used to mean non DNA damage effects but now it connotes something much more molecularly specific and well defined.

MR. JOHNSON: So move those to the cytotoxic section in the report?

DR. LIEBLER: Yes.

MR. JOHNSON: Okay.

DR. KLAASSEN: Yes, what you have written is okay it just has the wrong title.

DR. LIEBLER: Yes. If you just remove that heading, epigenetic effects because it's right under the cytotoxicity section anyway.

DR. BELSITO: What page from the PDF is that, Curt?

DR. KLAASSEN: 36.

DR. SNYDER: It's probably better under the title other cellular effects because it's more than just cytotoxicity but.

DR. LIEBLER: Well, I looked at it as cytotoxicity with some mechanistic insight thrown in so it goes under the setting toxicity basket.

DR. KLAASSEN: You just had it there.

DR. BELSITO: So just get rid of that heading.

DR. LIEBLER: Yes.

DR. ANSELL: That's not a sound you want. Not hearing that sound. With all the construction over here they could have just been offloading containers or something but then the air conditioning just went off.

DR. KLAASSEN: It's going to come back on tomorrow afternoon.

DR. BELSITO: What's that?

DR. KLAASSEN: Air conditioner is off. It's going to come back on tomorrow afternoon.

DR. BELSITO: Okay. Anything else?

DR. BERGFELD: Could you repeat your conclusion then or what you're going to?

DR. BELSITO: Safe as used when formulated not to be sensitizing.

DR. BERGFELD: Sensitizing.

DR. BELSITO: And the discussions say that you can use QRA whatever types of methods you want but the current NESIL we have based upon the most recent HRIPT in wave two at point five gives us a NESIL of 125 micrograms per centimeter squared.

DR. BERGFELD: Now what about the data on the 0.2 being the high threshold for sensitization?

DR. BELSITO: Well, I mean --

DR. BERGFELD: I know that point five was in there.

DR. BELSITO: Yes. So that's my whole point about QRA. It depends upon where you look at sensitization. I mean, where did my patient who while I haven't confirmed its polyaminopropyl biguanide allergic it looks like she has developed a sensitivity that allowed her to react to a contact lens solution that contained.00003 percent of this material. And yet, you know, she is cleared completely or either the dermatitis has gone away completely switching away from products without polyaminopropyl biguanide have improved it but was she sensitized in a wet wipe, was she sensitized -- where was she sensitized I don't know.

So that's what I'm saying that the point two yes, I mean, you know, if you used you know, 50 parts per millions of methylisothiazolinone in a wet wipe you could get sensitized. If you used it in a shampoo you wouldn't be so that's why I think you need to do QRA. We have shown on the back which is where QRA is based on with an HRIPT that point five it was 207 subjects if I remember off the top of my head. I mean, it was a pretty good study was fine. So I think we can start that as a NESIL but then we need to apply it depending upon where this product is going to be sued and how.

DR. BERGFELD: Okay.

MR. JOHNSON: Dr. Belsito, will you please repeat the language for the discussion relating to the QRA and --

DR. BELSITO: I think you can take it from the language where we have used QRA before. Just go into I think it was in the cocamidopropyl betaine report --

MR. JOHNSON: Okay.

DR. BELSITO: Going to that and look or betaine sorry, Christina. Report that we can go in and see exactly what we said, use the same language.

MR. JOHNSON: Okay.

DR. BELSITO: Anything else?

DR. LIEBLER: Nope.

Day 1 of the June 12-13, 2017 CIR Expert Panel Meeting – Dr. Mark's Team

Next is the polyaminopropyl biguanide, aka whatever name --

DR. HILL: PHBG.

DR. SHANK: I like that better.

DR. MARKS: At the April meeting of this year, an insufficient data announcement was issued. There are three data needs skin sensitization data. We need to evaluate the issue of anaphylactic reactions and, also, data from the Korean studies on lung injury and mortality; and we did receive new data.

So, let's first deal with, number one, the skin sensitization. I thought that looked good, and we got Wave 2 with.5 percent maximum leave-on, and a negative HRIPT sensitization threshold of one percent from previous data. So, I thought was okay from that point of view.

DR. HILL: So, explain to me goes on there with the threshold thing. You're looking at a threshold of -- I think, at one point, didn't they say.2 percent or something like that? But then we've got a study up to 5 percent, that's an HRIPT -- sorry, I need some education --

DR. MARKS: That was not enough to sway the thinking last time that's why it went as an insufficient data. In Wave 2, we had a negative HRIPT sensitization study with.5 percent, which is the maximum leave-on. So, that was reassuring to me. To me, I'd check that box.

DR. HILL: Okay.

DR. MARKS: From Wave 2.

DR. EISENMAN: Part of the problem with the original sensitization settings they were all done in aqueous solutions.

DR. HILL: Mm-hmm.

DR. EISENMAN: And these additional studies were done in actually formulations.

DR. MARKS: Yes.

DR. EISENMAN: One thought is to have a conclusion similar to what you did for MI say it's been formulated to the non-sensitizing, which can be too determined based on a QRA. So, if you wanted to base the -- if you didn't want to do an HRIPT, you would do a QRA calculation, probably use the approximately one percent which is approximately 1 mg/cm2 and that comes out to a level of about.1 percent in the highest exposure products, which is what the SEC ask conclusion is; but if you wanted to go higher and be sure your formulation was right, you wouldn't have to do a HRIPT.

DR. HILL: HRIPT, which they did. And there's a sun tan product that has.5, you said?

DR. EISENMAN: Yes.

MR. STEINBERG: Is this as the 100 percent active material, or as it's commercially sold; because it's sold as a solution.

DR. EISENMAN: I know; it's sold as a solution. That is part of the problem. I think -- I want to say it's as the commercial preparation, not as the 100 percent.

MR. STEINBERG: Yeah, because that changes your numbers now.

DR. EISENMAN: Right.

MR. STEINBERG: Because, I think, it's 20 percent solution -- is what it's sold as.

DR. EISENMAN: Mm-hmm.

MR. STEINBERG: So, if it's.5, it's actually.1.

DR. HILL: Well, on that other issue, it's not a single compound.

DR. EISENMAN: Right.

MR. STEINBERG: That's true.

DR. HILL: It's a mixture.

MR. STEINBERG: But it's still 80 percent water; it's 20 percent of the mixture.

DR. EISENMAN: But they're supposed to be telling me the concentration of PSO. I would assume its concentrate. That's what they're supposed to be telling me the concentration of a PSM base; so, I would assume it's.5; but they did the calculation themselves and came up with the 0.125 mg/cm2 of PHMB, so; but I can go back and check that.

MR. JOHNSON: Ms. Carol, you're talking about commercial preparations of polyhexamethylene biguanide hydrochloride; is that right?

DR. EISENMAN: Right; PHMB.

MR. JOHNSON: Okay.

DR. MARKS: Okay; next issue on the insufficient data announcement was the NFY-degree reactions; and it said we would get the paper but, due to copyright restrictions, there were two case reports, and after surgically-wound exposures, so presumably it's really a significant exposure to me. Two cases wound exposure -- we have no cases from exposure to personal care products. So, again, I found that reassuring; rare in a report. Is Tom, Ron, Ron is that --

DR. SLAGA: I have no problem with that.

DR. MARKS: Okay; and then, the last one was -- so, you have the paper, was there anything more from that, Ron Hill?

DR. HILL: You have it too in the pile they gave us this morning.

DR. MARKS: That was in this morning?

DR. HILL: Yeah.

DR. MARKS: Okay.

DR. MARKS: And then last was the lung injury.

DR. HILL: We got this paper right here.

DR. SLAGA: The Korean one.

DR. HILL: Yeah; that also came to us this morning; and from what we can tell, and come up with a (inaudible) of a different chemical than the ingredient.

DR. MARKS: So, it's a different chemical and, obviously, it's not relevant?

DR. HILL: Yeah, this is guanine instead of biguanide; is that correct?

MR. JOHNSON: Mm-hmm.

DR. HILL: Yes? So, we would presume that to not be relevant, but we don't know.

Let's see -- prevent the growth of micro-organisms, humidifiers disinfectants are placed in the humidifier water tank. These disinfectants contain (inaudible) biguanide chloride (PGH), polyhexamethylene guanidine (PHMG),

(inaudible), so MIT was in there. (Inaudible) would have known that one, and another one; but no PHMB. Yeah; so we think it's not relevant.

This is a serious precautionary tale.

(OFF THE RECORD)

DR. MARKS: So, the lung injury and The Korean's -- Ron Hill, do you -- different chemical, not relevant? We can move forward?

DR. HILL: Yeah, it's pretty clear.

DR. MARKS: Okay, so, I see both Ron Shank's still reading; Tom Slaga, shall we proceed with a -- our team will be moving tomorrow a tentative report with a safe conclusion?

DR. SLAGA: Yes.

MR. JOHNSON: Is it safe for the formulation to be non-sensitizing? I guess safe as used?

DR. MARKS: It's going to be safe as used; we have sensitization data that --

MR. JOHNSON: Okay.

DR. MARKS: -- at the maximum leave-on. It's not a sensitizer.

DR. HILL: And this other paper we got seems to be a different chemical, as well; I believe. It says chlorhexidine. It's a biguanide, but it's not.

DR. HELDRETH: Yeah, in the case study, they looked at both chlorhexidine which is a (inaudible) and polyhexanide which is another name for PHMB.

DR. HILL: And that was the one that was the problem-child, so-to-speak?

DR. HELDRETH: Yes.

DR. MARKS: They used chlorhexidine as a -- that is a reference, another disinfectant, that can cause anaphylactic reactions; but it's got to be extremely rare because that's one of the preferred disinfectants that's still being used. And the other thing that is reassuring to me is that these cases were from 1998; and we don't have any cases since that, so we got almost 20 years without other cases of anaphylactic, particularly from personal care product.

DR. SHANK: How are you going to handle that in the discussion?

DR. MARKS: Just with that -- that it's a rare occurrence, and there haven't been case reports since that one back in 1998; and that was in a wound exposure. I was looking to see if they gave the concentration, and they didn't give the concentration.

MR. STEINBERG: It was used in a drug, as opposed to a cosmetic application.

DR. MARKS: Yes.

DR. HILL: Well, yeah; it's actually the use of (inaudible) that might have resulted in the sensitization. I don't know if they're still marketing (inaudible) with that same stuff in there or not.

MR. STEINBERG: I don't know.

DR. HILL: I remember (inaudible). I just didn't much like it in the swimming pool.

DR. MARKS: Okay; so, does that sound -- team -- motion tomorrow, a tentative report with a conclusion safe.

DR. SLAGA: With a good construction.

DR. SHANK: And the Korean. The case report was on wounds.

DR. MARKS: Right; wounds, there was a rare occurrence.

DR. SHANK: All right; but what about the inhalation?

DR. HILL: Not the same chemicals.

DR. MARKS: Yeah; different chemical; therefore, not relevant.

DR. SHANK: Well, how do you -- because it just gives the initial.

DR. HILL: No, they're written out on page -- I'll show you where.

DR. HELDRETH: Do you think it would be helpful to add a comparative structure in that section where we say this is a different chemical.

DR. SHANK: I think so; yes.

DR. MARKS: You weren't here when Ron asked for chemical structures. You're going to be busy with chemical structures.

DR. HELDRETH: I like that; that's fun stuff.

DR. MARKS: And earlier a group of ingredients. We went from 25 to safe, to insufficient.

DR. HILL: It's on the second page; the back of the cover.

DR. MARKS: Yeah; I think the other good reason for putting that in there is because -- I know I wouldn't want our chemical here in my humidifier -- just a little too close. Do you want that put in there?

DR. HILL: No; I guess I just said it on the record, but, no.

DR. MARKS: That's obviously not a cosmetic use, but at the same time --

DR. SHANK: And, so, the child interstitial lung disease is going to be handled by saying a cosmetic ingredient was not one of the disinfectants.

DR. MARKS: Correct; any other comments.

DR. SHANK: Okay.

DR. HILL: Of course, if we were going to read them across, they are structurally smaller.

DR. SHANK: Well, can't have it both ways.

DR. HILL: That was my jab against excessive read- across; that's what that was. In case you didn't catch it.

DR. MARKS: Okay. Tomorrow I am going to move for a tentative report with safe -- a conclusion that's safe -- and we will -- I'm not sure we need to discuss the skin sensitization -- that'll be in the summary -- but I think the anaphylactic and the lung injury needs to be in the discussion for sure.

DR. HILL: There was something with the discussion. No, hang on.

MR. JOHNSON: So, that chemical structure isn't similar enough to a cosmetic ingredient to warrant any concern?

DR. MARKS: Correct.

MR. JOHNSON: Okay.

DR. SHANK: Pretty similar.

DR. HILL: Well, we have happily a raft if found there of how many of what I

consider to be new state- of-the-art sensitization studies and formulations we have. So, that's the point.

DR. MARKS: I guess what you're saying Ron, is you'd like to see inhalation studies to -- there would not be any lung injuries.

DR. EISENMAN: Or, it might not but (inaudible) uses are very low,.007 hairspray. So, you might want to call that out and say at that low level, but not higher; or something like that. The SCCS says it should not be used in spray products.

DR. MARKS: Yeah.

DR. SHANK: I think I would agree with that; but to say in the report that one of the many compounds in the disinfectant in this humidifier was not the same chemical, and that's true; but it was close. It just has a few more compounds .

DR. HILL: Yeah; the nitrogen's. The biguanide group is different from the guanidinium group, substantially; but yet.

DR. MARKS: How would you like to handle that, Ron, Ron Shank? I can see just in the end, in the discussion saying, we note the Korean experience, but it's a different chemical and it's not relevant. You are still uncomfortable because, chemically, it is similar.

DR. SHANK: But it's basically to be answered by the chemist, and if it's just not close enough -- if it were part of a series of compounds, would it be included in a read- across? And if the answer is clearly no, then it's

(inaudible).

DR. HILL: I would not include it.

DR. SHANK: Okay.

DR. HILL: But I have no strong basis for saying that because the problem with that kind of read-across is you've got, essentially, two data points. That structure class, which is arguably somewhat similar to that structure class, but yet guanidinium is different than biguanide. It's not a question for the chemist; it's a question for the biologist to look at that endpoint and see if they overlap or not, and that, I don't think, is purview here; but there are no inhalation studies, but we have good state-of-the-art -- and lots of them -- dermal studies; so, if that's a concern and they're in hairsprays, then you go to the concentration as.000-something or other, very low; doesn't mean you couldn't sensitize somebody, but it's very low, and no case reports right now.

MR. JOHNSON: The safety assessment includes acute and short-term inhalation toxicity --

DR. HILL: Yeah.

MR. JOHNSON: -- studies; and I'm wondering whether or not those should be mentioned in the discussion in relation to the humidifier, you know, studies?

DR. SLAGA: If there was no concern there, right?

MR. JOHNSON: Yeah.

DR. HILL: But I'm not an inhalation toxicologist.

DR. SHANK: I would just like the discussion to handle that clearly so that the average consumer who might be interested in this understands that it's not exactly the same compound, even though it killed 80 children; it's not exactly the same -- not the same as insufficient --

DR. SLAGA: Overly dismiss it.

DR. MARKS: No, no; I think your concern is right on, Ron. That's why I didn't move on. So, Carol, in this report, do we have inhalation move, or are you're implying in this report the inhalation --

MR. JOHNSON: Acute and short-term inhalation tox studies.

DR. MARKS: Now, that should be reassuring that they were safe -- the end, there is no toxicity. That would be another reason, Ron, that you can be reassured. It's a different chemical and this chemical has (inaudible).

DR. HILL: So many inhalation problems in those particular exposures.

DR. SHANK: When you have a --

DR. HILL: It's page 32.

DR. SHANK: Oh, I remember that the LC-50 is reported as greater than.36 mg/L. I think that was the highest concentration used and no one died. This is what, a dog -- no, rat. That's kind of misleading when you say the LC-50 was greater than this. No; the LC-50

wasn't determined is the way it should be stated. As tested, concentration was.36.

DR. MARKS: Besides this, it's just looks like it was worded, but the study --

DR. SHANK: So, that's just wording. So, yeah, I think, I'd repeat the reference to this inhalation study in the discussion that the cosmetic ingredient was tested for inhalation toxicity.

DR. MARKS: Yeah, to me that's --

DR. SHANK: That's stronger.

DR. MARKS: Yes; exactly, I agree. So, when you put together that it's a different chemical that caused a lung injury, we have inhalation studies in this report that are okay; then, to me, in low concentration and hair dyes we could mention that, but that's not, to me, as powerful as saying it's a different chemical and the inhalation studies --

DR. HILL: That's the acute one.

DR. SHANK: Yes.

DR. EISENMAN: It's at Table 9 is where the most details are.

DR. HILL: Oh, for the short-term inhalation.

DR. EISENMAN: Yes.

DR. MARKS: What page is that, Carol?

DR. EISENMAN: I don't know the page number
(inaudible).

MR. JOHNSON: I can tell you.

DR. HILL: She said in Table 9.

MR. JOHNSON: It's on page 54. It starts on 54; yeah; so, basically, just two short-term inhalation tox studies.

DR. MARKS: Ron, does that bring that into the discussion -- and does that, I think, support the safe conclusion and answer the issue of what happened in Korea?

DR. SHANK: That's the only data we have.

DR. MARKS: Right; but, I think, is it enough to say it's a different chemical, and our inhalation studies in this report are okay; therefore, we feel this is safe?

DR. SHANK: Yes.

DR. MARKS: Okay.

DR. HILL: So, no act is quite 0.025 mg/m3; so how would that relate to use of a hairspray? What's the concentration in the hairspray?

DR. MARKS: It was very small.

DR. HILL: .00-something percent, wasn't it?

DR. SHANK: I don't recall what the adverse was, but it wasn't --

DR. HILL: Anything above that, you had --

DR. SHANK: -- what the affect was. It certainly wasn't this.

DR. HILL: Well, it wasn't entire concentrations, it was at 12.5 and 26 mg/m3 all the rats died; at 2.75 mg/m3, signs of nasal irritation and dyspnea and moderate pneumonitis; thymus glands with severe depletion of lymphocytes and loss of normal architecture.

DR. SHANK: What's the point?

DR. HILL: That's at 2.75. At.25 mg/m3, one rat died; moderate nasal irritation and tachypnea in this group; and some histopathological affects: slight-to-moderately severe pneumonitis; thymus glands; three male and three female rats with red; patchy loss of cilia in tracheal epithelium of three rats; so,.025 mg/m3 seems to be fine;.25 is problematic.

MR. JOHNSON: Let me add that with respect to use concentrations, it's used at concentrations up to 0.0004 percent in aerosol hairsprays, and up to concentrations of 0.053 percent in pump hairsprays.

DR. HILL: .53 percent, so, yeah; so then you have to do some calculations to find out what that really is in terms of human exposure.

MR. JOHNSON: Mm-hmm; and I noticed that in one of the short-term studies, they're reporting severe nasal irritation and dyspnea.

DR. HILL: In some of the higher doses.

MR. JOHNSON: Yeah.

DR. HILL: We need to do calculations to find out. I mean that sounds like it's such a low concentration it shouldn't be problematic for the aerosol -- pump, you don't end up

breathing much of that, I guess.

DR. SHANK: When figured (inaudible).

DR. HILL: Mm-hmm.

DR. MARKS: So, back to lung injury, are we okay with different chemical at low concentration, hairspray's inhalation studies, in this report, are we okay; and that'll be handled in the discussion -- this supporting the safe conclusion?

Tom is yes; Ron Shank, are you (inaudible)? Do you like that for the discussion -- or I should say, more importantly, do you still like the safe conclusion?

DR. SHANK: I have to go back and look at reference five, does it have a good (inaudible); see if I can remember it.

DR. HILL: Reference five is the SCCS opinion.

MR. JOHNSON: Right.

DR. SHANK: So, we don't have enough information from the actual study?

DR. MARKS: Do you think this can be resolved between now and tomorrow, Ron Shank; or do you think we should --

DR. SHANK: No, because I tried to find the study and I couldn't. So, we don't know anything about the exposure conditions which are extremely important in inhalation studies; and many, many times they're not done correctly, especially in characterizing the particles.

DR. HELDRETH: Do you have the SCCS' summaries on that, already?

DR. SHANK: Just the summary. If I remember correctly, there's no detail. Though this has more detail than what I have. Thank you.

Well, if we have to get down to calculating the eight comparable exposure between the rat studies and what you think might happen in consumer use of sprays, that makes me a little nervous -- or not nervous, but concerned. More animal exposure data won't help. So, you'd either have to calculate a margin of safety, or just say this product ingredient shouldn't be used in inhalable products.

DR. MARKS: It sounds like that's where, Ron, you'd feel the most comfortable not using inhalation --

DR. SHANK: Inhalation -- products that can be inhaled.

DR. MARKS: Even though we have these other things, it's still not quite enough to sway you?

DR. SLAGA: You can say that they're somewhat similar in structure, and that would be a precautionary measure is not to have it in any inhalation-type products.

DR. SHANK: You have a significant number of human deaths associated with this chemical, and either you'd need a high margin of safety for exposure for using the cosmetic spray is a thousand times less than what these children were exposed to -- not children, rats.

DR. MARKS: Which would you prefer to go? At this point, I think we could wait for, as you said, it would be very difficult to calculate a margin of safety.

DR. SHANK: I think so.

DR. MARKS: It seems like the reasonable way to handle it would be insufficient data for use in inhalants.

DR. HILL: Currently, insufficient.

DR. SHANK: So, then you'll have to say what do you need.

DR. MARKS: Yeah; its --

DR. SHANK: We already have inhalation data.

DR. HILL: Inhalation data with particle-size carrier dries in such a way that it would relate to pump sprays and aerosol sprays as currently used, or something along those lines?

DR. SHANK: Yeah; I supposed you'd have to try to compare the exposure between the rat study and what you would expect from humans. Now, you do have the main difference between human exposure is a very short term, maybe repeated. But my assumption is when used as a spray once or twice, and then not again for a day, or at least hours; whereas these animals were exposed for several hours a day.

DR. HILL: Then, again, if you have a hairdresser who's using this spray several times an hour?

DR. SHANK: That's more like the rat then.

DR. HILL: I don't know because we don't have the calculation in the

characterization.

DR. SHANK: So, I guess to be fair to the manufacturers of this it would be to say insufficient if the lack of data is quantitative comparison between expected human exposures compared to the rat exposures in the short-term studies. (Inaudible).

Well, that's probably the way to go -- insufficient data; and what we need is quantitative comparison between expected human exposures compared to the short-term rat studies.

DR. MARKS: Okay; safe, except for an insufficient data for --

DR. SHANK: For (inaudible).

DR. MARKS: -- for inhaled cosmetics.

DR. SHANK: Yes.

DR. MARKS: And that relates, really, to the lung injury concern from these Korean reports; and even though -- but I think this all has to brought out in the discussion even though it a different chemical, it's close; even though there's low concentration in hairsprays, we don't know exactly how much is inhaled; even though the inhalation studies in this report are okay, we want to develop a margin of safety from rat studies, making a quantitative comparison between the rat's exposure and expected human exposure, both by the consumer and the beautician who may have much higher

(inaudible) since they may be spraying this, as you mentioned Ron, multiple times during the day, not just one or two. Does that sound reasonable? And, then, Ron, I'll probably ask you to clarify tomorrow, Ron Shank, if you want, but --

DR. SHANK: Okay.

DR. MARKS: -- does that sound -- so, tomorrow I'm going to move that a tentative report be issued that's safe, except for an insufficient data in inhaled cosmetics.

DR. SHANK: I think that's stronger and more logical than to say we dismissed Korean episodes because it's not the same chemical.

DR. MARKS: Yeah; no. If we're ever going to err -- how many deaths were there in Korea?

DR. HILL: 83 children.

DR. SHANK: 84.

DR. MARKS: If we're ever going to err, we better err on the safe side.

MR. STEINBERG: What were they exposed to there?

DR. SHANK: A humidifier.

DR. HILL: The vaporizer.

MR. STEINBERG: Vaporizer with the dimethyl sulfates

(phonetic) on it also?

DR. HILL: Well, you know, it's interesting because I don't think of -- you know, when you run a vaporizer, I certainly spell lots of menthol, but I never really thought there's a whole lot of aqueous particles in the air from the humidifier, at least the normal ones; and you have a compound that isn't volatile -- these ones, I guess, maybe the

(inaudible) is a little, but, yeah, that's what I thought too -- so, these would be in water particles. Effectively, they're coming up into the air with the dissolved substances from a humidifier which -- I mean, I don't know what the design of those Korean humidifiers was; but it just stuns me, really.

DR. MARKS: Okay.

MR. JOHNSON: Because, actually, you have polyhexamethylene biguanide phosphate and polyhexamethylene guanidine in those humidifier formulations.

DR. HILL: What was the two (inaudible)?

DR. MARKS: And this is a tentative report, so there can always be in the next --

(OFF THE RECORD)

DR. MARKS: Okay; I think we're at the point now, let's summarize -- I want to summarize --

MR. STEINBERG: We were just talking; one quick

(inaudible). You saying that it does contain the chlorohexidine ; and chlorohexidine breaks down to chlorobenzene, which is really a bad actor.

DR. SHANK: That's the wound.

MR. STEINBERG: Is that just the wound. It's not in this one? It's not in the humidifier?

DR. HILL: No.

MR. STEINBERG: Okay.

DR. SHANK: (Inaudible) in six different chemicals - - you don't know how much in each one; so you can argue well, why do you pick on this one; why not the others? But you want to be safe.

DR. HILL: Exactly.

MR. STEINBERG: Yeah; well, with those number of fatalities you'd want to be sure.

DR. SHANK: These aren't rats; these are children.

DR. MARKS: Well I think this is, to me, the prudent way to move forward. We can issue a tentative report that's safe, except for insufficient data for inhaled cosmetics; and whoever's making it for inhaled cosmetics come forward with more safety data.

As you mentioned, Ron, the big thing is get a quantitative comparison between rat exposure -- and these studies in this report, which would support the safety of it, but also the expected human exposure.

DR. SHANK: Right.

DR. MARKS: Okay; any other comments? Then, Ron, when we get in the discussion tomorrow --

DR. SLAGA: There's another red flag --

DR. MARKS: Oh.

DR. SLAGA: -- that Wilbur brought up about the nasal, severe nasal irritation; so that's another reason about not being in products that could be inhaled.

DR. HILL: And it might be after all the dust settles, it's still perfectly good in that aerosol spray at.0004 percent, or whatever.

DR. SLAGA: Right; that's fine. I agree with that but --

DR. MARKS: What page is the severe nasal irritation and what (inaudible)?

MR. JOHNSON: Page 55.

DR. MARKS: 55; and the concentration there was --

DR. HILL: There was a dose escalation study, whole range. So,.25 mg/m3, you saw that -- at.025 you didn't see it; at.25 you did see it.

DR. MARKS: .025?

DR. HILL: .025 was clean;.25 mg/m3, you begin to see that irritation.

DR. MARKS: And we have the maximum, well that's leave-on (inaudible).

DR. HILL: This is in mg/m3.

DR. MARKS: Okay; well, another indication of potential inhalant toxicity if you're getting nasal irritation. Okay; any other comments?

DR. HILL: In the dosing, there were 6 hours per day, 5 days a week, for 3 weeks total. So that's --

DR. SHANK: Standard.

DR. MARKS: Okay; any other comments? Well, this should be a robust discussion tomorrow, which will be good.

DR. MARKS: Okay. At the April meeting this year we issued an insufficient data announcement for polyaminopropyl biguanide, also known as PHMB, which is included throughout the report which is good. We needed sensitization data, and I felt -- our team felt that what we received in wave two met this requirement, but now we have a correction dated June 13th. And could you interpret this for me? It says the INCI name 0.1 percent and the trade name 0.5 percent, and we're basing our sensitization okay that 0.5 percent is the maximum leave- on concentration, and we had a negative HRIPT at this concentration, as well as in the previous data we reviewed that appeared that the threshold for sensitization was 1 percent. So I'm not quite understanding why you have a 0.1 percent for the INCI and a 0.5 percent for the trade name.

DR. BELSITO: Because it was 20 percent. The biguanide was only 20 percent of what was provided.

DR. MARKS: So how does that relate for the HRIPT?

DR. BELSITO: The actual concentration of biguanide was one-fifth of what it was thought to be. So the trade name product was used at 0.5 but only contained 20 percent of the active ingredient.

DR. MARKS: So now we have a HRIPT at only 0.1 percent?

DR. BELSITO: Right.

DR. ANSELL: Well, we still have the other HRIPT at 0.2.

DR. BELSITO: At 0.2.

DR. ANSELL: But you're right. The one that was reported as 0.5 is actually 0.1 active.

DR. MARKS: Okay. So that obviously changes our concerns about the sensitization. We could move forward and limit the concentration to 0.1 if we wanted to.

Second concern in the insufficient data was anaphylactic reactions. There were two cases reported in 1998 from wound exposure, and we -- our team felt this is obviously a rare event. We haven't heard anything since 1998, and there are no reported cases of anaphylaxis in the use of cosmetics, so we thought that we could take care of that issue.

And then lastly, data from Korean studies on lung injury, as well as mortality. So significant problems.

We had quite a bit of discussion about this lung injury issue. Presumably, it was a different chemical, but it was one that was related to the polyhexamethylene biguanide. It's low concentration in hairsprays, but in the present inhalation studies we had in this report it was okay. However, it does cause severe nasal irritation. So that insufficient data we felt was not met. We felt we needed a margin of safety which could be developed from the rat studies with a quantitative comparison between rat exposure in the studies that are in this document and the expected human exposure was both a consumer or beautician. So we didn't feel we would meet that. So we felt that. So we felt that we would move forward with a tentative report; that it would be safe except for insufficient data for inhaled cosmetics. I think with a sensitization issue maybe we need to put a limit on the concentration for the other uses besides inhaled cosmetics.

DR. BERGFELD: A comment from the Belsito Group?

DR. BELSITO: Yes. So first I'll let Dan address the Korean issue because it was my assumption we're dealing with a totally different chemical there.

DR. LIEBLER: Yeah. So the substance associated with the effect in the Korean effects due to the inhalers was polyhexamethylene guanidine, which is, I would say, it's chemically similar, but it's a guanidine as opposed to a biguanide structure, which is different enough to not be the same chemical. It's not, you know, I don't think we can say that that effect would be reasonably predicted to occur with the ingredient that we're reviewing in this report.

DR. MARKS: We had that same discussion. I'll let Ron Shank comment to that and Ron Hill possibly. But we had quite a bit of discussion that it was similar. We couldn't read-across in terms of would it be safe or would it be toxic? So that's why Ron Shank, why don't you go ahead and elucidate more?

DR. SHANK: All right. We discussed this at length. We realize that the chemical associated with the children's deaths in Kora is not the same as the cosmetic ingredient. But we do have inhalation toxicity data for the ingredient. And it is not inactive. The exposures,

especially the short- term inhalation toxicity exposures did produce a variety of adverse effects at relatively low exposures. And that is for the cosmetic ingredient. So I would like, rather than just dismiss the issue of inhalation toxicity by saying the Korean experience was with a different compound, I'd like to see a margin of safety analysis between human exposures to hairsprays and the rat short-term inhalation toxicity studies.

DR. LIEBLER: So you're referring, Ron, specifically, to PDF 32 under the acute inhalation --

DR. HILL: The subchronic.

DR. LIEBLER: So the acute inhalation is the one in rates that referred to the results with dark red lungs observed at necropsy and a dose related depression of respiratory rate reported in a study in which mice exposed --

DR. SHANK: On page 33, PDF page 33, there is short- term or subchronic toxicity studies which were inhalation. And --

DR. BELSITO: It was negative.

DR. SHANK: Pardon me?

DR. BELSITO: It was negative.

DR. SHANK: No, it wasn't. If you could go to --

SPEAKER: Table 9, page 15.

DR. SHANK: Yeah, Table 9.

DR. BELSITO: But there was no observed affect at.025 milligrams per meter cubed.

DR. HILL: .025. You're right. At.025 you're right, they're not, but at.25 percent there was. And so --

DR. BELSITO: Not percent; it's milligrams per meter cubed.

DR. HILL: I mean, sorry, not percent. Yes.

DR. SHANK: It's milligrams per cubic meter. I think with the issues that have recently been

brought up as to how much of these hairsprays are actually inhalable, we've been dealing with that. I would like to see a margin of safety analysis trying to find out what would be a reasonable exposure from the use of hairsprays and compare that.

DR. BELSITO: Look at the exposure. I mean, what are the concentrations of use in hairsprays that are extraordinarily low?

DR. SHANK: Well, yes, the concentrations are low. But how often are the hairsprays -- I don't think we can just dismiss it and say, well, these aren't inhaled and it has nothing to do with --

DR. BELSITO: I don't think we're dismissing it. It would be something we'd bring into the discussion.

DR. SHANK: Right. It's just a calculation. But it should be done by people who know the hairsprays, not by me.

DR. BELSITO: Okay. Well, I mean.

DR. MARKS: And then the other issue was by consumer it might be only one, two times a day, but if you're using it as a beautician, it could be multiple times a day, so there could be a significant more exposure in that setting.

DR. BERGFELD: Ron Hill, did you have a comment?

DR. HILL: Yeah. I was just going to say in the concentration in the pump spray is higher. It's.053, and I don't know if we have a good handle. I mean, I actually know we have, even from the material that we reviewed for that boilerplate preparation, there was some analysis of potential incidental exposure from pump sprays. So I think what we were looking for is to relate that potential at.053 percent is the information we have here with the way the exposures were done in the rats and say we have a 10,000-fold margin and I think where we landed was children died in Korea. Eighty-some children died in Korea. It's a different chemical so we don't have any reason to believe that this would be a problem with either of these, but we don't have any data to show that it wouldn't or analysis of that. I think that's where we landed. Is that consistent with what our discussion was?

DR. SHANK: Yes.

DR. MARKS: Yes.

DR. BELSITO: I guess I just want to follow up on your last comment, Jim, and just clarify what the purview of this panel is because I know that in RIFM, we're doing QRA. We're not looking at occupational exposures. We're looking at consumer exposures. Is the purview of this panel to look at safety of a "cosmetic ingredient" as used under all circumstances, including by beauticians? Or is it to look at the safety as used by consumer? Because I would think beautician safety in their workplace would be more OSHA and not more us. But I don't know. I just raise the issue because it's something that will go across many other different products.

DR. BERGFELD: Dr. Marks, do you want to comment?

DR. MARKS: I think, haven't we in the past, advised the cosmeticians or beauticians as I recall to protect themselves possibly with the acrylates that we gave advice of how they should use protective?

DR. BELSITO: It was more consumers for home use.

DR. MARKS: Yeah.

DR. HELDRETH: Certainly, the most common purview of this panel is to look at exposure to humans. But if this panel is aware of any perceived hazards or risks to other settings, I think it's worthwhile to make --

DR. LIEBLER: I mean, if there was no issue, if you completely set aside the issue of possible exposure of people who worked in salons, for example, your request for or your suggestion to do this quantitative or margin of exposure calculation doesn't go away; right? So I think it's really a side issue. I mean, I think the question really is more do we do this margin exposure calculation, which I personally think is very reasonable. We have the data. We could do it. And, you know, I don't think we need to decide whether this panel deals with occupational or individual consumer exposures to make that decision.

DR. ANSELL: Yeah. I think we've jumbled a number of issues all together. I mean, we started talking about Korea and you're talking about potential exposure to the material based on data on the material. And then we've thrown in this whole occupational, and I really think we need to detangle the discussions so we fully support the concept that the Korean issue is not relevant to this discussion. We also would support the calculation of a margin of exposure. And I would stay quiet on the occupational issue until it's demonstrated that it's of some relevance to the discussions.

DR. MARKS: Jay, I'd beg to differ just a little bit. I think the Korean incident that was reported is relevant because if that didn't happen we wouldn't be talking about it. It's just that since this chemical that we're reviewing is similar, that gave us pause. And that's why we liked the margin of safety so that we can say with this chemical we know that inhalation toxicity is not a concern. Does that sound proper interpretation?

DR. SHANK: Yeah.

DR. MARKS: That was the alert, really.

DR. SHANK: We have rat inhalation data, quantitative. I think we should use that to show that the margin of safety is sufficient.

DR. LIEBLER: Right. And I think that's the really, in my view, the only really compelling reason to do this. And it's perfectly appropriate diligence for this panel to do it and for CIR staff to assist us with the calculation. But I think that makes sense. You know, whether you buy into the cross structure comparison with the prehistoric --

DR. HILL: There's no data one way or the other.

DR. LIEBLER: You know, it's just a matter of opinion.

DR. MARKS: Right.

DR. LIEBLER: But we do have data. We can do the calculation. This is, you know, an acceptable procedure for a risk evaluation like this. So I think I agree with doing that.

DR. BERGFELD: All right. Bart?

DR. HELDRETH: I just wanted to clarify a little bit about the worker versus the consumer issue. Very much like in the report we just finished, the persulfates, we took this line out of the definition that gives instructions to the hairdresser of how they should use it to be safe, and we kept that in the discussion. I think that would be the appropriate level of concern that the panel could apply here for its concern to hair dressers, but it shouldn't be in the conclusion.

DR. LIEBLER: Correct.

DR. HELDRETH: It should just be for the consumer.

DR. BERGFELD: Correct. Paul, do you have a comment?

DR. SNYDER: I agree.

DR. BERGFELD: So I'll entertain a motion to table.

DR. MARKS: Well, do we want to table or do we move with a tentative report --

DR. BERGFELD: Well?

DR. MARKS: -- with insufficient data for inhaled cosmetics and then we get the margin of safety. If it's okay, then we go --

DR. BELSITO: There is more because we don't agree with their conclusion.

DR. MARKS: Oh, okay. Well, certainly, we have sensitization we need to clarify, too.

DR. BELSITO: We need to clarify sensitization big time because this is a sensitizer.

DR. MARKS: Yes.

DR. BELSITO: We need big studies. It's a moderate to, in some studies, strong sensitizer, and this is MI, about to happen if we don't regulate it. And I think this is one that we have to do like cocamidopropyl betaine. We don't come out with a single concentration that's acceptable across all product lines. We ask that QRAs or some other type of risk assessment be performed depending upon the product. And right now we don't have a NESIL to put into the QRA -- well, we do. We have a NESIL to put into the QRA which is 25 micrograms per sonometer squared. I'm not sure, Don, if we can use the.2 study. I would like to look at that in depth because that was really quirky. There were a lot of questionable reactions going on during the sensitization and challenge phase that they said were read as negative, but I would really like to look at that before, even if you can calculate the dose per unit area on that study before we sign off on it. So I think that when we do get an appropriate NESIL, it has to be with a conclusion as we did with cocamidopropyl betaine to be clear that we're not saying it can go out at.1 or.2 or whatever the HRIPT allowed but it has to be put to some type of quantitative risk.

Also not so certain that I want to dismiss the urticarial reactions. I looked at this last night. There are more than just two. The initial two were done by Oliveri and those were actually fairly well studied. They were confirmed in skin prick testing to react to the polyaminopropyl biguanide. They were also confirmed by blood testing, IGE levels. And both of those patients pretty clearly historically were sensitized by burn wound dressings. And then you have the one report coming out from Ann Goossens in Brussels or Leuven, and it's really not 100 percent because she tested with the dressing, which also contains polyethylene glycol 4000. She did not do controls but she then did some base fill activation testing and said it was positive in her patient.

And then there's another report of an additional patient again seems to be a burn patient. So the question is whether this is how we handle this. Is this something that we just de facto said, like we did initially for the polyethylene glycol should not be used on damaged skin or to what extent do we pursue it? But it's quite clear that you can get -- oh, and then the other reaction was tracheal during surgery where they were spraying in onto mucosal services. So it's quite clear that you can get severe, life-threatening anaphylaxis because the patient subsequently reacted to wet wipes with anaphylactic reactions from sensitization. But he question is how were they sensitized? And it's not 100 percent clear, but it suggests they were sensitized through use presumably on second or third degree burns. So how do we get to that? I mean, we eventually got rid of the damaged skin because we show that it was on burn patients, and when you tape stripped the skin you weren't seeing these effects, but we don't have any of that data for this molecule.

DR. BERGFELD: So what are you suggesting?

DR. BELSITO: You know, I hesitate to say damaged skin because I think the skin was probably more damaged, but that would probably be the safest thing to say. And pending some ability of industry to show us that when you tape strip the skin you're not getting urticarial reactions as they did for the PEGs. But I clearly think we need a defined NESIL and QRA, and right now that looks to be 25 micrograms per sonometer squared, which is going to be low, but this is used in very low concentrations by and large.

DR. BERGFELD: So are you suggesting we go out as a tentative insufficient?

Or are you suggesting table and requesting this?

DR. BELSITO: I think that we can do, you know, one or two things. We can go as insufficient and ask industry to provide us data on, you know, urticarial reactions on tape stripped skin like they did for the pegs or we can say not to be used on damaged skin and, you know, apply a QRA based upon a NESIL that currently exists of 25 micrograms per sonometer squared.

DR. BERGFELD: Jim and then --

DR. MARKS: Yeah, I'll retract my motion. So I think the issue to me is do we just table this to get more or do we do a second insufficient data notice? And we're going to suggest that on another ingredient.

I can go either way. It doesn't matter to me. Your points are very well taken, Don, and I agree with all the points you make about sensitization about anaphylactic reactions and we still have the lung to get the margin of safety. So it's just a matter of, I would say either table it or do another insufficient data announcement. I don't think we need at this point to issue a tentative report because there's a lot of things still hanging.

DR. BERGFELD: Jay?

DR. ANSELL: Yeah. We'll leave up to the staff to decide which of those two makes more sense. I think our position is this should not proceed to the next step of development. These are new questions and we would like an opportunity to address them, many of which are very straightforward and some of which may be a little more complicated. So whichever as long as we don't proceed to the next step.

DR. MARKS: Right. Jay, which do you think has a greater potential for getting response from industry, a tabling or another insufficient data notice?

DR. ANSELL: You know, I don't know that industry would respond differently to either.

DR. MARKS: Okay.

DR. ANSELL: Yu know, we are committed to the support and analysis and assessment of the material. I just don't want this to start a development clock because these are new questions. So we should, you know, go back to wherever the last step was.

DR. MARKS: We concur. That's why I withdrew my motion about a tentative report. And the decision --

DR. BELSITO: I guess the question becomes what are we asking for? I mean, the margin of calculation could be done from the data we already have; right?

DR. MARKS: Right.

DR. BELSITO: The NESIL, we currently have an acceptable NESIL of 25 micrograms per sonometer squared. If industry doesn't like it, if that's too low when they do run a QRA or whatever method of risk assessment they want to use to address the sensitization hazard, they can come back to us with new information. I don't think we are going to get within a reasonable period of time the kind of information that would allow us to fully understand the situations under which these urticarial reactions occur and whether they could IGE mediated sensitization type one could occur by using the products on damaged skin.

My bigger concern is that if we, I mean, Europe's along this at.1 and they haven't said you need to use QRA. I mean, it's across the board. And if.1 is going to start creating problems in underarm deodorants and wet wipes, then we're going to lose another preservative. So, I mean, I feel inclined, only because I just -- you know what will happen, if there is a mini epidemic, polyaminopropyl biguanide will just be banned in Europe. They won't look at any risk assessment at that point. I would prefer to move ahead and just, I mean, you know, say that this should not be used on, you know -- how did we handle the PEGs where it was clear that it caused renal issues in burn patients when it was -- when the skin was completely --

DR. ANSELL: The confusion in that for us was that damaged skin was undefined.

DR. BELSITO: Right. But, I mean --

DR. ANSELL: And so --

DR. BELSITO: -- how do we handle finally saying, okay, we could get rid of that but in the discussion that we said, okay, you know, it caused renal effects because it was used on second and third degree burns where it essentially went into the bloodstream.

DR. BERGFELD: Carol?

DR. EISENMANN: The dermal penetration study, the in vitro dermal penetration study that was tape stripped skin that didn't go through the skin so it doesn't -- so it wouldn't get to cause the renal issues.

DR. BELSITO: Right.

DR. EISENMANN: So this is a little different if the facts are right in the skin.

DR. BELSITO: Right.

DR. MARKS: It's in the skin and it's systemic. Contact urticants is not concerning, really. It's the anaphylactic reaction, the systemic reactions which are really concerning. And the contact urticaria is just a harbinger of what potentially can occur.

DR. BELSITO: But the sensitization can occur initially in the skin as happened with latex gloves.

DR. MARKS: Oh, yeah, absolutely.

DR. BELSITO: So Carol has a point; that just doing a penetration study showing that it doesn't get through the skin doesn't help us.

DR. MARKS: Correct.

DR. BERGFELD: I'd like to have Bart tell us what the administration or staff would like us to do here.

DR. HELDRETH: Our preference, of course, would be to not table it simply because it leaves it to languish out there. As Dr. Belsito said, this is something that needs to be acted on sooner rather than later. So we would support either continuing with a TR with some sort of insufficiencies, or if you don't feel that that will get you the data that you need, we could issue a second IDA with the preface that there's a clock to that and we plan to come back and continue this report in the near future. But we're just afraid if we table it, it's going to sit there and wait.

DR. MARKS: I've already withdrawn my motion.

DR. BELSITO: Okay. So then I think what I'd like to do is simply go forward and say that, you know, we let industry know we will be doing a margin of exposure calculation for aerosol exposure that we will be suggesting that this be formulated to be nonirritating, nonsensitizing using risk assessment methods such as the QRA. And ask for one data request for the clarification on the urticarial issue. And you know, maybe that can give me a little more time and perhaps we can get more articles to suggest that it really occurred only in settings of, you know, where there was obvious systemic absorption as occurred because, I mean, one guy it was instilled into the trachea and the other two patients, it was applied -- the sensitization historically occurred with a wound dressing for a second degree burn. And I can give Ann Goossens a call or an email and find out details about what she thought about her patient that she reported.

DR. MARKS: Was this -- were all these reports -- was not familiar with the subsequent ones other than this index, two cases in 1998. Is it still the same commercial product?

DR. BELSITO: Yeah. It was all with this European product Lavasept.

DR. SNYDER: Lavasept.

DR. BELSITO: Lavasept.

DR. SNYDER: Lavasept. And there is -- because I looked into that, too, because there's the Baquacil that's used in the U.S., and there's no associated issues with that.

DR. MARKS: So what's interesting to me is, why is it still on the market if it's that dangerous? And then actually, the authors of the 1998 report referenced similar reactions to chlorhexidine.

DR. BELSITO: Yes.

DR. MARKS: Which is still widely used, and even though they occur, I mean, it's used daily widespread chlorhexidine is. So again, if it's still being used in Europe, why is it still being used if they've had these severe reactions with wound exposure?

So there are a lot of questions. I think, Don, I think it sounds like the question now is do we do an insufficient -- a second insufficient data announcement, which I'm fine with, or if you want to propose a tentative report with restrictions.

DR. BELSITO: Well, I mean, you know --

DR. MARKS: Hearing industry, obviously --

DR. BERGFELD: And do just that request.

DR. MARKS: -- the tentative report is moving forward and there are a lot of

questions. I think I'd prefer a second insufficient data announcement. That alerts industry what's going on and puts the onus to get some of those questions answered. And obviously, we're going to get calculations done and that way it doesn't languish.

DR. BELSITO: Yeah. And I would like to actually see a copy of that.2 percent HRIPT to look at all -- a detailed copy with all the reactions. And then I'll call Ann and maybe we can actually get the SECS document to see whether they noted these urticarial reactions, and since it did occur in Europe, perhaps they have further data on them.

The Oliveri paper, several of the papers did look because structurally this is similar to chlorhexidine. They did look to see if these individuals were also allergic to chlorhexidine and they were not. So the sensitization did not occur to be from chlorhexidine and it occurred to be from the Lavasept product.

DR. MARKS: And then I'll just comment. We had this discussion yesterday in our team, is we'd really like to avoid a conclusion that says formulate to be nonsensitizing. We know we do that with botanicals a lot but, you know, the ultimate absurdity is formulate to be nontoxic.

DR. BELSITO: But I think in cases where you have moderate to strong sensitizers and the area where you use it can significantly affect the outcome in terms of sensitization, as has been shown by methylisothiazolinone where, you know, at 100 parts per million in most rinse-offs it was perfectly fine. What caused the issue was wet wipes.

DR. MARKS: Yep.

DR. BERGFELD: I'd like to ask Bart again what he'd like us to do, whether we move forward with another insufficient or we ask for the data request and then take this up in September again. Would you comment?

DR. HELDRETH: Sure. I mean, of course, that's the panel's prerogative how we move forward, but if you feel that we are going to have all these needs met in time to prepare the reports again in September, then certainly, you could go forward with a tentative report. If you think it's going to take a little bit more time than that, then we could go forward with another IDA, meaning that this report would get finalized most likely in December instead of September. So if you feel that the extra time is needed to make sure we get everything collected, by all means we could do that second IDA. But if you feel that it's just some small calculations and some contacts with some of these authors, then you might want to move forward with the tentative.

DR. BELSITO: How quickly can you get the full SECS document? Is it publicly available?

DR. HELDRETH: Typically, we can download the SECS documents right away.

DR. BELSITO: Okay. So, I mean, I think, why don't we just move ahead and look at it in September? I mean, I would -- I think that having a little bit more opportunity to pursue the urticarial reactions I'll have a better sense and they're probably on burn patients, which we can then put into the discussion that, you know, significant mucosal exposure is not the situations under which these would be -- the consumer would be exposed to in cosmetic products. And we'll satisfy Ron Shank's issues with the calculation which should be fairly quickly, and we'll give industry a chance to calculate the NESIL for the best data they have and, you know, we can always move ahead with a conclusion. And then if they don't like it in terms of restriction, you know, they can live without restriction until they can provide data to show us it can go higher. Again, I don't want to -- I mean, this is a good preservative. I just don't want to see it removed from the marketplace like MI has been.

DR. BERGFELD: So I'm going to entertain another motion.

Yes?

DR. HILL: Yeah, you're going to make a motion here in a moment. I just wanted to point out, I'm not sure of Baquacil in swimming pools is still on the U.S. market for swimming pool use. Does anybody know?

DR. BELSITO: I tis.

DR. HILL: It is still? Okay. The other thing we want to point out with the chlorhexidine versus the Lavasept is chlorhexidine is not a polymer, so it's a defined length. The poly PHMB that we're considering here has long chain -- is long enough that I presume could crosslink IGE, so that's a different scenario than chlorhexidine. I just wanted to

point that out. If we're worried that urticaria is a sentinel for type ones, then I think there's an unknown there that doesn't exist with chlorhexidine or the isothiazlesinone.

DR. BERGFELD: Jim, do you want to propose a motion?

DR. MARKS: Yes. I propose that Don issue a motion for the tentative report with all the issues you suggested, Don.

DR. BERGFELD: Will you propose a motion?

DR. MARKS: Since you want to move forward. Although, I see Jay over there with nonverbal communication.

DR. BERGFELD: Jay? Okay, I'm sorry. Jay?

DR. ANSELL: Wholly separate from the data discussion which I think has all been entirely reasonable, you know, I, again, would urge that we go for a second report with insufficiency. These are, you know, new items that we haven't had a chance to discuss, and to proceed with the thought that we might catch up or not in this report or future reports I think would be troubling. The panel has the right to ask all sorts of new questions and request new data at any time, but I think we also have the obligation to have some time to be able to respond.

DR. MARKS: So my motion would be a second IDA. I hear you loud and clear, Don. It isn't a huge amount of time. We've heard from Bart that for sure we'll have it by December. We may have it before for September and we'd urge that to occur. But it gives you a little bit more time in industry.

So I don't know, Don, I can go either way. If you feel strongly --

DR. BELSITO: I don't know what the rules are. Once we go insufficient, can we go with a second IDA again? I mean, is that -- is the next step to do a tentative final?

DR. SHANK: There are no new data needs identified.

DR. BELSITO: Okay. I mean, I'm fine. I just don't want to table it because --

DR. MARKS: Right.

DR. BELSITO: -- otherwise, it's not going to move along.

DR. BERGFELD: So is there a second to the IDA motion? And the list, again --

DR. BELSITO: Calculation, margin of exposure for inhalation based upon the 14 or 28 day study we have and the current use in hairsprays -- probably even better, deodorant sprays because they're said to have smaller particles, or a combination. Further clarification on the urticarial reactions. I've read the papers and I think I'm fairly certain those were significant burns. I'll find out from Ann whether she has a clue as to where her patient was sensitized. And we'll get a look at the hard data on the.2 percent study, and if industry has any HRIPTs that would give us a higher NESIL, hopefully they would provide those and go from there.

DR. BERGFELD: So it's been moved and seconded that we go out for an insufficient data announcement with the list that you've heard.

Any further comments?

DR. MARKS: No, it's just a clarification of all three points that we had in the first time insufficient data announcement.

DR. BELSITO: Right.

DR. BERGFELD: Okay. I'm going to call the question then.

All those in favor of IDA? Unanimous. Thank you.

(The motion passed unanimously.)

DR. BERGFELD: Thank you. Very good discussion. Thank you.

DR. BELSITO: Can we just have one little further discussion?

DR. BERGFELD: Sure.

DR. BELSITO: In reading this report, we understand very clearly Dr. Shank's desire to point out that polyaminopropyl biguanide is actually polyhexamethylene biguanide hydrochloride, but it became very confusing for me and even for the writer because at one point they called it polyhexamethylene biguanide twice when one was one and one was the other, to keep doing this with parentheses. And what we suggested be done is that the INCI name, polyaminopropyl biguanide be defined up front as polyhexamethylene biguanide hydrochloride and indicate that it would be represented in cap letters throughout and that the chemical ingredient polyhexamethylene biguanide hydrochloride would be in lower case. So when you saw the caps you knew it was actually polyhexamethylene biguanide and when you saw the regular you knew it

was probably polyaminopropyl biguanide. But putting the parentheses there I thought was extremely, extremely confusing in trying to read the data.

DR. BERGFELD: Ron Hill?

DR. HILL: Could you just define it as PHMB somewhere near the beginning and just keep using that all the way through except when you needed to explicitly refer to the polypropyl as the actual polypropyl, which is only maybe in two spots? I mean, I don't know. At least give consideration to that.

DR. LIEBLER: Just to clarify, I think what we were suggesting, if we are indeed on the same page, Don, is that in the first paragraph, the introduction, when this discrepancy between the INCI name and the chemical substance name is explained, we thereafter in the report just use the INCI name, which always begins with a capital letter for the name throughout the report, indicate up front what the difference is, not use the abbreviation since we normally don't do that throughout our reports. We use the INCI name throughout the report. You know, we don't normally, but this is a very exceptional circumstance where the chemical name is -- and I think there is a purpose in using the parentheses and reminding people that it's not polypropyl --

DR. LIEBLER: Well, you don't need to remind them 10 times on every page. So I think that, you know, basically what I'm suggesting is that we stick to our standard practice. We define the discrepancy up front but we then don't beat the reader over the head with it repeatedly throughout the report because it's just unnecessary. My two cents. Our team's two cents.

DR. MARKS: Fine.

DR. BERGFELD: That's agreed.

DR. HELDRETH: And would you keep the parentheses in the title or would they go there, too?

DR. SHANK: Definitely in the title.

DR. BELSITO: You could keep it in the title.

DR. SNYDER: No objection.

DR. BERGFELD: Any other comments before we move on? Seeing none, let's move on then. The next one is plant-derived proteins. Dr. Belsito

presenting.

DR. HILL: I'll just make a mention while they're getting settled on that particular issue because it's come up with me about this use of caps versus not caps is when you have toxicology data that's testing a chemical and we don't know that it is, in fact, the cosmetic ingredient, just that chemical, then frequently people are using -- our staff are using capital letters inappropriately in my opinion. If the material that's being tested in the toxicology study is not actually known to be the cosmetic ingredient, then why are we going to capitalize it in the report? So, I mean, I think this is a bigger issue than just that PHMB that we just talked about. We really need to discuss that practice. Because if you have a journal article from an academic group or from whatever source and they've tested something that has the same chemical name as the cosmetic ingredient but we have no idea if it is, in fact, purchased from a source that's the cosmetic ingredient, then I object to putting capital letters there in the report. So that's my issue with that.

DR. HELDRETH: It's very common that the data sources we get, whether they're published or unpublished, do not relate, whether or not that chemical tested was necessarily the same as what's in a cosmetic product. However, we only include those ingredients under the INCI ingredient name when we, to the best understanding, believe that it is the same chemical. When we do have a question about it, we point that out at the data set. So we'll put in parens, within the summary for that data point, that it was reported as this so that it gives the panel an inclination that this may not be exactly the same.

DR. HILL: So in a discussion of a chemistry section where you're talking about the chemical, that at least the chemical is the same as the ingredient, you think it's perfectly appropriate to capitalize all the way through. I mean, for generic drug names, for example, you don't ever capitalize those unless they appear at the beginning of a sentence or in a table heading or title.

DR. HELDRETH: Yes, but we're not dealing with a drug name.

DR. HILL: I know that.

DR. HELDRETH: The common practice in the cosmetic industry is to follow the format of the nomenclature dictionary. And their standard process is to capitalize the first letter of each name. So we're trying to keep that as a consistent thing so that the name that is in our report is the same exact name that the consumer or any stakeholder will find on a label.

DR. HILL: I don't disagree with that, but I think if it's capitalized, it should be referring to the ingredient -- clearly referring to the ingredient and not just a chemical purchased from Aldridge and tested in a lab. And that's where the gray area is for me.

DR. HELDRETH: Yeah. I mean, we would certainly like to see more of that direct relationship there, but I think that's beyond means.

DR. HILL: Unfortunately, we don't have cosmetic grade or product like we might have with food grades. That's -- I don't know if it's unfortunate or not but the point is that makes it more of a gray area than it might otherwise be.

DR. BERGFELD: All right. Than you.

DR. BELSITO: Okay. Just to point out, Dan, capitalizing only the first letter will make it confusing when the first word of the sentence is the material. So I really think we have to capitalize all the words -- all the letters, rather.

DR. HELDRETH: In this case, however, it's a two -- a two-word name. So the polyaminopropyl and the b in biguanide will be capitalized in each case.

DR. BELSITO: Okay, fine. As long as there's some way of differentiating it. Yeah, good. Okay.

Day 1 of the September 11-12, 2017 CIR Expert Panel Meeting – Dr. Belsito's Team

Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride)

Okay. Polyaminopropyl biguanide. So the issues surrounding this at the last meeting, just to briefly summarize, were sensitization and then the outbreak of respiratory in Korea related to polyaminopropyl guanide, not biguanide. And we wanted to review that data. We also wanted some type of quantity. We asked for the (inaudible) name because there was mention that there was one, but no EC3 value. And we were told that whoever generated that (inaudible) did not wish, for whatever reason, to share it with us, which always bothers me. And so which issue do you want to discuss first, the respiratory? The again, the women for whatever are criticizing us for the fact that we don't think the polyaminopropyl guanide is a good breeder cross for the biguanide when, in fact, in the papers that looked at the respiratory toxicity they actually used, the IPA or some agencies limits for the polyaminopropyl biguanide for their estimates. And then we were told that there were two papers that they could not give us in the electronic forum, but had available here for us at the meeting. Is that correct?

MR. JOHNSON: Yeah, Carl distributed those to all the panel members this morning.

MS. FIUME: We (inaudible) out of it.

DR. BELSITO: Okay.

DR. SNYDER: Yep. Isn't that with the long paper there, at the bottom of that long (inaudible) paper there.

DR. BELSITO: Okay.

MR. JOHNSON: In case you want to look at (inaudible).

DR. BELSITO: Well, I mean, if they're here, they're here. I have them. I just didn't realize that's what was below them. Okay, yes. The second lead paper.

SPEAKER: (Inaudible 0:09:06.)

SPEAKER: There's one down here.

SPEAKER: (Inaudible 0:09:08.)

DR. LIEBLER: The two lead papers.

DR. BELSITO: All right. And then we got comments from Linda. So I guess while you guys are looking through that, I mean, it wasn't reflected in the concentration of use that we're given in the document, although it was referred to and is reflected in the use concentration that Beth provided in July. But apparently these are no longer used in products that could be respirable. And, in fact, at least one manufacturer sent us a letter stating they should not be used.

SPEAKER: (Inaudible 0:10:20.)

DR. BELSITO: So that may put this entire issue to rest. But, Wilbur, I think we need to update the table that's in the current document we have to reflect what Beth sent in July.

MR. JOHNSON: Dr. Belsito, how does this relate to products that are still on the shelves and company inventories of those --

DR. BELSITO: Well, I mean --

MR. JOHNSON: -- (inaudible).

DR. BELSITO: Is the question, were they ever used or was this a misreport? I don't know.

MR. JOHNSON: Well, we had received a use concentration data earlier this year, and then subsequently received a, you know, a statement indicating that it's no longer being used in, you know, pump hairsprays or aerosol hairsprays.

DR. BELSITO: Was the statement that it is no longer or it wasn't used? I mean, we so often get information and corrections that, oh no, we weren't using that.

DR. ANSELL: Well, you know, I'm not sure that CIR needs to opine on stock management issues. I think that it is not appropriate for spray applications. These manufacturers in the industry do not support that application. It is a simple (inaudible). I actually don't know

whether it had ever been used or maybe they just don't think that we need to spend a lot of energy going through and correcting spray exposures which are going to lead to conclusions that we're going to accept up front which is, they should not be used in spray applications.

DR. BELSITO: Okay. So then we have to justify that use, which means we are going to use the guanide as a read across for the biguanide? I mean, we can't say that it's not safe to use without giving a reason why it's not safe.

MR. JOHNSON: Well, we also have some inhalation tox data on polyaminopropyl biguanide in the safety assessment.

DR. BELSITO: Yeah, I know. In fact, that's the data that this individual used to read across for their calculations, right? Because they had no data on the guanide. They used the EPA or someone's dataset.

MR. JOHNSON: (Inaudible 0:12:50.)

JAY ANSELL: So we suggest we just go as insufficient. You know, you're looking for more data. No one's going to provide it because no one uses it. It'll go insufficient and then after two years it'll go to safety unsubstantiated.

SPEAKER: What about unsafe?

DR. BELSITO: I mean, is it? You know, this was all beyond my area of expertise. And for the respiratory endpoint, you know, we did go in and calculate margins of safety. Now the lead paper didn't talk about -- at least the one we had in the document. Was that waved too? Is that why I'm not seeing it? Or it didn't, you know, it was at the end of -- yeah, it didn't talk about margin of safety. It used some other term that I had never heard before.

DR. BOYER: Yeah, actually what the lead group did was to use a risk assessment. So what they're calculating are basically hazard indices. And, you know, it's similar to the outcome of the QRA, that ratio. And --

DR. BELSITO: So the health risk quotient?

DR. BOYER: Right.

DR. BELSITO: And you want that to be less than 1000?

DR. BOYER: Well, you know, they calculate that hazard quotient, and they incorporate safety factors and so forth into that calculation. And what we do is we calculate margins of safety, which is basically a indication of what that safety factor is. So the outcome of a margin of safety calculation is, essentially, what is the safety factor? And typically for these types of calculations of safety factor for a margin of safety is about 100 or so is satisfactory.

DR. BELSITO: Right.

SPEAKER: Right.

DR. BELSITO: Okay. And --

DR. BOYER: So and it's just --

DR. BELSITO: -- in using these calculations, they say right here that they didn't have the information for the guanide, that they used the information, the NOACK of 0.24 micrograms for liter for the biguanide, which I believe is the same reference that we're using.

DR. BOYER: That's correct.

DR. BELSITO: So their data was calculate off of the biguanide as a read across, which was one of the criticisms that we were getting, saying that, oh well, you know, the biguanide is different from the guanide. And she was saying, well, if it's that different, why does this other -- why is this other group using the biguanide data for read across for the guanide. That's all I'm saying. So his calculations in these papers are based upon the data we have in this paper. You know, the point of the matter is, if your calculations are correct, and I don't know how to do margin of safety calculations for, you know, respiratory toxicants. I'm pretty good at QRA, but I'm not good for that. If your calculations are correct, this could be safely used in aerosolized products, but for the pumps, I think, it was 12, so the margin of safety was not adequate for pumps.

DR. BOYER: Because the concentration of use that was reported to us was very, very high.

DR. BELSITO: Right. But my point is, you can't say that the data are insufficient. In fact, the data would support, at a certain level, the ability to use these, perhaps. This.24 was chronic or was subacute?

DR. BOYER: It was subchronic.

DR. BELSITO: Subchronic?
DR. BOYER: Yes, right. Twenty-eight --
DR. BELSITO: So you could have --
DR. BOYER: -- days (inaudible)
DR. BELSITO: You could argue that we need chronic data because these will be used chronically, but this subchronic data, these animals were exposed what, six hours a day or something like that?
DR. BOYER: Mm-hmm. It was six hours, yes.
DR. BELSITO: I mean, so that's pretty extreme, too.
DR. BOYER: Right.
DR. BELSITO: You know, you're not going to be exposed six hours a day to a pump spray. My whole point is, let's be consistent. Let's not say, oh my God there was this outbreak in Korea and, you know, so now -- and we got one manufacturer saying it shouldn't be used in products that could be inhaled. And we say the data is insufficient when, in fact, the data -- I mean, you calculated margins of exposure, and based upon the information that we were given for propellant sprays, it is safe as used. And based upon the information we have for pump sprays, it could be safe as used if you reduce the concentration eightfold, right? Because you go 12 to 96, so reduce it a little bit more than eightfold, and it's safe in a pump spray. So we have the data. I mean, I'm just --
SPEAKER: (Inaudible 0:17:47.)
DR. BELSITO: I'm not arguing for it to be used in aerosol products at all. It'd be very nice if it's not, but that's only one supplier, and I doubt if that's the only supplier in the world.
SPEAKER: Right.
DR. BELSITO: And it doesn't stop what he says from other people using it. And then we do have data. It's not like we can say, oh, it's insufficient because we have absolutely no respiratory data on this. You've done the damn calculations.
DR. LIEBLER: Right. So I don't think I'm -- I mean, I think it's worth noting the comment from the industry person, but, I mean, I don't think that that drives our assessment. It's worth knowing, but it, you know, our assessment's driven by data, and we have data, as you just said. So I think it's a no-brainer to include. So it's safe.
DR. BELSITO: At certain concentrations.
DR. LIEBLER: Right, yeah. So we have it in the report.
MR. JOHNSON: Well, we also have a inhalation toxicity data on polyhexamethylene guanidine phosphate, you know, in addition to the Polyaminopropyl biguanide inhalation toxicity data.
DR. BELSITO: Well, but polyhexamethyline biguanide --
MR. JOHNSON: Guanadine.
DR. BELSITO: -- guanidine is, I got and I guess it's also structurally related, so we could bring that in, too. I mean, it's not the same molecule, either.
DR. LIEBLER: And you're saying the phosphate sol as opposed to the chloride sol.
MR. JOHNSON: The data on poly -- we have data on polyaminopropyl biguanide, and also data on polyhexamethyline guanidine phosphate, which is the chemical that was responsible for the child deaths in Korea. And that's on PDF page 73.
DR. LIEBLER: See, I don't like reading across from the PHMG to the PHMB. So I think the phosphate data, you know, it's got two BHMG is the chemical implicated in the Korean deaths. And the PHMB on the left, the structure on the left, is our material of interest, correct?
MR. JOHNSON: Yes, but --
DR. LIEBLER: That's why you showed it again, side- by-side.
MR. JOHNSON: -- (inaudible) the INCI name is polyaminopropyl biguanide, but it's really --
DR. LIEBLER: Right.
MR. JOHNSON: -- polyhexamethylene.
DR. LIEBLER: Right. So, you know, they're structurally similar, but, you

know, in light of the Korean experience, I'm not comfortable trying to read across safety.

DR. BELSITO: But we have subacute for the actual material.

DR. LIEBLER: For the polyhexamethylene or --

DR. BELSITO: Biguanide.

DR. LIEBLER: The biguanide, yeah.

DR. BELSITO: And are you comfortable with that data for using -- for calculating margin of safety?

DR. LIEBLER: Yep.

DR. BELSITO: Then a margin of safety can be calculated. I mean, we can say that we're being told that it was -- it's no longer being used in inhalation products. We can say that at least one manufacturer has reported that it not be used, however, the panel has looked back at reported prior use concentrations in propellant and pump sprays, and has found that based upon the available data, the use in the propellant sprays was safe, and the use in the pump sprays, the margin of safety was only 12 due to the higher concentration of the preservative in those products. And a reduction in concentration could result in a margin of safety greater than 100. Then just go ahead and say, safe as used. And in the correction to the concentrations of use, there will be no inhalation uses.

MS. FIUME: So I think one of the issues that needs to be pointed out is that the U survey took out anything that was definite inhalation concentration reported usage.

SPEAKER: (Inaudible 0:23:10.)

MS. FIUME: But according to the VCRP, there are data categories that we don't know whether or not they're sprays, that some of those products could be sprays or --

DR. BELSITO: Okay.

MS. FIUME: --- or not be sprays. So that's where the concern, I was -- comes in. So even though there's no definite sprays recorded in the (inaudible) U survey, there is possible spray use based on the VCRP category.

DR. BELSITO: Then we go ahead with the calculations. And if they're in propellants at the reported, you know, we do the calculations for what was previously reported. I mean, I don't know how you do that. It was.053. I'm doing this off the top of my head in a propellant. Is that right?

DR. BOYER: In the pump spray.

DR. BELSITO: In a pump.053, and in a propellant.006 or something?

DR. HELDRETH: (Inaudible) page 3 or something like that.

DR. BELSITO: I mean, we need to decide how to handle that respiratory. Paul and Curt, you haven't chimed in.

DR. KLAASSEN: Well, I think, you know, we have the data for the appropriate chemical and I think, you know, we should use that. On the other hand, I think we need to mention this other, but we do not think it is an appropriate reader card.

DR. BELSITO: Yeah, I know. And we need to mention the epidemic or, not epidemic, but with several hundred deaths in Korea which caused us -- which gave us pause.

DR. KLAASSEN: Right.

DR. BELSITO: And apparently has given at least one manufacturer pause who recommends that his product not be used and that, you know, prior reports indicated that there was use at these levels and pumps and propellants and there are

(inaudible) issues. And Monice, if you could identify where we're not clear whether there are potentially aerosolized products which -- what are those and what are the concentrations?

MS. FIUME: So the concentration where it could possibly --

DR. BELSITO: It would be in Beth's new (inaudible). So what PDR is that, or PDF page?

MS. FIUME: The use --

DR. BELSITO: It's towards the end.

MS. FIUME: -- table is page 79. Beth's information --

DR. BELSITO: And then she gave us the breakout, right?

MS. FIUME: Yes. So right now it's listed as the categories that could be aerosolized have the highest concentration of.1, which is higher than what was reported as being

aerosolized before. So it seems that a limit would need to be set if it's going to be okay for use in aerosolized products. Because, like I said, we don't know whether or not these products were sprayed, but we don't know whether or not these products were sprayed.

DR. BELSITO: Well, wait a minute. The table 3 on page 79 is incorrect. It hasn't been updated to what the corrections that were given. Those corrections are in Beth's table or at the end of document which I had printed out but failed to bring with me. So if you go to PDF 154, on July 18th, Beth said the updated concentration of use, and that pretty much has gotten rid of sprays. It's deodorants non- sprays. That's where she says every -- not face and neck products, not spray, not spray, not spray, not spray. I mean, she clearly indicated in that memo that there was no longer any aerosolized use. Do you see where I'm at?

MS. FIUME: I do. But on that same page, tonics, dressings, and other hair grooming aids, are used up to.1% and that is one of the use categories that could possibly be sprays.

DR. BELSITO: Okay. So then we could mention that, that, you know, I think that's where we do our margin of calculation and come up with aerosolized and pump, and go that, we noted that in this category, which could include sprays, uses of up to.1%, levels that high would be inappropriate in a spray based upon our margin of exposure calculations. The highest concentrations that would be considered safe as used would be "X" for a propellant and "Y" for a pump. And the margin of exposure that we're accepting is 100, is that correct?

DR. LIEBLER: Right. And so, but are you thinking about having that in just the discussing?

DR. BELSITO: Yeah.

DR. LIEBLER: Okay. So, I mean, it seems to me that you've got this issue where, on the one hand industry doesn't- the industry seems to be moving away from using these in sprays, but they could still be used in sprays. There is a margin of safety calculation that gives us guidance to the amount that could be used in sprays. And if we just say, safe as used, even if the spray language is in the discussion, it might give the impression that there's no limits to how much could be used in a spray. So maybe what we need is the conclusion to say, safe as used, and then for safe as used in products that may be sprayed, (inaudible) --

DR. BELSITO: Safe as, I mean, we've done --

DR. LIEBLER: Below the level --

DR. BELSITO: -- maximum concentration for
(inaudible).

DR. LIEBLER: Below the maximum concentration is based on a margin of exposure chemical issue.

DR. BELSITO: Right. I mean, we put limits before on products, so we can go (inaudible).

DR. LIEBLER: I think what we might need to do is that, because we have no other way of assessing the safety in the spray and the conclusion. I mean, it's these, the safest one, I think is the safest formulated to be non-sensitizing, right?

DR. BELSITO: Well, wait a minute. We haven't gotten to that one yet.

DR. LIEBLER: All right.

DR. BELSITO: I'm saving the best for last.

DR. LIEBLER: All right, well, hopefully we can get out of this soon.

DR. BELSITO: I don't know that we will, but we'll see.

DR. LIEBLER: Anyway, but I mean that I don't know if you would prefer to just discuss it.

DR. BELSITO: No, I think --

DR. LIEBLER: (Inaudible) discussion.

DR. BELSITO: -- they're right, because we -- it will, you know, if we just say, safe as used, some of them will look at a tonic and say, well, that or this could be sprayed and it would be fine up until point one. So I think we should say that, you know, if used in aerosolized products, propellants, it would be safest used in propellants up to and pumps up to. And set --

DR. LIEBLER: Right.

DR. BELSITO: -- those limits based upon our margin of exposure calculations.

DR. LIEBLER: And do we quote a number there up to.1?

DR. BELSITO: Yeah, we've always quoted --
DR. LIEBLER: And then as --
DR. BELSITO: -- numbers.
DR. LIEBLER: -- as supported by a margin of exposure calculation, and that goes to the conclusion.
DR. BELSITO: I don't think we need to say it's supported by (inaudible). I mean, that would be --
MS. FIUME: That would probably be discussed --
DR. LIEBLER: In the discussion.
DR. BELSITO: No, because --
MS. FIUME: (Inaudible 0:30:22.)
DR. LIEBLER: Okay.
DR. BELSITO: -- the statements always --
MS. FIUME: (Inaudible 0:30:24.)
DR. LIEBLER: Fine.
DR. BELSITO: -- begin, you know, based upon the available data, and that will be part of our data. Okay. So we're clear with that, what we're doing with respiratory there? Okay. So now to dermal. Okay.
DR. BOYER: Quick, before we leave that topic, could I just introduce another (inaudible)?
DR. BELSITO: Sure.
DR. BOYER: This (inaudible 0:30:50 calculation that you're basing your conclusion on, it's based on a certain set of default assumptions, and so forth. And these kinds of calculations can always be refined if you have good data. The various parameters and can be -- the default values for many of these parameters could be replaced by actual experimental data, test data, and so forth. And maybe the result would be less conservative than the calculations that you're looking at right now. So --
DR. LIEBERMAN: But do we have any reasonable prospect of getting more data that are good enough for a product that maybe industry is leaning away from spraying in the first place? I mean, this may be as good as it gets and we're just stuck with the conservative assumptions.
SPEAKER: Mm-hmm.
DR. LIEBLER: Skin.
DR. BELSITO: Okay. So skin we need to go to wave 2, basically.
MR. JOHNSON: Dr. Belsito, may I just say one more thing before you move on? The section on polyhexamethylene guanidine phosphate versus Polyaminopropyl biguanide, that should remain in the report.
DR. BELSITO: Ask Dan. He just says he doesn't believe it can be used as a read across for the respiratory toxicity.
DR. LIEBLER: Wilbur, point me to page and ask me specifically, sorry.
MR. JOHNSON: Okay.
DR. LIEBLER: I are you starting --
MR. JOHNSON: PDF (inaudible) 73.
DR. LIEBLER: -- (inaudible) and I'll look at it. PDF 72?
MR. JOHNSON: Right. Mm-hmm.
DR. LIEBLER: Where on that page?
MR. JOHNSON: Well, we're talking about the subheading polyhexamethylene guanidine phosphate.
DR. LIEBER: Oh, that's 73.
MR. JOHNSON: Yeah, 73.
DR. LIEBLER: Okay. So that's the description of the events in Korea.
MR. JOHNSON: Yes.
DR. LIEBLER: And the PHMG phosphate is the responsible agent.
MR. JOHNSON: Right, mm-hmm.
DR. LIEBLER: And --
MR. JOHNSON: So my question is, should that section remain or should it

(inaudible)?

DR. LIEBLER: Oh, yeah.

MR. JOHNSON: It should remain?

DR. LIEBLER: Yes. That's all about PHMG phosphate.

MR. JOHNSON: Mm-hmm.

DR. LIEBLER: And so that's there because it's a chemically related compound --

MR. JOHNSON: Mm-hmm.

DR. LIEBLER: -- that is associated with a severe toxicity, and we can't ignore it, so it has to be in our report, but it's a distinct chemical entity and that we actually have safety data on our compound. Okay. So we leave it in, I think, pretty much as it is. I thought, you know, you've dealt with -- fine. I thought that section is fine. It does not need to be changed.

MR. JOHNSON: So but in the discussion, you would have a statement indicating that polyaminopropyl biguanide is not similar enough to be used for read across for that other chemical.

DR. LIEBLER: I think, no, I wouldn't even invoke the word read across --

MR. JOHNSON: It's not --

DR. LIEBLER: -- in that discussion.

MR. JOHNSON: -- (inaudible).

DR. LIEBLER: That's not --

MR. JOHNSON: -- not aminopropyl biguanide.

DR. LIEBLER: So I think what I would say -- oh, you already have some. So no, there's some discussion text already. You've got the second to last paragraph in your draft discussion right now. Regarding the issue of inhalation exposure, the panel noted clinical studies relating to child deaths in South Korea associated with inhalation exposure for humidifiers. I might work that paragraph a little bit, but --

MR. JOHNSON: Okay.

DR. LIEBLER: -- PHMG is structurally related to the cosmetic ingredient, although it is not the same chemical. I would say it's a structure related chemical, but however the panel noted safety data supporting polyaminopropyl diguanide. All right, I mean, we have that, which is what we were just talking about in our margin exposure calculations. So I think the main purpose of that paragraph is not to use the data from the Korean episode to inform the safety judgment. It's just to point out that we're aware of, that it's a different chemical, and that difference is significant because we have safety data on the polyaminopropyl biguanide. Okay?

MR. JOHNSON: Okay, thank you.

DR. BELSITO: Okay. Wave 2, page -- PDF page 6, the QRA that we asked for. So I still have concerns. Let me start by saying, I have the utmost respect for Don from working with him on this panel. I've worked with Petra extensively. She's a superb toxicologist with P&G. We've sat on this committee that meets in Brussels way to often. And Cindy Ryan was, I believe, one of the original authors on the QRA document. So basically what we're being asked to do is to accept the (inaudible) of 1000 micrograms per centimeter squared based upon a weight of evidence. And an HRIPT at 1000 micrograms per centimeter squared, the N was only 26. And they readily admit that for a chemical that is a weak sensitizer, that N may not be sufficient. But then argue that the animal data can be included in and given a weight of evidence, we can accept the 1000 microgram per centimeter squared level as a nestle. Quite honestly, I'm not happy with doing that. First of all, even at 1000, we find that an eye lotion will exceed that limit if we go as one limit. So again, that stresses the fact that we need to say, it's product category specific. I don't think you can just say, like Europe did, you know,.1% is fine. It may not be fine for all categories, although it would look like, based on a QRA of 1000 micrograms per centimeter square -- for a nestle of 1000 micrograms per centimeter squared, it would. Where my concern is, is that even in the -- if you look at the hard data, and I spent a huge amount of time looking at this, because God, I do not want to get this preservative wrong, because Europe's reaction to any epidemic is not to go back and look at risk assessment, it's simply to ban it. They've done it to methyldibromo glutaronitrile. They've done it to methylisothiazolinone. And when Europe bans it, that means P&G doesn't use it, L'Oreal doesn't use it. It goes away. And, quite honestly, dermatologists, including myself, are seeing increased reactions to benzalkonium

chloride because it's being used more as a preservative. I got my first positive reaction to phenoxyethanol. I've never seen a reaction to phenoxyethanol before. It was thought to be the inert component of methyldibromo glutaronitrile. It's the

(inaudible) effect. We're getting so limited in terms of preservatives that they're just being grouped up. So I'm on a bandwagon with this one. I really don't want to get it wrong. So when you go back and look at the -- let me pop up my comments so I can get to the right study here. Oh, come on. Why aren't my comments coming up? When you go back and look at the study that was done that would apparently clear the 100 micrograms per centimeter squared nestle. And you look at that. Where's that hard data? Is that in the original report, Wilbur, where you gave us -- I think -- yeah, that data's in the original report. So on PDF page 109 of the original report, in table 16, they did a study. This is the study that's used to derive the 1000 microgram per centimeters -- no, the 100 microgram per centimeter squared. It's the neck cream containing.2%.

SPEAKER: Right.

DR. BELSITO: It's 115 male and female subject, so this would support a nestle of 100 micrograms. So if you look at the study, 37% of subjects, okay, developed a plus five, which is a little bit of pinkness. Okay? At some point during either the induction or the challenge phase. However, when you go into the hard data on that study, 50% of he subjects were African-American, and it's very, very hard to read arrhythmia on dark skin tones. Okay? And only one of those African-Americans were among the 37% who were noted to develop pinkness at the site. So if you get rid of the 50% where it would be difficult to see early -- potentially early reactions, then what you really have is that 74% of the lighter skinned individuals, rather than 37%. So 74% of Caucasians and Hispanics, which is no longer a racial group in the United States. You can be white Hispanic, or you can be black Hispanic, 74% of lighter skinned individuals where it's easier to see arrhythmia develop some type of arrhythmia. No one developed significantly positive reactions. I'm not saying that. But that's a large number of people, and that would clear a nestle of 100 micrograms per centimeter squared. So I'm really not comfortable. And even the guinea pig studies are all over the board. Some of them are negative. Some of them are positive. And, you know, if you go in and you look at your QRA calculations, and you reduce them by 10 to account for 100 micrograms, then you're knocking off more products than just the eye motions. A lot of them are still safe. I think we need an HRIPT on at least 100 people with 1000 micrograms per centimeter squared to confirm that that is actually a nestle, and quite honestly, I know you can't do this, but I would hope that it would be representative of the U.S. population, and so that there'd be an increasing number of Hispanics, a decreased number of African-Americans and the appropriate number of Caucasians and Asians in that study to be reflective of who we -- since we're looking at safety in the United States, are. I just am not happy accepting a nestle based upon an HRIPT of 26, particularly when I have issues on the HRIPT at 100 micrograms per centimeter squared. I mean, there clearly were no positives, but there were just quirky reactions throughout in light skin, and 74% of the lighter skinned individuals in that study. And quirky reactions in the guinea pigs. And again, if we get this wrong, you guys in the industry and we as the public, we're going to suffer from lack of preservatives in our products are going to be in big trouble. And, you know, again, even at 100, a lot of products still sell through your QRA. I would like to see (inaudible) that would -- I think it's insufficient for sensitization, meaning HRIPT and you may want to do it at 500 and 1000 just in case you get back results at 1000. Because it may clear 500 and might not 1000. You know, with guinea pigs the OECD guidelines are you have to have, like, 30%. And so, you know, but, you know, again, with rare sensitizers as they readily admit at the beginning of the report. You have to do large numbers, you know, to see those come out. You know? I mean, methylisothiazolinone was not such a rare sensitizer because it happened to be thrown into baby wipes, and all the products where it really caused problems. If it had not been put into the products where it caused problems, it may have been many years before we saw it.

DR. LIEBLER: Well --

DR. BELSITO: That's just my --

DR. LIEBLER: -- I mean, I --

DR. BELSITO: -- point.

DR. LIEBLER: -- certainly, I don't think any of us would have this and we appreciate your, you know, going through this in detail. I mean, I think there are two key points. One is that because of the regulatory politics surrounding this family of issues, this -- our assessments need to be absolutely bulletproof.

DR. BELSITO: You know from the fragrance. I mean (inaudible). I mean (inaudible) can't be safely used. It was used at the wrong concentration, but screw it. It's getting bad.

DR. LIEBLER: But got to have good data to hang this on and so I agree with you. I fully support your suggestion.

DR. BELSITO: That's my recommendation repeat an HRIPTN of a hundred. I would really recommend doing both 500 and a thousand, impound a panel that's representative of the U.S. population.

MR. BJERKE: Does the epidemiology data help you in the fact that in Europe you know, this was approved early at.3 percent and now moving down to.1 percent, so there were likely some products with a higher concentration. It at least didn't seem to be problematic and now they're moving lower. We're kind of relying you know, to do the dose per unit area of.1 percent, seems to be okay for the product types that are being used?

DR. BELSITO: Yeah, I mean -- the issue though there with that Don, is A, we don't know what kind of product types are was being used in. And B, the frequency of use was quite low. But, now that all of the parabens -- I mean this is a great biocide. It is very active at low concentrations.

You know, I mean 12.0003 percent in contact lens cleansing solutions. I mean, the amount that you can use to make it very effective is low.

So, we don't know at what concentration it was being used in Europe before. It wasn't being used in a lot of products. You know, I mean J&J has come out and said they're removing formaldehyde and soon they're going to be removing formaldehyde releasing preservatives from all of their cosmetic products. What are they going to use instead?

You know, methylisothiazolinone can't be used by any of your multi-national people on leave on products. (inaudible) can't be used. I mean again, as someone who's patch testing, I'm starting to see reactions to preservatives that I've never really seen before, and it's you know, the (inaudible) Effect. You know, that there's a limited pallet and so you've got to you know, more and more products containing phenoxyethanol. You're using things like Benzalkonium chloride, and chlorhexidine as preservatives in cosmetic products, that you never used before.

Yeah, so I just think we need to be very careful with this one, because it's -- I mean when you starting reading labels as I do, and patch testing people, you're seeing this pop up -- I mean before, the only time I ever saw a Polyaminopropyl biguanide was in a contact lens solution, and now that's not true anymore.

DR. LIEBLER: Let's move on.

DR. SNYDER: I agree. I mean I think to concur with (inaudible) I mean if you looked at this with a expertise that none of the rest of us can bring to it, I think we need to capture that though if we're going to go in with insufficient data now?

DR. BELSITO: Yeah, I mean I think what we need to say is that you know the HRIPT and the.2 percent neck cream was theoretically negative. You know, I mean there was the.5, the scoring system.5 is not a pinkness. It's really faint. It's what we would call questionable you know.

DR. SNYDER: Ambiguous?

DR. BELSITO: Ambiguous. But it happened in 37 percent, which was a large number of ambiguous participants. And then when you look at the racial background of the people where it happened, it happened in only one African American, everyone else was Hispanic, or most of them Caucasian, and I know many Hispanic people are lighter skinned than I am.

So, you don't know what the color of their skin is, but I can tell you it's very difficult to read redness in African American skin. You know, even as a dermatologist, I still,

after practicing for 40 years, African Americans will come in and go my skin is red, and I'm having problems really appreciating what they mean by that.

So, I just -- it gives me pause, because that to me means 74 percent of individuals where it's easy to have redness or pinkness, had some degree of something happening at 100 micrograms per centimeter squared and now we're going to clear it on weight of evidence from animals where there's a lot of quirky data and an N of 26 and an HRIPT of 1,000.

Because again, of you go through the QRA, beautiful calculations, and you reduce them by 10, you'll pick up another I think seven or eight categories, where the concentration of use is too high.

Okay, so, we're going to calculate margins of safety if botanics are in fact sprays or aerosol pumps, and we're going to go insufficient for sensitization, ask for HRIPT to justify the nestle of a thousand; and perhaps suggest that if they're going to go ahead and try to impound a panel that's more representative of the U.S. population.

Also, you know, which actually is doing studies for NIH that's what you're sort of required to do, is to try and recruit individuals of a racial mix that representative of your geographic location. And maybe suggest that industry might want to at the same time run 1 of 500, just in case.

DR. LIEBLER: Your reporting on this tomorrow?

DR. BELSITO: Yeah.

DR. SNYDER: And has it (inaudible), did you say?

DR. BELSITO: What?

DR. SNYDER: How big of an end did you want?

DR. BELSITO: A hundred.

MS. FIUME: So this will go out as a tentative report of with a message.

DR. BELSITO: Okay.

MR. JOHNSON: But (inaudible) has never been requested before this 100, so it still would be (inaudible) rather an insufficient that are (inaudible)?

DR. BELSITO: I don't know, where are we in this process?

DR. SNYDER: Just animal basis data now.

MS. FIUME: We did to I guess. I'm assuming.

DR. BELSITO: So, this would be a tentative final?

MS. FIUME: It should be the second IDA asked for half a mission of margin safety.

DR. BELSITO: Because we decided not to table it at the last meeting (overlapping conversations) --

MR. BJERKE: At the time we asked for a HRIPT.

MS. FIUME: -- urged to provide.

DR. LIEBLER: So, it's tentative, final but an insufficient per sensitization?

DR. BELSITO: -- Dan, you know, quite honestly, I mean, I would really encourage industry to do this. Europe has already set limits which I believe have already gone into effect, is that correct, it's.1? Europe's limits are binding, ours our not as we know. So, I'm somewhat comforted by that, and you know, if industry wanted to come back and say to me, you know, we can get you this data, but obviously we cannot get to you by December because the data doesn't exist, but here's a timeline where we think we can get you this HRIPT, would you be willing to table it? I would table it.

You know, I mean the SCCS obviously, you know, very vigilant in re-looking at this, but we both got (inaudible) wrong. I mean we both let it go out of 200 parts per million and they were no better than we were. I mean it was a mistake in the interpretation of the LL&A. The EC3 got it right the third time.

DR. LIEBLER: But for tomorrow, you're going to --

DR. BELSITO: Suggest.

DR. LIEBLER: -- move for a tabling?

DR. BELSITO: I'm going to move for a title of insufficient, and see if industry wants to give us any promises, if that they can come up with anything or you know, they can always come back at the next meeting, where at some point now asked us to table it, and then we'll just table it at whatever point it is. I mean we're not going as final.

DR. LIEBLER: Right, okay.
DR. BELSITO: I mean we could table at any point up to final, right?
DR. LIEBLER: Yeah.
DR. BELSITO: Okay.
DR. SNYDER: Is that going to get strong enough (inaudible) industry is doing?
DR. LIEBLER: Our message has been received (laughing). Let's move on. We got a lot of ground to cover still. Beat this to death.

Day 1 of the September 11-12, 2017 CIR Expert Panel Meeting – Dr. Mark's Team

Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride)

Okay, let's move on to the next ingredient. And that's the polyaminopropyl biguanides. So Ivan you're back up. It is a draft tentative report on this ingredient. And it's an insufficient data announcement was issued in June of this year. And there are a number of points here in your memo Ivan.

DR. BOYER: Actually, this is Wilbur's report.

DR. MARKS: Oh, I'm sorry.

DR. BOYER: I did the air exposure modeling.

DR. MARKS: Okay. So -- and we have a response from Lanza on an insufficient data announcement. And then also a memo from Bart on W2 data. Ron, Ron and Tom where do you want to move with this? Do we want to set limits not using applications that can be inhaled, limit leave on to 0.1 percent?

There are several things we could do, I don't know if we want to go down each one of these points 1a, b, c, d. And then in response there was to the insufficient data announcement, there's the a and b portions of the memo. So Ron Shank.

DR. SHANK: Okay I had a split conclusion. For leave on formulations except products around the eye. I felt we could use the Proctor & Gamble reference limit that they did.

DR. MARKS: And that's the (inaudible) 1 percent?

DR. SHANK: That's.1 percent.

DR. MARKS: Yeah.

DR. SHANK: Based on an exposure of 1 milligram per square meter. So I think that makes it interesting how we handle that. Because one is a concentration in the formulation and one is an exposure on the skin. Or...

DR. MARKS: Now, why did you limit -- you excluded the -- this is leave on products. Yeah, this is for --

DR. SHANK: This is for leave on.

DR. MARKS: But you excluded the eyes. Did I hear that right? Are eyelids?

DR. SHANK: Yes.

DR. SLAGA: That's what you said.

DR. SHANK: Well, no. Leave on formulations except around the eye. Did I get that wrong?

DR. BERGFELD: You're not allowing them around the eye?

DR. MARKS: Yeah, why not around the eye if you have a leave on limit?

DR. SHANK: I'll have to --

MR. JOHNSON: Because you said 0.1 percent.

DR. MARKS: Yes.

MR. JOHNSON: No, because it's used in eye lotions at 0.2 percent.

DR. MARKS: Well, that's okay you can still say a limit legal limit on it.

DR. BOYER: Well, it also has to do with the QRA in which it's perform. If the result indicates that the current use levels that's been reported that there could be a problem with that.2 percent.

DR. BERGFELD: So it's.1 or.2?

DR. SHANK: .1

MS. FIUME: Previously with a QRA you've said safe and formulated to be non- sensitizing which may be based on QRA. Which is --

DR. SHANK: But this is for a single compound not a botanical. So we got --

DR. EISENMANN: No, you've done that that's how MI was done, that's how -- I'll let since Don Bjerke did the QRA let him take over.

DR. BJERKE: Yeah, so if we look at all the current product uses and the maximum concentrations reported by industry. If we use that nessel then they'll expect that sensitization induction level of a thousand micrograms per centimeter square. It supports all the existing uses with the exception of the eye lotion.

And in that product the concentration was.2 percent. So using all the default

assumptions for the quantitative risk assessment, I could not support that. So in order to support the.2 percent and leave on eye lotion, they would have to have a refined assessment. In other words, perhaps they could refine the matrix uncertainty factor, if the same product was used in the HRIPT that's used for that product. But just given default assumptions based on what I know, I could not support that product, that.2 percent.

DR. SHANK: Thank you.

DR. MARKS: So Ron, couldn't we just then set a leave on limit to 0.1 percent? Because that's what the QRA in nessel suggest. And I wouldn't even mention the eye, we're not -- we can't validate the safety of the eyelid application at 0.2 percent.

DR. BJERKE: I would caution against that -- I guess we can go back and look at all the different reported use concentrations. What I did is, took the reported use concentration did QRA. So I think it's -- when doing a QRA is preferable to use the dose (inaudible) area combined with the habits and practices for the cosmetic product type. As oppose to a.1 percent limit.

Now we could go back and recalculate that very easily, saying if.1 percent was the max that was use for all these different product types, will still be okay. Probably would be but we could do that if needed. And that would be consistent with the SCCS approach of.1 percent.

MR. GREMILLION: I just surprised that by the recommendation against the.2 percent in eye lotion, but having.1 percent baby lotions. It seems it's only half the amounts and just kind of idea that -- I guess that's the function of the QRA but that caught my eye.

DR. BJERKE: Yeah, exactly. It's all based on exposure. Amount applied, frequency of application, surface area applied and then the uncertainty factors. The sensitization assessment factors, so they're different for each product type. So for the baby product, it was using the assumptions that were cited in the reference that margin of safety of acceptable.

DR. GREMILLION: Well I guess, I would just make the obvious point that a product that used with babies and infants maybe a particular margin of error is a good idea.

DR. BJERKE: Again, I think the most important factors dose per unit area, based on having some practices.

DR. MARKS: So how would you -- if you didn't want to set a limit of leave-ons to 0.1 percent, how would you address that issue, because we don't...?

DR. BJERKE: Yeah, I think you could do a couple different things, you can ask for a refine risk assessment for the 0.2 percent eye product. Perhaps there's additional refinement of the exposure for, like I said, if the HRIPT was done with the exact product often times, you can revise the uncertainty factors. So one approach is to ask for a refinement risk assessment with a.2 percent eye product. Another option would be to say, safe as used when formulated not be sensitizing is based on a QRA approach. Or to basically say, safe and current practices with the exception of the one eye product for sensitization perspective only.

DR. MARKS: Which one of those three options? I like the option of moving forward rather than refine, but...

DR. SHANK: Okay, well then, the easy way is to say, formulated to be known sensitizing.

SPEAKER: That would be.

DR. SHANK: Then that would include the eye.

DR. MARKS: Um-hum. That's kind of what I like. Puts the onus back on the eye -- the eye manufacturer.

DR. SHANK: That's half of the conclusion.

DR. MARKS: Yeah, okay. Deal with the other half.

DR. SHANK: Should not be used in products that are respirable.

DR. MARKS: Yes, not in applications that can be inhaled.

DR. SHANK: Or what you say unsafe, for respirable formulations.

DR. MARKS: Now we have to -- is it inhaled or respired?

DR. SHANK: Respirable.

DR. MARKS: You're not worried inhaling this ingredient?

DR. SHANK: Well, no, because that's the difference between upper respiratory and obviously the alveoli cells. We're not worried about getting it in our nasal, pharynx, trachea.

So that's why I want to clarify is it inhaled or aspiratory. Yeah, that was...

DR. HILL: Lanza says they don't support the use in any products might leave to incidental inhalation.

DR. MARKS: Yes, they used the word inhalation.

DR. HILL: They used the word inhalation.

DR. SHANK: Less specific.

DR. MARKS: Which -- I know you used respired, I'm going to go with the terminology you want Ron Shank, said do you want to use respire? Not used in applications that can be respire.

DR. BERGFELD. You topic things as innovation studies. I mean...

DR. MARKS: Or we can put both inhaled and respire.

DR. SHANK: It depends on how deep into the lung you want to go. So if you say, formulations that can't be inhaled that's more general.

DR. MARKS: Um-hum.

DR. SHANK: And it kind of hedges --

DR. MARKS: Um-hum.

DR. SHANK: -- the actual response.

SPEAKER: That would be safer.

DR. SHANK: It would be a safer conclusion.

DR. HILL: Yeah, so this is going to be in liquids and based on what I hear today, be highly depended on the nature of the liquid. Whether it would be respirable or not. Because we're talking about things like the type of sprayer that's used, evaporation rates of the solvent. What's in there besides preservative, so bond (inaudible) such a conservative road and said inhaled. So you're suggesting the sensitization only occurs deep in the lungs, because...?

DR. MARKS: No.

DR. HILL: Is it the alveoli.

DR. MARKS: No.

DR. HILL: Okay.

DR. MARKS: I was concerned about the entire respiratory tract.

DR. HILL: Yeah, okay.

DR. MARKS: Wanted to differentiate whether we're really just talking about the end or whether we're talking about also the oral pharyngeal bronchi trachea, the whole respiratory tract.

DR. SHANK: Okay.

DR. MARKS: So a second tentative report in which we set limits in the conclusion. And those two limits are not to be used in applications that can be inhaled and formulate to be non- sensitizing, does that sound good?

DR. SHANK: Yes.

DR. MARKS: Does that meet all the -- there was some clarification urticarial reactions. I looked at the memo there were non-reported to this specific ingredient. I think we addressed the issues we have here.

DR. GREMILLION: So when you go and formulate to the non-sensitizing that was in lieu of making a more explicit reference to this conclusion that.2 percent is not safe for use in

(inaudible).

DR. MARKS: That will be captured I think in the discussion.

DR. GREMILLION: We will not -- in the discussion would capture the nuances of our discussion about the.1 percent, the quantitative risk assessment. The dose per unit area in why the 0.2 percent is in question.

DR. MARKS: Okay. It would all be covered in the discussion.

DR. GREMILLION: I did want to note in the report there's a line that says, in the data supplemental on page 13. It says, the (inaudible) um, there's no indication that it's not being used in sprays and that -- there's some products that weren't picked up in that survey. That are spray products that use those (inaudible) of -- I think there is a reason to be to err on the side of safety. And go with inhale (inaudible) respirable, respirable and maybe the language in the (inaudible) should also have a qualifier of some sort to say, of the surveyed products this chemical

is not being used. But there's at least two products currently on the market that list sprays. A hairspray and a -- blanket on the other one. But they're there and they have the product.

DR. MARKS: Again, that can be captured in a discussion. Okay any other comments. Yeah, Wilbur.

DR. JOHNSON: (Inaudible) the data on polyhexamethylene biguanide phosphate, PDF page 73. Should those data be addressed in any way in the discussion? Particularly, you know, any similarities between or dissimilarities between the two chemicals.

DR. MARKS: Yeah, this goes back to our discussions about these fatal lung injuries and why we were really concerned about the inhalation. Ron Shank or Ron Hill do you want to respond to Wilbur?

DR. SHANK: Let me see the discussion.

DR. HILL: I can at least talk about that because that was a concern that was specifically and prominently raised in the Women's Voices of the Earth memo. And while I assert that these are quite different that a biguanide is different than a guanide. And that fundamentally makes a big difference. I think it's also important to be a little conservative and I put some weight behind the Lanza assertion that they don't support the use, in products that could be inhaled.

So if we were restricting it in that way anyway in our conclusion, I think we've addressed that. If you're asking whether the language should stay in in the similarity instructures, I think if you were to -- is that what you're asking?

DR. JOHNSON: Yes, yes.

DR. HILL: I think what's in here is fine and I think if you were to ignore that would be a big mistake. If we were just simply to say these are different structures and we're not going to pay any attention to it. But I think you've got the nicely illustrated side-by-side, you can see the difference sensitization is a very specific molecular level process, where there's recognition between presentation cells and the immune system and the cells that are going to cause the reaction.

And you can have a very small change in structure and it could be incredibly sensitizing and not at all and I think that's probably what's going on here. So I think it's fair to say -- that's all we can say until we actually get molecular level -- I like to think at some point somebody would look at this in the context of those actual protein structures in the immune system and figure out exactly what's causing that.

I mean, this is a beautiful bit of science that ought to be done but we don't have that right now. But it's a very specific recognition phenomenon involved, so -- first of all, I repeatedly write in my comments to the staff writers that similar means nothing. Because in pharmacology the difference between methyl group being there and not being there can sometimes result in a ten-thousand-fold difference in activity.

So and when we have a specific toxicological end point where there's specific protein recognition involved here. A small change in structure could have a huge effect. So from that point of view we don't know at the molecular level exactly why these sensitized. If there's conjectures but we don't really know other than the typical things that are involved in immune recognition.

DR. JOHNSON: So nothing needs to be added to the language that is already in the discussion.

DR. HILL: I don't think so.

DR. MARKS: Okay.

DR. GREMILLION: (Inaudible) is pointed out to me that the Kim study that was discussed last time, the 2016 study on Korean which you refer to the packet but not included for copy right reasons it said, but that author does discuss the similarities between these two substances. And it provides some explanation of why they see it as very similar and talk about other function of the two substances as antimicrobials are similar in breakdown cell walls in a similar way. So that that's recognizing that there's, you know, a lot of complexities to comparing different chemicals.

DR. HILL: Well maybe we need something to say we -- and I think we got the copy of the paper in our packet, didn't we?

DR. JOHNSON: (Inaudible).

DR. HILL: The 2016. There are actually a couple of 2016.

DR. JOHNSON: Two additional ones were handed out this morning and you received

(inaudible).

DR. HILL: These are not the ones though because this is a 2014. So I see that but there are two newer papers, right.

DR. JOHNSON: Right.

DR. HILL: And I think we got them -- I actually wrote notes on what we had where. So we got 2016 and data three and the 2017 April materials. And I think that was the one that the Women's Voices of the Earth were referencing.

DR. MARKS: Um-hum.

DR. HILL: I remember I had to check my notes again. I don't want to sit here and take up the panels time -- anybody's time to do that right this second but...

DR. GREMILLION: But you're fine.

DR. HILL: And I agree -- yeah, I mean, maybe we need, maybe need to respond to those specific papers. So I'll look at that more closely again this evening. If we want to -- I can draft a sentence or two to add. Because I mean, I can't disagree with you that we need to be sure we capture the most current information that we know that. But the recognition process is in the cell while protein recognizing compound is not going to be the same as what happens with sensitization.

DR. MARKS: Um. Okay, any other comments?

MS. FIUME: Dr. Marks, can I just ask for clarification? So for the conclusion, it will be as it was in the MI where we'll refer to as determined based on a QRA, right, in the conclusion itself? Or is that something that's only in the discussion, referring to being non-sensitizing for the language for the conclusion.

DR. MARKS: I would put it in the discussion and just put formulated to be non- sensitizing. Because if the 0.2 in an eyelid preparation and a HRIPT that would show that it's non- sensitizing then I'd be satisfied with that.

MS. FIUME: I was just asking for clarification because in the MI conclusion, if you want to keep things similar for the same type ingredients reference to the QRA was actually done in the conclusion. It said, when formulated to be non-sensitizing which may be determined based on a QRA.

DR. BERGFELD: I don't think you need that.

MS. FIUME: You don't need, okay.

DR. MARKS: I would agree. I'd put that in a discussion study, but I like to formulate to be non-sensitizing, make it straight forward. Okay.

DR. JOHNSON: Well should the QRA that's been completed be addressed in anyway in the discussion?

DR. MARKS: Oh yeah, yeah sure. Yeah. And that would support the legal and use for everything other than the eyelid product that contains 0.2. And that was how we dealt with that.

DR. BERGFELD: But they did have a 0.2 hedge test, I think on the neck, that was the new that came in. But the neck skin is different than the eye skin, is that what you're basing that on?

DR. MARKS: Was that an HRIPT?

DR. BERGFELD: Uh, let me see what that means. It was in the list from material

(inaudible).

DR. BJERKE: That wasn't HRIPT but if you look at dose per unit area from that study it was 100 micrograms per centimeter square instead of 1000.

DR. BERGFELD: Oh.

DR. BJERKE: So again, it's this distinction between percent wide and dose per unit area.

DR. MARKS: Okay.

DR. BERGFELD: That should go in the discussion. Thank you.

DR. MARKS: Any other comments. Okay.

DR. HILL: (Inaudible) always give an upgrade thought because it's always

concentration that drives the fusion rate. And yet definitely the dose matters, especially in a (inaudible) and over time so...

Day 2 of the September 11-12, 2017 CIR Expert Panel Meeting – Full Panel

Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride)

Okay. All right. The next ingredient is Dr. Belsito, the polyaminopropyl biguanide, I guess.

DR. BELSITO: Yes. So at the last meeting, we issued an insufficient data announcement and what we wanted was calculations for a QRA in terms of dermal sensitization and also calculations for a margin of safety for inhalation. And we actually got both of those, but along the way, we got updated concentrations of use that indicated that there were no spray uses for this, at least not as currently reported.

We also got a letter from one manufacturer indicating that at least his company did not recommend this be used in products that were meant to be aerosolized. However, we felt that we did have sufficient data to look at the safety in aerosolized products, that it's not clear to us why we originally got some reports that it was used in propellant in pump sprays and now we're being told that it's not. Could it be used?

I mean, our major dilemma I think in here is that we truly can't say that it's unsafe because we can generate margins of safety of 100 or greater by limiting the concentration for aerosolized use. So we felt that we could go ahead and rule on safety for aerosolized use.

The problem I had was with the QRA and particularly with the selection of the NESIL. The people who did it, Don and Petra and Cindy, are excellent people. I know all of them. However, I beg to disagree with their selection of a NESIL of 1000 micrograms per centimeter squared based upon an HRIPT that was performed on only 26 individuals.

When you look at the other HRIPT that was performed in over 100 individuals with a.2 percent neck cream, what you'll see is that 37 percent of them had some faint pink reactions that occurred at various times during challenge and/or induction. What you also see if you look at the specific data is that 50 percent of the individuals in the study were African American, and only one of them were noted to have some faint erythema. And I think, as Jim will testify, it is very difficult to note faint redness in very dark skin.

So if you take out the African Americans from that study, what you have is 74 percent of the individuals -- and this was at a 100 micrograms per centimeter squared, not 37 -- developing very minimal reactions during the course of induction or sensitization. So I am not comfortable going ahead and saying that the NESIL for this is 1000 micrograms.

Even at a 1000, you'll notice that one of the eye products was above the acceptable concentration. I'm very concerned that if we get this wrong that it'll be in Europe another MI where it ends up getting banned and we're losing more and more cosmetic preservatives. So I felt that we could go ahead and do safety for the respiratory endpoint.

I thought we needed, if industry wants to go with a NESIL of 1000 micrograms, then they need to do an HRIPT on 100 people at that concentration. And I'd also recommended that the panel that was recruited for that study be more representative of the U.S. population in terms of skin colors. And so we felt it was insufficient for dermal sensitization.

DR. SNYDER: (Inaudible)?

DR. BELSITO: Well, I had recommended to industry because I'm concerned that 1000 may end up being positive that they might want to consider looking at a lower dose of 500 as well. But that's their decision as to what they want to do. But if they're going to push ahead and push for a NESIL of 1000, then they at least need to do 100 people at that concentration because the guinea pig data -- I mean, it is a weak -- as a sensitizer in most guinea pig studies.

In one, it's weak to moderate. And as the authors of the QRA point out, that with a weak sensitizer, an N of 26 is really insufficient to pick up individuals who might be becoming allergic at those levels. We can keep the respiratory in there but it's insufficient for dermal.

DR. BERGFELD: Jim, you want to respond?

DR. MARKS: Yeah. Our team, of course, struggled with both of these issues, also, or discussed it. And so, we felt we could handle both these issues by setting limits in the conclusion. That this ingredient should not be used in applications that can be inhaled. And then, I'll let Ron Shank respond to your reasons that you put forth, Don, for your team.

The second limitation, we had the same difficulty dealing with sensitization, and we decided to handle that by "formulate to be non-sensitizing" and not settle on that.

DR. BERGFELD: Ron Shank, you want to respond?

DR. SHANK: For the inhalation --

SPEAKER: Could you turn your mic on, doctor?

DR. SHANK: Sorry. For the inhalation, or use in aerosols, there was a margin of safety determination which showed it was not safe in pump sprays.

DR. BELSITO: But you can reduce the concentration and make it safe. It was not safe in pump sprays because of the concentration. You can get -- I mean, it may not be reasonable to include it in a pump spray to provide biocidal activity at whatever level would be safe, but you can -- the margin of safety was 12. So if you reduce the concentration by eight and a half, you now have a margin of safety of 100. Right? I mean, it --

DR. SHANK: By calculation, I think this is close enough to be concerned toxicologically for the aerosols. And especially, when you have a manufacturer saying they shouldn't be used in aerosols, or inhalable. I forget how it was worded.

DR. MARKS: It should not be used in a --

DR. SHANK: Shouldn't be used --

DR. MARKS: -- way it can be inhaled. That's what we said. Not used in applications that can be inhaled.

DR. LIEBLER: That's not a substitute for data. It's true that they said that. But I mean if we have data to work with, I think we should work with the data. And then, you know, to Don's point about the margin of safety, I agree that the margin of safety in the specified test of concentration or the specified concentration is borderline. But you can use a lower concentration and be well over 100, so --

DR. SHANK: And is it still effective as an antimicrobial?

DR. BELSITO: Then they wouldn't use it, Ron. I mean, so then effectively, it would be banned in a pump spray is my point. But, you know, how can we go and say that it's unsafe when we have data, we have a NOAC that's been accepted by the EPA and OSHA for, you know, inhalation exposure.

We have those numbers, we can calculate a margin of safety. So it's not like we don't have a respiratory endpoint, you know. I mean, then I think we could say insufficient. But we can't say that it's unsafe for -- I mean -- because then, essentially, you know, I mean, it would be unsafe for workers manufacturing this and that's not the case. I mean, there have been limits set, you know, for chronic exposures on these and we can calculate margins of safety.

I mean, otherwise, we, you know, I mean, we have no credibility. I mean, we're just saying we have data and we're not going to use it. I mean, I just don't think we can do that. We have data and we have to use it. And, you know, maybe given the Korean epidemic or mini-epidemic and deaths, it would be wise for manufacturers not to use it. That's their choice and we have one manufacturer of the product who suggests that it not be used.

But on the other hand, we have data that shows that it could be safely used in a cosmetic product that is intended to be aerosolized. So I just have a philosophical problem, you know, saying that it's unsafe or insufficient when we have data. I mean, it's just -- it's not true. It's not a true statement.

DR. MARKS: So, again, Ron -- or Don, how would you then state it in the conclusion? Would you set a limit? You went down in terms of in a potentially inhaled product.

DR. BELSITO: I would --

DR. MARKS: Would you set a limit in the conclusion?

DR. BELSITO: You could base it upon, you know, the margin of safety calculations it could be safely used up to, what was it? .053 parts per million in a pump. And then, we would have to recalculate the concentration that would provide a margin of safety in, you know, say "safe as used in products intended to be aerosolized up to these concentrations that provide a margin of safety 100 or greater."

DR. BERGFELD: Ron Shank?

DR. SHANK: I'm thinking.

DR. BERGFELD: Tom?

MR. GREMILLION: Could I ask a clarifying question? Is the margin of safety

that you're referring to -- is there a similar margin of safety for the PHMG that was involved in the Korean deaths?

DR. BELSITO: Yeah. They actually used the same number that we're using because they did not have a value for polyaminopropyl guanide and that was part of the argument for Women's Voice. They said that the Korean group read-across to the data we have for polyaminopropyl biguanide.

And so we're saying, fine. You know, we're actually buying into that read-across. But they had used the respiratory limits that we are currently using for polyaminopropyl biguanide and it is for the polyaminopropyl biguanide. There was never a NOAC that was determined for the polyaminopropyl guanide. Their calculations were all based off of a NOAC for the polyaminopropyl biguanide.

MR. GREMILLION: I got you.

DR. BERGFELD: Tom?

DR. SLAGA: I could go with that approach.

DR. BERGFELD: Ron Shank?

DR. SHANK: I'm still uneasy. We don't have inhalation toxicology data except acute.

DR. BELSITO: We have a 28-day where they were exposed for six hours per day.

DR. LIEBLER: That was used for the reformalized.

DR. SHANK: Okay. Let's see that.

DR. BELSITO: And there were absolutely no effects seen. Five days per week, six hours per day, for four weeks,.26 milligrams per cubic meter.

DR. SHANK: There is not very much information there. It says there's no observed adverse effect concentration at 0.025 milligrams per cubic meter. The concentrations tested went up to 1000 times higher without a comment.

DR. KLAASSEN: You know, I'll go back to what I was saying yesterday is that, one really needs to know how much people would be exposed to. And you know, this number that we might be able to get from Europe is great. I mean, if it's 23 seconds that we're exposed at such-and-such a concentration, and then you compare that to a rat that's been exposed for not

seconds, but 60 seconds times an hour times six hours, I mean, I think we're forgetting about the dose again. The total dose that the mouse could be exposed to.

DR. BELSITO: And the margin of safety therefore is incredibly, incredibly conservative because there are already conservative numbers put in to reduce it. And what Curt is referring to is there's a group in Dublin called Crème Global that does habits and practices for use of cosmetic products. That is funded by RIFM. I don't know if RIFM would share that data with us or we could buy it from RIFM, but they would have data on the 95th percent maximum consumer use for both Europe and the United States.

They could provide us just with the United States data since we look at only the United States. Or they could give us both and tell us how many times people use pump and propellant sprays during the course of the day. And this would be aggregate. This would not just be hairspray. It could be underarm deodorant sprays, it would be also those foot powder sprays, whatever. I mean, Curt's point is well-taken. No one is sitting around there spraying cosmetic product for six hours, or even probably six minutes.

DR. BERGFELD: Ron Shank, are you willing to give an opinion now?

DR. SHANK: I still feel there is sufficient concern about inhaling the compound and uncertainty in what the actual exposure is in --

DR. BELSITO: I mean, we're going out as an IDA for the dermal. If you agree with that, we can ask for additional information on consumer exposures to pump and propellant sprays, get that information, any additional information on inhalation toxicity and readdress it. Is that fair?

DR. SHANK: I would like that, please.

DR. BELSITO: Okay.

SPEAKER: That's a good point (inaudible).

DR. HELDRETH: So would be going out as an IDA or with the synthesis still

at the tentative stage where we'd be going out with an insufficient data conclusion.

DR. BELSITO: Insufficient data conclusion. As I indicated yesterday, obviously, industry would not be able to get this HRIPT to us in three months. So if they came back with a promise date that was reasonable, I would be willing to table it at that point, rather than proceeding. But I'm just not comfortable with the dermal sensitization data at this point.

DR. MARKS: And I agree. Rather than having a conclusion of non-sensitizing, let's see if we can get the data to back that up.

DR. BELSITO: I just -- yeah. I'm a little concerned about this non-sensitizing. I mean, I'm a little comforted by Europe going at.1. But if the NESIL is 100 micrograms per centimeter squared, even.1 is too high. And again, the typical response in Europe is if there's a mini-epidemic with a preservative or a fragrance, instead of reassessing the risk, they say there's a hazard and they just banned it. I mean, that's methyldibromo glutaronitrile, it's methylisothiazolinone, you know, it's some of the parabens that have been further lowered. So I mean, I don't think we should get this wrong.

DR. BERGFELD: So your motion is going to be to go to insufficient data announcement, looking at dermal sensitization and the inhalation studies that they requested.

DR. BELSITO: Yes.

DR. BERGFELD: And is that a motion?

DR. BELSITO: It's a motion.

DR. MARKS: Second.

DR. BERGFELD: Is there any further discussion

(inaudible)?

DR. MARKS: Yeah, I'd like to address Curt's point. If you were using personal care products in a salon as the worker in the salon, you could potentially have a lot more than 30 seconds exposure because you'd perhaps repeat using of an aerosolized product that's sprayed on the hair or whatever

(inaudible).

DR. BELSITO: I raised that question. That question was raised at the last meeting as well. We're looking at consumer safety. That would be OSHA who would be looking at workplace safety.

MR. GREMILLION: I guess I would make a point, the line between consumers and kind of a professional hair stylist may not always be so clear, too. I think a lot of people would see -- you know, consider people operating home salons as consumers and not, you know -- certainly not people subject to OSHA regulations.

DR. MARKS: I think as long as it's handled in a discussion and clear (inaudible), that's fine.

DR. BELSITO: And we'll see what comes out of this.

DR. MARKS: Right.

DR. BERGFELD: Okay. Ron Hill, do you have a comment?

DR. HILL: Just that we have a lot of people in our area operating home salons and they're definitely not under OSHA oversight. A lot.

DR. BERGFELD: Any other comments before I call the question? Wilbur?

MR. JOHNSON: At the last panel meeting, there was discussion about the contact (inaudible) potential for polyaminopropyl biguanide and also on PDF page 70, there are data indicating that the chemical is an irritant. So should those issues be addressed in the discussion?

DR. BELSITO: In the discussion, yes.

MR. JOHNSON: What should we say, Dr. Belsito?

DR. BELSITO: That the contact (inaudible) seemed to occur under the situation of use in burn dressings where the skin is severely damaged. And I really -- the irritation issue is a non-issue in terms of the concentrations at which this is being used.

MR. JOHNSON: Okay. Thank you.

DR. BERGFELD: All right. I'd like to move the question then.

All those in favor of going out as an insufficient data announcement, please indicate by raising your hands.

Okay. Unanimous.

(The motion passed unanimously.)

Day 1 of the December 4-5, 2017 CIR Expert Panel Meeting – Dr. Belsito's Team

Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride)

Polyaminopropyl biguanide, one of the handouts we received this morning stated in a memorandum dated December 4th from the polyaminopropyl biguanide interested party task force that we tabled the CIR report, that they have a commitment to complete a 100-person human repeat insult patch test in a product containing this, and they're starting to form an interested party. So we received a comment that data will be forthcoming at some year after 2020 -- I'm only joking. Hopefully forthcoming as soon as possible so that this doesn't create an issue, unless -- this really came up because of my concerns with sensitization. I still remain concerned. I have to say that I put polyaminopropyl biguanide on my cosmetic and medicament panel. I don't know the concentration off the top of my head. But except for that one patient that I had that reacted to the contact lens solution cleaner at a very low concentration, like.003 percent, I've not had any other positive since. I'm little bit less cornered about this and willing to go along with the table and delay a conclusion.

DR. BERGFELD: Can I ask a question, what are you doing about the letter from the Women's Voices of the Earth where they say --

DR. BELSITO: This goes to the respiratory issue and I think we fully addressed the respiratory issue, but I'll put this back to Curt, who was the one who brought that up, and Dan.

DR. LIEBLER: What was the question again?

DR. BELSITO: The Women's Voices, again raising the whole issue of the Korean mini-epidemic of children's death. It's at the end of the document.

DR. LIEBLER: Well, it's in Wave 2, so the Wave 2 submission contained this letter, which I was surprised when I read it. I was concerned because this specifically -- it is about the pulmonary issue, but it's about -- the question of whether or not our risk assessment, our quantitative risk assessment, is correct, because we were under the impression from the data that we had available that this preservative wasn't used in pump sprays. She sent us a series of links that she found by basically Googling polyaminopropyl biguanide and came up with a series of products I had never heard of, but they're kind of mist and sprayed on your face and wipe or fluff your hair up kind of thing that were easy to find. The listings on Amazon and other online sellers for these ingredients list ingredients list polyaminopropyl biguanide as an ingredient leaf. It seemed to me that this may not have been captured. In fact, the letter suggests that this is not being captured in the VCRP survey so if -- and there were maybe a dozen of these, something like -- it wasn't like one or two, it was a page and a half.

DR. BERGFELD: Actually two pages.

DR. LIEBLER: So I saw that and I just kind of swallowed hard and I thought, wait a minute, are we missing something here. So we were correct I think to do a quantitative risk assessment. We may have been incorrect in some of the assumptions that were used to set the perimeters in that calculation and I'm even more concerned about missing ingredients that are in use. So I don't know if you guys have looked into this or if council is going to look into this, but obviously we can't be doing our work correctly if we're not getting that kind of information and it's actually out there.

MR. JOHNSON: In that that information is coming from the internet, what FDA need to confirm those product registrations to indicate that there are indeed valid?

DR. LIEBLER: I'm not the person to answer that question.

DR.KATZ: Not necessarily, depending what it's saying. Because remember it's a voluntary system and not everybody has to register, so what may be out there may not necessarily reflect what's registered with the FDA. Since the discussion came up in the other panel discussion, a request was made today to see what kind of preliminary information we have in the VCRP related to what's in the letter. It looks like there was one product that was found. It's Brume De Thé Body Mist and it contains the ingredient and that's only thing that was listed there. We may also have a filing for a professional, Sebastian Texture Maker, texturizing spray, but it's not clear whether this is the same product as what's actually registered in the VCRP. That's the only -- those are the only listings that we have. We don't have all the rest.

DR. BELSITO: But I guess -- yeah, I forgot this component of her issue, that I

can -- I can see how a lot of these seem to be like mom-and-pop shops, like One Love Organic Vitamin D moisturizer, but then you have Sebastian, which is a huge hair company, you have Pantene, you have Matrix Biolage. These are things you pull off your shelf at almost any drug store. Why those weren't coming up...

DR.KATZ: Because as I mentioned, we just have one of them, which is a professional use product. So whether or not that's the same as what you can get via Amazon or elsewhere on the internet, it's unclear. Again our list is very incomplete, because even those who register their products with the VCRP may not register all of their products with the VCRP. It's selective.

MR. ZIMMERMANN: One of the issues that I've always had when I've used the VCRP is that companies do not withdraw their VCRP registrations. As a result, they just stay in the database even though they're no longer available, no longer on the marketplace. I know for a fact that the first one that was on the list was Pantene and they took that preservative out of Pantene spray a couple years ago.

DR. LIEBLER: Yeah, but that's the opposite of the problem we're talking about here. We're talking about not be able -- not knowing that these products are on the market when you can go and buy it right now online.

MR. ZIMMERMAN: The issue I have -- and this goes back over years ago. I had a patent infringement case that I was

dealing with and the lawyers asked me to buy certain sun screens, this was a drug case, and I was able to buy virtually every one of these sun screens on the internet and all of them had been discontinued by 1996. I could still go on Amazon and buy them.

DR. LIEBLER: You're talking about old products?

MR. ZIMMERMAN: They're very old and that's what they're finding, old products that are probably no longer available, the use of this preservative in those types of products to place when the marketing people destroyed the preservative that's we were using.

DR. LIEBLER: I get your point now, but it's still -- if it's an old product and you can buy it and we're not capturing that, that concerns me.

DR. ANSELL: We're not asking to assess this or to approve it, that is not an application the industry is supporting. To the extent that someone is doing it, they're doing it outside --

DR. BELSITO: We did a safety assessment of the respiratory toxicology. We are supporting it to be used in aerosolized products, but the point is that we didn't do a safety assessment for pump sprays.

(Talk over)

DR. BELSITO: Yes.

DR. ANSELL: We have comments concerning the margin of safety calculations associated with the hair spray products, but I think our first position would be to remove them, because it's not an application that we support.

DR. BELSITO: Well, you need a reason to do it, so why don't we do a margin -- recalculate a margin of exposure for a pump hair spray and then say that they should not be used in pump hair sprays, that they're unsafe?

MR. GREMILLION: Yeah, I think that's exactly -- that's why this institution exists, right, is to not have Amazon selling unsafe cosmetic products. So if the industry is saying you shouldn't be putting this chemical and these pump hair sprays or facial mists that are -- you're not instructed to breathe in, then that would be --

(Talk over)

DR. BELSITO: Why don't we see what it looks like and do the margin exposure for a pump hair spray, keep the margin of exposure that we have in, and then we'll worry about the respiratory end point and how we address Women's Voice for the Earth.

DR. BERGFELD: You probably have to respond to them any time that we're going to be acting on it.

DR. LIEBLER: Right.

DR. BELSITO: But at the same time say unfortunately the report has been tabled for skin sensitization data.

MS. FIUME: I guess I just wanted to ask for a some clarification, because I

think I'm a little confused saying we didn't look at this information. On PDF page 87 we refer to a concentration use in tonics and hair sprays, which we always state are possible to be sprays. Our concentration of use data acknowledge VCRP data with footnotes that we these ingredients -- I believe PDF page 87 is discussing -- I'm sorry, the last paragraph on page 86.

DR. BELSITO: You're back on polyaminopropyl biguanide?

MS. FIUME: Yes.

DR. BELSITO: In Wave 2.

MS. FIUME: We acknowledge that there was a concentration that had been reported at one time. In the calculations for the margin of safety done on 1/14, that concentration was used in trying to develop a margin of safety. In the discussion, it talks about the margin of safety that was done and acknowledges that industry doesn't report any concentrations for use in sprays but we do acknowledge that the VCRP data has it. Therefore, we're asking for information as part of our insufficient.

DR. BELSITO: What page is that?

MS. FIUME: I'm trying to find the discussion. Is it page 100?

DR. KLAASSEN: 98, it starts --

MS. FIUME: The last paragraph on page 99 right before the conclusion, we're asking for consumer use data on pump and propellant hair sprays for determining extended exposure. So we're asking for a lot of the information. I don't think the panel missed it, I think it's just not explicit because we don't have concentration of use for those type of exposures, but we do have VCRP data that's acknowledged in the report with a footnote caveat saying that they may be used in spray products and we just don't have any information. Because I think as far as -- we've had this come up before where we've had someone say I've searched the internet and I found this information. We can't search the internet for every ingredient group that we do. While there are some that we can say, well, this is so important for this ingredient, why haven't we done it for that, we can't validate those data. So we've always used VCRP and council data as surrogates, the best that we can have that we have some validation for -- as data points in the report.

DR. BELSITO: We have the data there. So we actually -- we can respond to her saying that, yes, we didn't have specific information on whether they were pump or propellant hair sprays. However, for our margin of exposure, we stated that we needed that information to evaluate the safety and we will continue to request it.

MS. FIUME: Because I don't want to look like we've excluded it, it's just that we didn't have the rest of the supporting information.

DR. LIEBLER: No, your clarification is helpful, because I didn't get the connection.

DR. BELSITO: So we are tabling it, we're writing a letter back to Women's Voice of the Earth saying we completely agree. In fact, if you look at the last paragraph of our discussion, we were asking for that specific data and we'll continue to ask for it.

Day 1 of the December 4-5, 2017 CIR Expert Panel Meeting – Dr. Marks' Team

Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride)

Okay, next ingredient. Where's the memo from this morning. So we're at the polyaminopropyl biguanide.

DR. HILL: I make a move to table.

DR. MARKS: So I think it's important though. Obviously we got a memo this morning from the Interested Party Taskforce.

DR. SHANK: Who is that?

DR. EISENMANN: That's a group the council's putting together to complete the study; people that are going to pay for the study.

DR. SHANK: Okay, and it's put together by - -

DR. EISENMANN: The council.

DR. SHANK: Okay.

DR. MARKS: So was the repeat patch test the main concern? I see that. That's one of the things they're saying. The memo says we have a commitment to complete a 100 person HRIPT of a product containing polyaminopropyl biguanide. They're in the process of forming an interested party task force and will provide ongoing updates on this effort. But that's not the only concern, is it?

DR. HILL: Inhalation.

DR. MARKS: Yeah and I think we need to acknowledge again the woman's voice for the earth letter and that came in wave 2. So let me see where that is. And that's - -

DR. SHANK: They have information saying the ingredients used in facial mists which apparently are sprayed directly on the face.

DR. HILL: Five or six times a day potentially.

DR. SHANK: And in one case it says exposed to inhale five times. So there's no question that that use would lead to - -

DR. EISENMANN: And history has said we're not interested in supporting inhalation exposure - -

DR. HILL: LOZSA has said - -

DR. EISENMANN: No it's more than LOZSA. It's the Sierra SSC has been asked multiple times if they're interested and they are not interested in supporting inhalation exposure. It's not allowed for use in inhalation products in Europe, so we'll be fine with an insufficient data for that type of product or if we decide to do something else on that, that would be fine too. But you've always been saying you could do a risk assessment based on that 28 day study. So I mean - - and I haven't gotten any company to stand up and actually do more details on a risk assessment because they're all getting - - from my understanding that the products that they're moving forth is that they're frowned on from our members - - the one from our members. I can't speak to all the products, are likely historical products as they're still on the market.

MR. JOHNSON: With that in mind, should we ask FDA to confirm those product used?

DR. EISENMANN: They may not have been reported to the FDA. I mean, you can but - -

MR. DEWAN: We can go back to the VCRP if that's what you want us to do.

DR. MARKS: It's interesting because one of the points of letter, the first point in the letter is all about inhalation toxicity but the VCRP doesn't really reflect consumers so I - -

DR. EISENMANN: My suggestion is to wait, because if you're going to table it, then by the time that study is completed, then we'll look at the VCRP again at that point rather than relooking at it now. Because if you're going to table it, it might change in the - -

MR. DEWAN: The numbers at the top.

DR. EISENMANN: I don't how - - it may take awhile for us to get the study. I mean, I'd like to say we're going to do it quickly but there's a lot of reach deadline. There's a big reach deadline coming up so it's hard to prod people to get the study done until after that is over.

MR. JOHNSON: Are they going to include Fitzpatrick skin types for all of the individuals on the panel?

DR. EISENMANN: Since that was the request. The group hasn't actually gotten together and really discussed details of the protocol yet. So when we get them, hopefully it will be this month, we will discuss that.

DR. HELDRETH: And just to clarify we don't typically do a Google search to find cosmetics for a number of reasons. For one, we don't know if these are still in use. Two, we don't even know if these are cosmetics even though they came up in a search for a cosmetic, one of these may have some active ingredient on it. The label might say this actually reduces wrinkles instead of reduces the appearances of - - and so it may be classified as a drug and not even within in our purview. So that's why we typically do not rely on doing a Google search. It just doesn't have a whole lot meaning for what we do. And that's why rely on VCRP data.

DR. MARKS: I think in the past we probably I should say, Bart, you have responded to a letter like this or I think Ivan the last time, actually it was the last time responded a point by point response. Are you planning on doing that because for me the VCRP data saying that's why we only use that is important to respond otherwise it will be left hanging why didn't we do a Google search or why didn't we look elsewhere?

DR. HELDRETH: I can certainly respond to her.

DR. MARKS: And I think that would be helpful to have that again for the next meeting.

DR. HELDRETH: Okay, so you want it to be part of the report package?

DR. MARKS: Yes, I think so, team, what do you think? I think, I don't think we should ignore this letter.

DR. SHANK: No, we can't do that.

DR. MARKS: Yes, and that's why I bring it up point by point.

DR. HILL: Well, if our conclusion would say unsafe for are we going to say insufficient data for inhalation or potential inhalation uses are unsafe because --

DR. MARKS: Well, this is going to be it. We are looking forward, that's, we are going to have new VCRP data. We are going to have probably for inhalation we are going to, it's going to be insufficient because we aren't going to have data to -- on that and that's as I recall where we were before is insufficient data. And then the HRIPT is pending so we need to see what that shows.

DR. SHANK: We have animal data inhalation and did a margin of safety calculation.

DR. MARKS: And is that do you think adequate to say --

DR. EISENMANN: But see, we are saying margin of safety calculations have been done correctly, it's done, it should be done on dose versus concentration.

DR. HILL: I think the big thing is and I didn't, I made a very cavalier statement last time I don't remember who was in the room and who wasn't but the activity on bacterial cell membranes is very different than on the (inaudible) cells and that this is a very different structure than the PHMG that happened in Korea but there were a couple of papers that I hadn't seen that I thought I had seen at that point in time and I asked Wilbur to send me one right after the meeting and he did that same Tuesday and I read it on the way home and then there is a 2018 one, it says 2017 in there but it's actually a publication date of 2018 which you have referenced and you did reference in this study and it's a cumulative effect.

It's clearly that this fibrosis that happens is over and over and over exposure again to where you get to a threshold to where this fibrosis kicks in and the mechanisms now I think are pretty well nailed down and the problem is of course the research hasn't been done on PHMB but there is no reason to suspect based on what is known about this fibrosis mechanism now that this would have exactly the same issue, exactly the same issue as what happened with the Korean compound in the data (inaudible).

So then the question is is that margin of safety calculation done correctly? It might be but is it fully taking into account what we now know about the mechanism and this, the fact that it was a cumulative exposure that we can probably defend against as long as we don't exceed those thresholds of exposure. So if somebody is really spraying this stuff and inhaling it at their face four or five times a day or even once a day, there could be a big issue and honestly that's an FDA at that point to go out and find out what products really are being sold because this is probably something that's egregiously unsafe if that's the case.

DR. MARKS: Okay. Wilbur, does that clarify so tomorrow I'm going to move, we are going to table it. We are going to acknowledge the letter that we received from the Woman's Voice for the Earth that and if we will have new VCRP data in the future. There will be a letter from Bart explaining the reason why only the VCRP is used as our use data. Inhalation for the time being is insufficient unless we get more data and then we are awaiting the HRIPT studies and the reason is that as I recall from the last meeting, Don Belsito was very concerned about what happened with methylisothiazolinone and he doesn't want this to be well, endorsed or used as a preservative at a concentration which may be sensitizing and then we end up losing this preservative because it gets banned because of sensitivity.

DR. SHANK: That last part you don't want in the report do you? Our concern is not availability but --

DR. MARKS: No, no, no. That's all just a context for us and why the HRIPT isn't working.

DR. SHANK: Okay.

DR. MARKS: Yes, no I -- one could say why are or why do you really need or want that. Okay.

DR. HELDRETH: So I have to greatly appreciate that we are going to get updates on the progress of this data that we are tabling it for. Could we set a reasonable deadline just so this isn't left out in the ether?

DR. MARKS: Yes, I think that's --

DR. SHANK: How long does it take to do a HRIPT from beginning to end?

DR. EISENMANN: It's not going to be the length of doing the study, it is going to be the length of putting, collecting of --- putting the group together and making decision on the protocol and where to place the study and all that.

DR. SHANK: Do that --

DR. EISENMANN: As soon as I can, I mean, I hope to give you an update at the next meeting if we have made progress, whether or not we have made progress I should say towards this. But until we actually place the study I don't think we can give you a good timing of when it will be done. So and I don't know, like I said we are just getting started.

DR. MARKS: Well, I think that's probably reasonable, let's just have an update at the next meeting rather than arbitrarily say we want to see the results in six months. Now maybe the Belsito team would like to set a deadline but I think an update is reasonable. And if the update says it's not going to be done until 2020 then we may say okay, we think it ought to be done by the end of 2018 or something.

DR. HILL: Well and they have a, I mean, there's a two year clock even if you said insufficient so --

DR. MARKS: Well, that's if we come out, we are tabling it now.

DR. HILL: No, I know I get it.

DR. MARKS: Basically for the HRIPT is my understanding.

DR. HILL: I guess what I'm saying is if a year from now nothing has happened then --

DR. MARKS: Yes, and then we can issue that's why I think it's an update. Bart, does that sound reasonable, update next meeting and then just that as an update, where we stand. We won't be reviewing it I don't think.

DR. HELDRETH: So as long as we keep it under control because I think this is such an important ingredient.

DR. MARKS: Right.

DR. HELDRETH: Our palate of preservatives is going smaller and smaller.

DR. MARKS: Carol, what would you estimate as a reasonable time period to have the results of the HRIPT?

DR. EISENMANN: Like I said I don't know. We are working with one supplier and some other companies and I know the supplier is deep into breech and there is a big breech deadline the end of May.

DR. MARKS: Oh, end of May.

DR. EISENMANN: End of May there is a whole lower, low, lower volume materials are due at the end of May. So --

DR. HELDRETH: Could we maybe have an estimate at the next meeting?

DR. EISENMANN: We hope to meet with them this week.

DR. HELDRETH: Okay.

DR. EISENMANN: But I don't know.

DR. HILL: I wouldn't be concerned at all about the timeline other than I think it is important for this report to go out with the inhalation information in there now that we have more, I mean, it may be with those margin of safety calculations is fine but I think that in terms of there is enough information now from this other compound in terms of how they calculated and came to their conclusion that if you applied the exact same logic to this one in an abundance of caution you can get some solid numbers which might land in the same spot because they put in some pretty good sized margins or it might not but I feel like that's, I feel like that is probably the more compelling thing to get out there because sensitization worst case scenario somebody has blistering. They have an effect like what they saw in Korea and you have got people dying.

DR. MARKS: Yes, there is no question the two are not comparable but I can tell you that if you get enough people blistering --

DR. HILL: Oh I know.

DR. MARKS: -- the ingredient will be removed and unavailable.

DR. HILL: I'm not trying to minimize that and I get the point. We don't want to lose another preservative that's in a different class.

DR. MARKS: Okay.

DR. SHANK: I don't want the margin of safety calculation (inaudible) if what the Women's Voices of the Earth have found that this is used in facial mists so it's a spray probably. If it's a pump spray it's going to be worse, directly into the face and in one case it said you should inhale five times.

DR. HILL: On the flip side if it's not size of particles because it's the deep lung where this pathology happened that was in the Korean tragedy I would characterize it as. It has to be things that can get into the deep lung so it's possible the pump spray would be just fine but I think the point is that the aerosol --

DR. SHANK: Well, to calculate the exposure may not be correct.

DR. HILL: Yes.

DR. SHANK: In our calculation.

DR. HILL: Yes, and I'm not arguing that. I agree.

MR. JOHNSON: But, Dr. Marks, you had mentioned the new VCRP data.

DR. MARKS: Yes.

MR. JOHNSON: But will we also would be receiving updated use concentration data from industry?

DR. EISENMANN: Depends on how long it takes us to get the HRIPT done. If we can get it done quick then we might not need it but I suspect you will need it because I suspect it will take us a while I presume. I mean, there weren't that many companies that responded the first time to using it so I don't know.

DR. SHANK: Well, if we can confirm it's no longer used in the inhalable products in this country --

DR. EISENMANN: Well, there is no way to act, to absolutely confirm that, I mean, I have gone out to the companies that reported hair spray use to me and now they are no longer using it in hair sprays so but then again they could find the product still for sale on the internet but those are old products.

DR. SHANK: Okay.

DR. EISENMANN: So they are reformulated.

DR. SHANK: But if it's current that they are no longer, it's no longer in use in such products in this country and if we say see under current use we are correct. Because the current uses exclude inhalation.

DR. MARKS: That could be handled in a discussion for the other again because the gravity as you mentioned, Ron Hill, what happened in Korea with the deaths, we could put in the conclusion and not just insufficient, we can say it's unsafe for use in inhalation.

MR. JOHNSON: Is it possible for FDA to confirm those uses, Dr. Dewan, or?

MS. DEWAN: So are you trying to say that we should confirm the uses that's

the products mentioned in this label?

MR. JOHNSON: Right, is that possible?

MS. DEWAN: We can do it but again we could go back and look at the VCRP and that's what we can provide. That's what you want to look at it, correct?

DR. EISENMANN: Because those products may or may not be registered.

MS. DEWAN: Yes, that's what I'm saying so you have to tell me and I think it would be nice if you can officially let us know so since this is a letter from VWG it would be good to know officially if you want to check these products in VCRP if they are registered or not.

MR. JOHNSON: Well, because I know some of those categories are very broad and, you know --

MS. DEWAN: Yes.

MR. JOHNSON: -- may include products that are sprayed but we don't know specifically.

MS. DEWAN: Yes.

MR. JOHNSON: From those data whether or not they are spray products.

MS. DEWAN: Yes.

DR. MARKS: Okay, well that's a long discussion for tabling.

DR. HILL: But an important one.

DR. MARKS: What?

DR. HILL: But an important one.

DR. MARKS: Oh yes, no, I have on questions. And I will bring up those points tomorrow and then we will see what the Belsito team brings up but I don't think anybody is going to disagree with let's have an update next meeting, Carol, as to the progress of the committee. And as you know (inaudible) the interested party task force. Why don't you just get rid of interested? It sounds more official if it's just the polyaminopropyl biguanide party task force. We will get rid of interested and party. Just task force.

DR. EISENMANN: We've been calling them that.

DR. MARKS: Yes, good.

DR. EISENMANN: Because that is why we have been calling them interested party task forces.

DR. MARKS: Yes, why don't you just call it an interesting -- why don't you just call it a task force? Yes. That covers everything. And if the task force wants to further clarify the pump spray we will be expected to address that too.

DR. EISENMANN: They don't.

DR. MARKS: They don't. They are only interested in --

DR. EISENMANN: They are not interested in supporting inhalation exposure.

DR. HILL: Not interested.

DR. MARKS: And it would be interesting --

DR. HILL: I think that is smart.

DR. MARKS: Yes, definitely. And with a -- which do they support? Insufficient or not used?

DR. EISENMANN: I don't think I have -- well, I don't think they have announced. Our main supplier is a company that is not used as somebody out there.

DR. MARKS: Oh, that's it, that's what --

DR. EISENMANN: Might be so.

DR. MARKS: Okay. Well that was actually robust.

DR. HILL: I mean, (inaudible) was very clear, we don't support the use of --

DR. MARKS: Yes, I know but I think again the --

DR. EISENMANN: And they are the supplier so the name is familiar.

DR. HILL: Are they the main supplier?

DR. MARKS: Yes. But I think rightfully so the Women's Voice of the Earth pointed out that they aren't the only ones using it even though they're the --

DR. HILL: Well, they're selling it and whoever reformulates it.

DR. MARKS: Yes, and it's the formulator, exactly. Yes. Okay.

DR. HILL: But the letter to the FDA getting them to find out what they do have and don't have is so --

DR. MARKS: So we move on to the persulfates.

MS. DEWAN: So before we move can I quickly ask for your other one to check all the products in the label if it is registered in the VCRP, correct Mr., Dr. Marks?

DR. MARKS: Yes.

MS. DEWAN: Okay, thank you.

DR. HILL: And were the products listed in the last months or last meetings communication as well? I think that will work.

DR. HILL: Those products --

DR. MARKS: Were there additional products in the letter that we got from last meeting? Seemed like there were listed, things listed in that one too. You can go back and check.

DR. HILL: Okay, sure.

DR. MARKS: And you can add if there are different ones there too.

Day 2 of the December 4-5, 2017 CIR Expert Panel Meeting – Full Panel

Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride)

And moving on to the next is the biquanide. Dr. Marks polyaminopropyl biquanide.

DR. MARKS: Table. Let me pull up that -- so we received a memo yesterday indicating that a task force has been formed and they are going to look at the insufficient data concerning the HIRPT and conduct that study as requested. So we felt we should not move forward but table a conclusion on this ingredient. I can make some comments after that, but the motion is to table it.

DR. BELSITO: Second.

DR. BERGFELD: Second. All those in favor of tabling the discussion. Approved. This is tabled. Do you want to make your remarks now, Jim?

DR. MARKS: Yea, we should note that the Women's Voice for the Earth letter you all read that. There is -- we need new VCRP data. Bart is going to compose a letter as why only the VCRP is used in that letter that was concerned that the VCRP was not a so to speak, large enough net to capture the uses. We -- our team is still concerned about inhalation and we discussed the possible end point of either insufficient data versus do not use in inhalation possible products. The margin of safety may not be correct if in a pumped spray.

And then, as I mentioned, what triggered the tabling was awaiting the study results of the HIRPT and then we charged industry to update us at the next meeting. We didn't want this to be happening indefinitely for the next couple of years. It's too important an ingredient.

DR. BERGFELD: Don, do you want to comment?

DR. BELSITO: Yea, I agree that we should respond to Women's Voice for the Earth, as you know, pointed out by Monice yesterday we actually didn't dismiss the possibility that they could be used in sprays. If you look at the request just above our conclusion it is consumer use day on pump and propellant sprays for use in determining the extent and exposure to polyamino byquanide during product use was one of our unmet needs for this, number one.

Number two, we are told that the VCRP may reflect current use and that products sold on Amazon and on the internet may be old products that have been withdrawn by a company. So the VCRP data may actually be correct.

And lastly, we were told that perhaps we might be able to get some information if these products are registered in Canada from Health Canada as to what concentrations they were used in. I don't know if Monice is going to follow-up on that. I think it was just pointed out in our discussion t hat looking at what is available on Amazon may not really reflect what actually is being manufactured at this point in time.

DR. MARKS: Yea, we had that discussion also. And board was going to handle that in the letter.

DR. HELDRETH: Yea, we'd just like to add we mulled over the idea of doing the searches to find other places where we can find out if these ingredients are used in cosmetic products, but there is no verification that even the things we are going to get in those kinds of searches are cosmetic products. The list that we received from Women's Voices as you mentioned some of those may not be even being used anymore. But additionally we don't know what the full list of ingredients are in those products, what the labeling is. Those things may be considered drugs by the FDA and not necessarily cosmetics. And so that is another part of rationale for why we don't depend on that type of searching to figure out the exposure.

DR. BERGFELD: Linda, do you wish to comment -- or Tom first?

DR. GREMILLION: I just made the point that some of the products listed in the Women's Voices letter for clearly cosmetics and big name brands. Dr. Belsito made the point yesterday Pantene and other recognizable brands and some things sold ion Amazon for use. I think most people would intercept that as being in use even if there is some disconnect between the manufacturer.

DR. BERGFELD: Linda?

DR. KATZ: Just the one thing I need to just remind people about the VCRP --

the V is voluntary and it's important to make sure that people understand when it says voluntary that industry manufacturers, distributors, whoever do not need to file anything with the VCRP. So the fact that you see things on the marketplace potentially in Amazon or someplace else and that we may not have it in our VCRP does not necessarily mean that the product is no longer being manufactured. It just means that within our records we do not have a record of it.

And what we presume from what we have looked at because again not only are we regulators, but we are also consumers that probably we get only about 47 percent registered of what is truly out there marketed and we really don't have a full estimate of what is truly marketed in this country.

DR. BERGFELD: And again, you make a comment about how long you keep an ingredient or a product on your list.

DR. KATZ: It's variable. And we will remove products if the manufacturer contacts us to say it is no longer used and then we will go head and delete it from our records. Periodically we go through and we try to clean the records. By that I mean we will send out notification about products and to manufacturers where we have not received much in the way of interaction to ask if certain products are still on the marketplace.

If we don't get a response we'll actually issue three such requests for information and by the third request if we don't hear then we will assume that the product is no longer being distributed in this country and we will remove it. So it is the last time that we are in the process now of going through and trying to rectify what's in our records versus what's out there. But it's usually done about every years or so that we'll go through.

DR. BERGFELD: Thank you. Any other comments, Jay?

DR. ANSELL: I feel I should add that the council does strongly support the conclusions of the CIR and to the extend that products are using ingredients that are inconsistent with the CIR findings. The council does not support that. So if people are using them it would be inconsistent with our standards.

DR. BERGFELD: Thank you. Ron Hill?

DR. HILL: I just because of things that I said at the last meeting I had not seen the most recent several -- actually, couple of papers that dealt with the mechanism as it relates to the comparability of the structures of PHMB with PHMG and the possibility of mechanistic commonality. I think the gist of those most recent papers is there is at least reasonable probability to agree that the mechanism for this fibrosis that led to the fatalities almost certainly led to fatalities in Korea, would be uncommon. There might be some differences in dose response and we don't have any hard science on that yet, but there is at least reason to believe that could be uncommon and it is a cumulative effect. In other words, I think we can defend against a certain amount and once it exceeds some threshold and the science of how well we defend on any particular compound is not yet known. But it is also a deep lung exposure. So the biggest concern would be things that could get into the deep lung. So I don't know if pump sprays are the problem because in general, those don't. But things are aerosolized -- most definitely.

So that is in contrast to what I put in the transcripts last time because I made a comment that I think was a little too cavalier. After I got to read these last few papers in great detail the most recent one is from 2017 that actually have a 2018 publication date and it is the same group over there it is referenced in Wilbur's most recent draft.

DR. BERGFELD: Thank you. Well, we have a lot to record and keep in the minutes to update us while we deal with this ingredient next time in the near future.

Day 1 of the June 4-5, 2018 CIR Expert Panel Meeting – Dr. Belsito's Team

DR. BELSITO: In December we tabled this because we were promised we were going to get an HIRPT. Six months later we don't have one, but we're told they have now formed a group and we might get one. So, do we go ahead and table it again; or do we put them up against the wall and go insufficient?

MS. KOWCZ: No, we should definitely put it up again because there's an actual group that is definitely doing this. So, I just want to make sure that the data is coming.

DR. BELSITO: Okay. Well, that's a comment from industry.

DR. EISENMANN: They wanted to make sure they had found everybody that would want to participate in it. Then it took a little longer than we expected.

DR. BELSITO: I understand, but we can go insufficient and put you up against the wall to get it done.

DR. EISENMANN: It's not going to make a difference whether or not you do that. I mean, it takes as long as it takes.

DR. BELSITO: Okay. I mean, it's been six months. It'll be a year in September, but we agreed to table it in December. So, I'm asking my teammates. I can sort of go either way, but do we go insufficient, or do we table it because industry is now telling us they're finally ready to begin the study?

MR. GREMILLION: If it doesn't matter then, you know, go with the integrity of your process.

DR. BELSITO: Well, because if we go insufficient there's a timeline that starts, and in two years, if we don't have the data, it shouldn't be used.

MR. GREMILLION: Yeah. So, great.

DR. LIEBLER: I think if it's on the way, that's great, and then we should still be able to go insufficient and expect the data.

DR. SNYDER: According to the memo, the protocol hasn't even been finalized.

DR. EISENMANN: Part of it now, we're running into the summer; and companies don't like to do studies because they get a lot drops during the summer. So, now we've got to wait until September. So, I mean, that's kind of a delay that way too.

MS. KOWCZ: There were a number of delays. It was the funding, it was the interested parties to really actually pay for the study. And normally, the industry does not do studies in the summer for compliance issues, for other factors issues. So, we're hoping to start the study in September. I just wanted everybody to know the factors that delayed it.

DR. BELSITO: I certainly can understand not doing it in the summer because not only, you know, are there dropouts because of vacation, but the sun exposure reduces your delayed type hypersensitivity responses and you'll end up with a lot false-negatives. I just am -- you know, again, it's dragging the feet and it seems like unless we force you people up against the wall, we just don't get the data. Sorry to be so forceful.

MR. GREMILLION: I think that makes a lot of sense and, you know, it could be -- it doesn't have to be seen in necessarily kind of an adversarial way. It's just signaling that it's a priority, you know, rather than something that's going to be indefinitely prolonged.

DR. BERGFELD: I'd like to take the opposite stance. The ability to come forward with some interesting data would be good. Industry has said they will do it. They got their act together. I would say that we give them another six months or eight months -- six months from September. That would be my opinion.

DR. BELSITO: But if we table it, we're giving them two years from whenever.

DR. BERGFELD: We can always put a timeline on it. We can say next December we want to see the data.

DR. LIEBLER: And a timeline for insufficient?

DR. BELSITO: It is two years.

DR. LIEBLER: So, I say insufficient and it looks like we're actually doing something.

DR. BELSITO: I would agree.

DR. EISENMANN: One other concern is, Wilbur, did you do an updated literature search on PHMB for this meeting?

MR. JOHNSON: No, that was not done.

DR. EISENMANN: Okay. So, the date on the file report, you don't have what might be most recent data.

DR. BELSITO: Most recent data from?

DR. EISENMANN: Published literature. So, your final report, the last literature review on it

was done in December?

MR. JOHNSON: Actually, it was the September panel meeting; that was the last time that the report was reviewed.

DR. BERGFELD: So, almost a year ago.

MR. JOHNSON: And the reason why that was not done is because it was anticipated that the report would be tabled, so a literature search was not performed. But that will be done, you know, prior to the next review.

DR. EISENMANN: But if it goes insufficient at this point, there's a certain gap that this report does not cover.

DR. SNYDER: So, what's our procedure? So, we'll be a year and a half to almost two years, prior to the September 2017 review of this document, waiting for data. We get the data, we say the data are adequate, but then we have a year and a half/two-year gap where there was no literature search, we don't know if any new studies came out. So, what do we do then? Do we reset and go all the way back to a review process?

DR. HELDRETH: Since it was in a tabled status, the reports sits, and we don't focus on doing new work for it. We're just waiting for the gaps, that the panel asked to be filled, to be filled. And now we're bringing it back for the panel to take a look and say, you know, the gaps are filled, or the gaps are not filled, or we're willing to table it or we're willing to wait, or we want to move forward and put out an insufficient data conclusion at this point.

If that happens, and you put out a final report, then there's a two-year clock for that information to come in. And if that information does not come in to the panel's expectations, then the report would be moved to the use not supported category.

However, if in that two-year process, the studies do come in, we'll bring the report back to the panel again, we'll bring in any new literature at that point, and the panel will have the opportunity to reopen the report, essentially, and decide if the conclusion should remain the same or if they feel like they've got the data gaps filled.

DR. EISENMANN: But in the meantime, you have a final report sitting out there that the date really shouldn't be today, it should be back in September. Because the literature search isn't up to date.

DR. HELDRETH: If the new information that you're talking about, though, is not something that's filling those gaps.

DR. EISENMANN: But you still should check. I mean, I did a quick check and found one study. But I didn't do your thorough look everywhere for information. I just did one quick set and there was one study. It was on discussing liver cancer, was the study that I found.

DR. HELDRETH: I see what you're saying. So, there should be a date marked there that says this was when the panel stop looking at any new information going forward. I think we have to be careful and make sure that the date of the report is not set back to that timeline, because then your two-year clock is going to run out really fast.

DR. BELSITO: The issue here is skin sensitization. And to my knowledge there has been no published data that would answer the question that we're looking at. The other thing is there are reported incidental inhalations in sprays, and we have no margin of safety calculated out for inhalation, and I think we need to do that.

DR. SNYDER: I thought we had it at 100.

DR. BELSITO: I thought we did too, but I I'm not seeing it.

DR. SNYDER: It says margin of safety for inhalation 100.

DR. BELSITO: Where is this? I don't see it in the document.

DR. SNYDER: Page 98. We're on Page 98.

DR. HELDRETH: Yeah. One of your additional insufficiencies was to get consumer use data on pump and propellant hairsprays in determining the extent of exposure.

DR. BELSITO: Right. And we haven't gotten that?

DR. HELDRETH: Right. So, that's still an insufficiency.

DR. BELSITO: Right.

DR. EISENMANN: We are working on a survey, but it's not specifically for this ingredient. CIR SSC agrees with the conclusion in Europe, it should not be used in spray products. Regarding the risk assessment that's in the report, it compares concentration, but we think it should compare dose.

DR. BELSITO: Of course. And I have mentioned -- and I don't know if you've attempted to contact them -- that the RIFM has contracted with a company in Ireland by the name of Creme who looks at habits and practices and could give you a 95 percent confidence interval at which this would be used in propellants. They have that kind of data for both North America and Europe.

They don't look at just fragrance ingredients, they look at all types of personal care products that presumably could contain fragrances.

DR. LIEBLER: Does the fact that this is tabled for the sensitization data, remove urgency for requiring the data from industry on spray exposure? Is that an unintended consequence of our tabling?

DR. BELSITO: Yes.

DR. EISENMANN: Well, we are working on surveying particle size information. We already have completed a survey where they gave hairspray to so many consumers and they determined how much hairspray was used. We have that data. That's quite a while ago; so, you know how many milligrams per day of hairspray somebody uses. A number of companies have provided us their data, on their products, and we're working to put that information together for you.

It's for the general inhalation. They didn't necessarily want to apply it to PHMB because they say they're not using it in spray products.

DR. BELSITO: Okay. But are hairsprays the only source of exposure. I mean, if you're using an underarm spray, isn't that a potential for inhalation?

DR. EISENMANN: We don't have an evidence that it's in that type of product?

DR. BELSITO: Okay. So, the only products –

DR. EISENMANN: So, in other words, they'd be happy if you came up with the same conclusion as Europe, should not be used in spray products.

DR. BELSITO: I mean, I would love that conclusion. My concern always is, is that we're being asked to look at could this be safely used.

DR. EISENMANN: Well, you have a NOAEC so you could say the exposure from a spray product should be 100 fold like QRA. You could calculate how much a rat breath, you know, come up with a dose at that NOAEC; and so, a company would be responsible for having their product to be 100-fold less than that value.

DR. BELSITO: Well, that's what I mean. Scientifically, that's what we should be doing, rather than just saying, okay, we can't be bothered with the math or the science here, and we'll just say, hump, it shouldn't be used.

And I'd be happy with that conclusion. I'm just curious what my colleagues think about that type of just walking away from it and going, you know, we don't want to deal with the complexity of this issue.

DR. LIEBLER: Well I think if we have data that we can apply we should do the evaluation. And then if the conclusion is that the data doesn't support the safety, then we draw the conclusion at that point.

DR. HELDRETH: The way that it's laid out currently, this is an insufficiency. If you feel that insufficiency isn't met and you go with the final conclusion of that, and two years pass by, the conclusion will be for use in pump and propellant hairsprays, use not supported.

That's how we would procedurally go forward when you don't feel you have the data to do it. That's going to be your ultimate conclusion, use not supported for those uses.

MR. JOHNSON: I just have a comment. In the use section, it is stated that polyaminopropyl biguanide is used in a fragrance preparation. There is that possibility of incidental inhalation exposure.

DR. BELSITO: It's listed in Table 3 that there is. It's 1; 28a, multiple exposures and 30b, not specified, these products as sprays or powders. But it doesn't say the product type, whether they're fragrances or hairsprays; but it indicates that they are potentially used in sprays.

Okay folks, where are we? Table or move ahead?

DR. LIEBLER: I still support insufficient.

DR. SNYDER: Are we comfortable with how we're going to report on the inhalation use? Have we had that discussion? How are we going to word the inhalation use? We're saying it's insufficient for sensitization, but what's our conclusion going to say about inhalation use?

It gets complicated. It's not just insufficiency because we may have a "should not be used" in inhalation, in hairsprays at the levels where the margin of exposure --

DR. BELSITO: Our insufficiencies at the last meeting were in HRIPT involving a diverse population; because the one that industry came to us, at 1000 micrograms per centimeter squared, were almost entirely very dark-skin individuals with -- yes Carol?

DR. EISENMANN: I think there's two issues. The 1000 micrograms per meter cubed was only in 26 individuals.

DR. BELSITO: And they were darker skin.

DR. EISENMANN: No, that wasn't the darker skin study. That was a different study. That study was not at a high enough concentration to give you enough margin of safety.

DR. BELSITO: Okay.

DR. EISENMANN: That study included a statement in the inclusion criteria that they accept all races, except if they thought the skin pigment would be too difficult to read -- I think you may have missed that -- too difficult to read redness.

The real issue of that study was concentration; you wanted a higher concentration.

DR. BELSITO: No, we wanted a greater end because it was very quirky at 1000 micrograms per centimeter squared.

And then the second issue that was insufficient, Paul, was consumer use data on pump and propellant sprays for use in determining the extent of exposure to polyaminopropyl biguanide during product use. So, there is a respiratory request in there.

DR. EISENMANN: I'm not sure what you're requesting there. Are you requesting particle size information on products?

DR. BELSITO: No, we're requesting a margin of safety based on upon consumer use and under the assumption that this is used in hairsprays at the maximum-reported concentration.

DR. EISENMANN: It's not anything we're going to give you.

DR. BELSITO: Then we'll go insufficient for it. And as Bart said, in two years it will be unsupported.

DR. EISENMANN: For use in spray products.

DR. BELSITO: Right. Or, we can do what Europe did and what manufactures suggested and say it shouldn't be used. But we don't have the data that says that; that's my problem. That's my personal problem; is just punting and saying, okay, well we don't have data so we're just going to make these conclusions.

But, Paul, you didn't answer the question, table or move ahead as insufficient?

DR. SNYDER: Sensitization data, even if we get it in December, we're still insufficient. Does that mean that the insufficient data announcement for the calculations for the pump sprays and propellants is going to --

DR. BELSITO: It starts today if we go insufficient.

DR. SNYDER: Right.

DR. HELDRETH: If you issued a final report today, the clock would start for both insufficiencies. If the study is completed, that the group is putting together, and we get the HRIPT data, we'll bring it back to the panel as basically reopening of the report. And if the panel feels that it meets the gap, then you'll put out a new conclusion.

Then the process of the report will go back to an earlier stage so that there's time for public comment, because the conclusion will have changed. But if the data comes in and the panel feels that it didn't fill the gap, and the insufficiency still remain, then it'll just stay closed.

DR. BELSITO: Just to question, Bart; okay, so if it comes back to us and we change the conclusion, then the clock for the respiratory inhalation issue is reset as well?

DR. BELSITO: Well, we don't have that specific in the procedure, for having those split conclusions like that. My understanding is if you put out the final report, that's when the clocks starts.

So, if you're putting out a final report at this meeting, with that conclusion, it would not restart the clock if we reopen it, just to change the sensitization insufficiency. So, no, that clock would not restart. Two years from tomorrow, it would go "use not supported for spray."

MR. JOHNSON: I have a comment. If you issue a final report, to date it will be a report that has not been updated with literature that has become available since the last review.

DR. HELDRETH: True, but there's always some point where you're going to have to stop the data input. If there's something out there that will change the conclusion, or fill that gap, or create new questions, then certainly the panel can request that we go back and do that search. But at some point, we just have to say we did your literature search up to this point, and that's what's in this report, that's what's reviewed.

MR. JOHNSON: So, it will be announced as is?

DR. HELDRETH: Correct. And if that information needs to come back into the report, then the report can be reopened for that information.

MR. JOHNSON: Thank you.

DR. BELSITO: But this would be a tentative final; or it would be a final?

DR. HELDRETH: It would be a final.

DR. BELSITO: Okay. So, it would not be coming back to us?

DR. HELDRETH: It would only come back --

DR. BELSITO: Well, because it was a tentative final that we tabled, so, yeah. Okay.

DR. HELDRETH: But it'll only come back to you if we get new data or there's some reason to

open it back up.

DR. BELSITO: So, Paul, where are you?

DR. SNYDER: I'm concerned. I mean, Carol expressed that she did a literature search and found a new publication on affects possibly on the liver. I mean, I'm not seeing that data or anything to do with that data. So, I guess it's a procedural conundrum we're in here.

Because I think that we're insufficient for two things, and one of the things likely will be met. The other one is going to remain insufficient and likely going to go out as an insufficient report with a "safety not supported" conclusion after two years. I don't see any reason to stop, what we know is already going to happen in December, today.

DR. BELSITO: We don't know that it's going to happen, number one; and number two, if we're saying it's insufficient for any reason, then it's use is not supported in a cosmetic product. I mean, I think it would be different if we're going ahead and saying, okay, it's safe as used and there's some data on liver cancer out there that we haven't looked at. But this is just the opposite. We're saying that it's use is not supported.

And, you know, if industry comes back to us with data that will support the sensitization, then presumably there will be a check of the literature -- correct, Bart -- where we will update everything. And if the liver becomes an issue, we can always make another comment on the liver.

Again, we've been through this situation before, and two years later we don't have the data that was promised. What I'm saying is, that I appreciate what I'm hearing form PCPC; I appreciate the issues of carrying studies out in the summer, but you have two years. Let's move it ahead so that in two years from now we're not going, oh, well, we had problems with the study.

DR. LIEBLER: This is a little bit unusual because we are concerned about the inhalation exposures. I think that any information we can give to the consumers and to the stakeholders that we're concerned about this, the sooner the better. I don't think we should be delaying this.

Because I'm not certain how we're communicating that concern that we have. I mean, I guess it would be in our minutes, but it's certainly not as forthright as having a final report coming out insufficient with these concerns.

DR. BELSITO: So, Paul, Dan says no table. What are you saying?

DR. SNYDER: No table.

DR. BELSITO: Okay. Curt?

DR. KLAASSEN: I'd like to, first of all, bring up this Table 12, and the so called "margin of safety" that we have in the text. I really do not understand what this table is telling us or what the text is telling us. If you go up into the text, it talks about -- let's see what page that is in the text. It's at 106, right before the summary.

In a refined risk assessment -- I don't know what refined is, but -- the concentration in the bedroom air was 0.06 milligrams per millimeter cubed (calculated value, which is 250 times greater than the exposure concentration of. . . . which is derived of the margin of safety of 100) for this scenario, averaged over eight hours. . . . this concentration is 27 times higher than the exposure concentration that yields a margin of safety of 11.

What I'd like to know is, what is the amount that causes injury in laboratory animals versus what is the dose that causes injury -- well, or what humans are exposed to? What really is our margin of safety here? We're mixing these margins of safeties of 11 and 12.

I can't read that paragraph and know what it says. Nor can I read that Table 12, later on, to kind of figure out what is our margin of safety. Do we know? Or what's our best guess? I mean, we should be able to.

But to do a margin of safety, you ought to know the exposure. So, what is the exposure in the laboratory animals and what is the exposure in humans?

DR. SNYDER: Well, there's a 21-day and a 28-day inhalation study in rats. They do come up with a no observed adverse effect concentration level, the .025 and .0239. So, we do have that data.

DR. EISENMANN: What we're suggesting is that from that concentration you should calculate a dose. And then compare dose rather than compare the concentration.

DR. KLAASSEN: Right.

DR. BELSITO: And so they need consumer habits and practices, which we're told you're working on.

DR. EISENMANN: Well, we're working on particle size information. Human habits and practices has been published already, two thousand -- I don't remember, quite a while ago -- where we did hairspray. I think we've shared that paper. It's a Loras (phonetic) et al. paper where they gave pump and aerosol and they can get how many grams per day.

DR. BELSITO: Okay. So, you're looking at particle size and --

DR. EISENMANN: Correct.

DR. BELSITO: Okay. And is this because of the comments we've heard from Woman's Voices for the Earth about the fact that we're probably wrong in terms of pump sprays size?

DR. EISENMANN: Correct.

DR. BELSITO: Okay. Thank you. So, I agree we need to look at that as well. So, Curt, I haven't heard from you; table or insufficient?

DR. KLAASSEN: Well, let me continue on with what I was talking about. Can we fix this, in this document? I mean, I can't read the paragraph and tell you what it says. Nor can I look at this table and figure out what's really going on.

DR. BELSITO: Well, the table would suggest that they're all fine except for pump sprays, which come in at 11.

DR. KLAASSEN: And so, what's the real difference between -- what is the pump sprays, the two studies? What is this?

DR. BELSITO: Because there's a different concentration reported for polyaminopropyl biguanide in a pump spray as opposed to non-pump.

DR. KLAASSEN: But they have two different pump sprays. Is that because of two different brands? Where is this data coming from?

DR. LIEBLER: That's the concentration of use survey, that .053 in the second column from the left, of numbers under pump sprays.

DR. EISENMANN: Which they have since come back and said that they're not using it in hairsprays anymore.

DR. LIEBLER: This says pump spray. And you said hairspray. So, pump hairsprays, or?

DR. EISENMANN: But they've come back and said they're not using it anymore, so it's theoretical now.

DR. SNYDER: The maximum concentration for propellant hairsprays was .004 percent. For pump sprays, the maximum concentration use was .053. So, it's significantly higher for pump sprays.

DR. LIEBLER: So, that drives the 11?

DR. SNYDER: Yes.

DR. KLAASSEN: Is there two different – how come there is two different numbers, .053 and .0058, why is that?

DR. ZHU: So, .0058 is based on the marginal safety 100.

DR. KLAASSEN: What?

DR. BELSITO: The .0058 would be what they would need to reduce it to, to get to a margin of safety of 100.

DR. ZHU: Yes.

DR. LIEBLER: That's not clear from just looking at the table.

DR. KLAASSEN: Yeah.

DR. LIEBLER: That needs to be labeled in the table somehow, as a theoretical calculated amount needed to achieve a margin of safety of 100.

DR. ZHU: Okay.

DR. LIEBLER: For example, the .0058 could have a superscript.

DR. KLAASSEN: Actually, shouldn't be in the table.

DR. ZHU: Okay.

DR. EISENMANN: It actually needs to be changed to calculate dose, not concentration. This whole table needs to be revised so the MOS is not based on concentration; it should be based on dose. So, how much the rat breathes and how much does a human breathe. If a hum was exposed to a hairspray, how much would they actually breathe in, because it makes a big difference.

DR. KLAASSEN: Yeah. And probably for all of these we're going to have a margin of safety of 1000.

DR. BELSITO: Well, I guess this raises an interesting question based upon what Carol just said. Because if we're told they're no longer being used in spray products, and this does come back to us, eventually, for skin sensitization, it will come back with no inhalation exposures. In which case, a "safe as used" conclusion would be what would be delivered, assuming it's safe for skin. But now it's where we've already wrestled with the fact that we're not sure that it could be safely used in a spray product. How would we address that in a conclusion?

DR. KLAASSEN: Why did we think it's not safe by spray? Just because some kids in Korea died?

DR. BELSITO: That's a good reason. And the rat studies.

DR. KLAASSEN: I don't think the data is there, that I've been able to find that it's a problem here. All I'm saying is where is the data? And what is calculated data and what is real data?

And we have to have the amount that these animals were exposed to, which we have. And then we can kind of calculate the amount that people would be exposed to. Then once you know that, you can calculate a margin of theoretical safety. If it's 10 it's a worry. I'm not sure it's not 1000.

Because we haven't done the right calculation. Do you agree, Carol?

DR. EISENMANN: Yes.

DR. BELSITO: I mean, so again, we haven't done the right calculation, but there has been a concern about inhalation. It's been addressed by European authorities by saying it should not be used in sprays.

If Carol's information is indeed correct -- and I'm just throwing this out here as something to consider when we see this document again, regardless of whether we agree to table or go insufficient. If that information is correct, it's going to come back to us with no inhalation exposures. In which case, under those circumstances, our usual conclusion would be safe as used.

But we would have never addressed the respiratory issue. It's not something we need to answer today; but as we look at this document going into the future, once we decide what we're going to do with it today, I just want you to be aware that if in fact that's true, we struggled with the respiratory issue, and what do we do with the conclusion when we're being told that it's not used in products that could be inhaled?

So, just with that as background, we're still dealing with do we table or go ahead as an insufficient.

DR. KLAASSEN: I have no problem going ahead with it being insufficient in regard to the inhalation, if Carol can find out that it's not used by inhalation. If the information that we have in this document is that it is used in inhalation, how do we kind of say that data isn't any good, it's no longer used that way? Can we do that?

DR. HELDRETH: If you want to make a substantive change and take out the inhalation data or change what we're saying there, or exclude that insufficiency that we have in there currently, then we would put this out -- if you don't want to keep it tabled, if you want to put out a new report, it would have to go out as an amended tentative report. And then you would have an opportunity to either retable it or finalize it at the next meeting. Because if we're going to make a substantive change like that, at this last point, it has to go back out for comment.

DR. LIEBLER: It appears that -- if you look at the footnotes for Table 3, which is the usages, Footnote (a) --

DR. BELSITO: PDF Dan?

DR. LIEBLER: PDF Page 112. Footnote (a) says, "It is possible these products are sprays, but it is not specified whether the reported uses are sprays." There the incidental inhalation spray, with three numbers, 1, 28 and 30.

So, the 28 has Footnote (a), which is possibly these products are sprays, it's not specified whether the reported uses are sprays. The 30 next to it has Footnote (b) which is, "Not specified these products are sprays or powders, but it is possible the use could be a spray or powder; therefore, the information is captured in both categories."

It appears that these weren't actually reported to be used as sprays. It was that the reports were ambiguous? Am I reading that correct, Wilbur?

MR. JOHNSON: You're right, Dr. Liebler. But in FDA's database, use and one fragrance preparation is indicated; but, you know, as to whether or not that's a spray product, we don't know. That one refers to, we know it's used in a product, in which exposure could result in inhalation. But for those others, there's no certainty as to whether or not those are products that could be inhaled.

DR. LIEBLER: It sounds to me like what you just told me is for none of the products do we have any certainty that they were actually sprays.

MR. JOHNSON: That's true.

DR. LIEBLER: This gets back to the issue of Carol having said it's not used in sprays, and then we're saying, but we've been told it was in sprays. But actually, we weren't really told it was in sprays, it was essentially listed here as a possible inference.

MR. JOHNSON: But now also, we had received data, previously, indicating use in sprays, but then subsequently learned that wasn't true. So, we did have data, but no longer used --

DR. LIEBLER: I just want to make sure that we're not doing something that simply looks like a convenient way to get rid of the spray issue, by saying, oh, it was a bit of confusion, it's not used in sprays. We need to be able to verify whether it's used in sprays or not used in sprays. The question I have for Carol is, is there

additional information that we have now that clarifies the ambiguity that's represented in Table 3?

DR. EISENMANN: There will always be ambiguity in the use table because the information comes from FDA and they don't collect what type of product form.

DR. BELSITO: That's always there, Dan.

DR. LIEBLER: Right. Okay. But you're not bringing us any new, good stuff here?

DR. EISENMANN: No. I haven't done an updated concentration of use.

DR. LIEBLER: So, we're where we were?

DR. EISENMANN: I haven't done another survey. But the survey was completed just before the EU opinion -- I don't know if it's become a regulation yet, but -- came into effect. So, people heard that, and I think they're starting to -- if they had it in spray products, they've been dropping spray products.

DR. LIEBLER: Okay, but we can't go on that.

DR. EISENMANN: Right. I know. I know. So, in other words, we probably will do another concentration of use survey just before this report goes final -- I mean, once the HRIPT is completed.

DR. BELSITO: Yeah. And you can't assume just because it's been banned in EU that it's not going to occur here; because I can tell you methylisothiazolinone is still being use in products in the United States that are not sold in EU.

DR. EISENMANN: Correct. But this also has the supplier not supporting inhalation use too.

DR. BELSITO: Supplier doesn't support it doesn't mean that companies can't use it.

DR. EISENMANN: I know that. I know that. Which is why I'm saying, well, we'll do another use survey once we get the HRIPT; and be more specific about -- even the concentration of use survey has certain categories that CIR may say could be a spray. So, I will be even more specific about those product categories to see if I can really confirm whether or not they're spray products.

DR. LIEBLER: Okay. But at this point we have no choice but to consider spray usages and to continue with our evaluation and request the data. What we want to do is sharpen up our margin of safety calculation, I think, based on consumer use data, relative to the scenario in the rat inhalation study, which was nose only for -- what -- six hours a day, for five days a week? That's not how people use these things.

Our need, as indicated in the insufficient announcement, is still there. We still need to consider inhalation.

DR. KLAASSEN: Carol, is it possible to get the information why the Europeans say that it should not be -- you know, was that based on science or imagined science?

DR. EISENMANN: I'd have to look back at the opinion, but it was probably based on the same issues that you've been reviewing though.

DR. KLAASSEN: It'd be nice to know.

DR. BELSITO: The SCCS is usually very thorough and I'm sure they probably have a calculated margin of exposure. I don't know where they got their data from, but if you look at their reports, they are very, very well-written, scientific documents. So, it should be there.

DR. SADRIEH: I just wanted to highlight, you know, you mentioned VCRP; VCRP doesn't have many, many, many of the products on the market. Depending on what data you get from VCRP, is really not kind of like a justification for saying that it is or it isn't in a certain type of cosmetic product.

DR. BELSITO: Okay. So, respiratory is not going to go away regardless. Curt, table, move ahead?

DR. KLAASSEN: Yes.

DR. BELSITO: Yes?

DR. KLAASSEN: I'll move ahead.

DR. BELSITO: Okay. So, our team is going insufficient for the previously requested data for repeat insult patch testing and inhalation.

DR. HELDRETH: The question is that -- maybe Wilbur is going to ask the same one -- is the inhalation insufficiency now different? Is it that we need to do a different calculation, or do we still need that consumer use data that we put in our insufficiency?

DR. BELSITO: I think Curt has outlined the type of data we need to be able to calculate an adequate margin of safety. Dan, you want to comment on that too?

DR. LIEBLER: I think our discussion frames the uncertainty. Our existing discussion, which is on PDF 106, right? Is that right? No, sorry. Just to refresh our memories, it's on PDF 111, I'm sorry. Okay.

In the middle of the paragraph -- I'm just going to read this to refresh our memories here. "Given the potential for inhalation exposure, CIR performed a risk assessment using the ConsExpo Web Spray Model. . . . The maximum concentrations of use. . . . included in this risk assessment to estimate the inhalation exposure. . . .

during the use of cosmetic spray products were based on results from a previous Council survey that submitted to CIR.

The ConsExpo Web Spray Model and a no observed adverse effect concentration (NOAEC) from a 28-day inhalation study in rats were exposed, nose only, six hours a day, five days a week were used in the margin of safety calculations for inhalation exposure. MOS value for pump and propellant hairsprays were calculated, exposure concentration.

Okay. So, the next paragraph then says, after reviewing this, the panel noted that the exposure scenario in the 28-day inhalation study is not representative of consumer pump and propellant hairspray product use; and determined that data more relevant to consumer use are needed. So, we still need that. Correct?

DR. BELSITO: Yes.

DR. LIEBLER: So, in other words, our --

DR. BELSITO: So, we need the data for consumer use and then recalculate the margins of safety.

DR. LIEBLER: Exactly. Our needs are clearly spelled out in the document and they haven't changed.

MR. JOHNSON: One question. Does the discussion need to be changed in any way? Or is it okay --

DR. BELSITO: There's no new data. The discussion is fine as far as I'm concerned. Dan? Paul? Curt? Discussion is fine, yeah. So, it just goes out as it is, insufficient, and these are our names.

DR. SNYDER: Does this report have our boilerplate for inhalation in it?

DR. BELSITO: I would be just a little concerned about putting that boilerplate in, because it would say that respiratory issues are not an issue. And yet we had these deaths in Korea from humidifiers.

I think that it's critical that we get the information from industry about consumer use and pump spray size. Particularly, in light of the fact that we got criticized by Women's Voices for the Earth for overstating the size of pump sprays.

DR. SNYDER: Yeah, I was just looking for it to refresh my memory. I have some pause because it's been a while since I really thoroughly read that. But I'm bothered by the significance difference between aerosolized spray, a propellant spray and a pump spray. Because there's a dramatic difference here that this shows us. And I want to see what our boilerplate says, in regard to those three sprays because they can be vastly different.

DR. BELSITO: I think that that can be brought back into the document once we have all the data. But again, I think that what I'm hearing from Carol is that PCPC has engaged, at least in studies, to reassess the diameter of pump sprays. Is that correct?

DR. EISENMANN: No. It's only going to be aerosols.

DR. BELSITO: Aerosols, okay. And was that the major issue that we were criticized for? I thought it was pump.

DR. SNYDER: Pump sprays.

DR. EISENMANN: We understand the pump spray products are much larger and they don't routinely measure. They routinely measure aerosolized products. They don't routinely measure pump spray.

DR. BELSITO: Okay. So, pump spray particles are irritant, dynamically larger than propellant sprays.

DR. EISENMANN: Right.

DR. BELSITO: Okay, so that's good. So, we're looking at worse-case scenario in terms of --

DR. EISENMANN: Right.

DR. SNYDER: And that was sort of the language I was concerned with, in our boilerplate for aerosolized.

DR. KLAASSEN: I'm willing to look at the data comparing humans and mice with the amount that's even exposed at the nose. I think this is where we're making the big mistake; is we're comparing a mouse, that's been exposed for 5000 hours, or something like that, compared to a human that's exposed for 14 seconds. And that's why you have to compare doses -- I mean, you have to really compare exposure, okay. That is concentration times time is what's important.

That's the first thing that's of importance. After you get that figured out, you can play around with the particle size if you want. But first of all, you've got to figure out that concentration times the time. It's a world of difference between 5000 hours and 14 seconds.

And that's why I think it's probably not a problem with inhalation here. And many of the other compounds that we put all of our weight on the particle size, that's a kind of secondary, minor importance, in relation to the amount that even gets to the nose.

DR. BELSITO: Hopefully, we'll get that kind of data back when we get a response back to our insufficient data announcement. But right now, I mean, you've heard what we need. You've heard an assessment of exposure of humans versus the animal models, nose only, for six hours a day. But right now, our data needs still haven't changed. I think, let's end this because it's going insufficient. We have no new data. We have a lot of other --

MR. JOHNSON: One question. So, Table 12 definitely needs to be revised before the –

DR. BELSITO: Table 12 will probably need to be revised based upon the data that you get from PCPC. Right now, the major criticism of Table 12, is it wasn't clear that that second line was a recalculation of what you would need to get margin of safety greater than 100 for a pump spray. Right now, it's not an issue, but yes it will clearly need to be revised when we see this document back.

Day 1 of the June 4-5, 2018 CIR Expert Panel Meeting – Dr. Marks' Team

DR. MARKS: Polyaminopropyl biguanide. Am I saying that correct, biguanide?

DR. HILL: Yes. Yes.

DR. MARKS: Okay. In December of last year, we tabled it because we wanted to have industry complete 100-person HRIPT. And then we also wanted consumer data information. We just got a memo, dated June 4TH, that a lab has been selected to do this study. The taskforce expects the study to begin in September.

And the request is to -- the taskforce would request to be tabled again. I don't have a problem with tabling it again. If there was not some movement, I would say yes, we need to move on as an insufficient data conclusion. But Tom, Ron, Ron?

DR. SLAGA: I don't have any problem with tabling it. I mean, it sounds like we're going to get the data.

DR. MARKS: Yeah, exactly. If we had no response from industry, then I would be saying okay we need to do the final report. I don't think there's an urgency, because this is not the same chemical that was in Korea and had deaths associated with it.

DR. HILL: I think industry has already responded in removing the ingredient, as far as I understand it, from certain more worrying aerosol sprays for example. I noted there were several large clinical studies, of fairly large populations, and it looks across those studies. The sensitization to this stuff is about .5 percent across the population. And that seems consistent one group, to one group, to one group. If you do the calculations, if you do the numbers, it's always about .3, .4, .5 percent.

The issue is, have a high enough concentration, repeatedly, to get the fibrosis. There is a mechanism that we know that looks -- I mean, I think that study is done pretty well in the Korean group. So, if you don't present exposures where you have this problem, the only clinical study that caught my attention was the one from page 93 with the 77-year-old female who had the anaphylactic response where they did repeated wound washings, with a lot of this stuff over and over.

And chlorhexidine use has gone up quite a bit. I don't know what that number is because it's a drug; so, we don't have that number. But the person who did my implant for my tooth, they were pushing that wash. Swab your mouth with that. Swab it multiple times a day. But chlorhexidine, I don't know if it's more -- we're not for sure. But anyway, the point is I think it's fine.

There were some points in the draft discussion, we just table it and wait until we get to the end of all this and come back and revisit.

DR. MARKS: Wilbur here?

DR. SLAGA: No.

DR. SHANK: It's tabled, so.

DR. MARKS: Yeah, table.

DR. ANSELL: That's our position; is that the panel requested a study, we've committed to do the study, and Linda's team is working with the lab. And we'll keep you informed as it develops. And then bring the results back and we can continue talking about it at that time.

DR. MARKS: And it refers to Bart, somewhere, in one of these memos or documents. Bart, I'll attribute you to the CIR procedure of good faith to test and can table again. And I feel there's good faith at this point.

Are we going to be able to address -- and we're going to table it, but the second need was consumer use data on pump and propellant hair sprays. Are we going to, in the end, say it's insufficient for that after waiting all these months for the HRIPT? And say, yup, we got the HRIPT, but what about now, the pump and propeller. And I don't want to come to the end of this and say, okay, the HRIPT is fine; but we don't have the pump and propellant.

DR. HELDRETH: Well, if you kept this insufficiency and we got the HRIPT study back, and you agreed that it filled the gap and you felt that there was no risk of sensitization, then you could have a split conclusion, where you say that it's safe as used, expect for the data are insufficient for use in sprays. And that's not altogether different from what the rest of the world is saying. Because other parts of the world are saying use in sprays is not recommended.

Now since this ingredient has reported uses, after you make a final report of that, a two-year clock would start for data to come in to fill that gap. And then the conclusion would change to use not supported in sprays.

DR. SHANK: The problem is, if we say it's insufficient for inhalable products, then we have to

say what data do we need. And I find it stressed asking for something specifically. I agree with we don't have enough information to say it's safe for products that are inhaled. But I think the way we can handle that is in a discussion.

In a cosmetic spray or aerosol, you have a very short exposure, short duration. And all of the other studies that show that there is an inhalation toxicity, are continuous exposure for hours at a time, repeatedly daily, which is quite different. Maybe that's not the answer, but that's what I consider. We can handle that.

DR. SLAGA: Yeah, I think we can handle it in the discussion.

DR. ANSELL: Yeah, I think we could. Although, I think industry would support a more pointed conclusion that we do not support its use in aerosol products.

DR. HILL: The most recent counsel survey --

DR. SHANK: That's my position, okay. I'm trying to be flexible.

DR. MARKS: Interesting. Because, I think, you know, if anything you're giving the rationale why we don't need the data on pump and propellant hair sprays.

DR. SHANK: Well, I don't know what data -- we asked for a margin of safety analysis. We got it. And for pump sprays, the margin of safety was very small. For aerosols it wasn't that big.

DR. ANSELL: It's a real conundrum isn't it? Because we can't say it's unsafe, because it would be hard to generate the data and spend time on material that's not being used in those applications anyway.

DR. SHANK: Yeah. You can't ask for a clinical trial in children.

DR. HILL: I'm sorry, no you can't.

DR. MARKS: I know this is going to come down, but I kind of like getting a sense now. It would be interesting if it came up tomorrow. I'm going to be seconding it. Do we want to have the discussion now anticipating?

We aren't going to get anything more; so, do we want to end up with a final conclusion which is a split -- is a safe and an insufficient? Or do we like the idea of safe and then handle the issue of the pump and --

DR. ANSELL: We've done that in the past, without explicating stating all the other conditions in which the safety was not substantiated. Hydroquinone and, you -- what was it, nail polish or something?

DR. HILL: The Mellitates?

MS. LORETZ: One use. Onetime use.

DR. SHANK: Have we ever said insufficient and not say why it's insufficient, what data do we need?

DR. ANSELL: We have drawn conclusions of safety which are very specifically tied to application and concentration, without iterating why other applications were not included in the safe conclusion.

DR. MARKS: Okay.

DR. HILL: Well though, what they're asking for and the insufficiency basically covers it, which is consumer use data on pump and propellant hair sprays. And even though the calculation suggests we do have margins of safety -- because the end point fatality -- the risk is a little too extreme. Even though science suggest it might be okay.

DR. MARKS: Well, is the risk fatality?

DR. HILL: Yeah. That's what happened with the vaporizer incident in Korea. It's a different chemical, but the mechanisms almost certainly the same.

DR. MARKS: That's the key.

DR. HILL: But the mechanism's almost certainly the same; because there was enough research done mechanistically on that Korean chemical. And based on that mechanism, there is a very, very, very high probability that this one has the exact same mechanism; and in the same circumstances would cause the exact same problem.

DR. MARKS: Okay. That's important.

DR. HILL: And until I had read the paper, that we didn't get two meeting ago, I asked Wilbur and he sent me the paper. We didn't actually have that paper that had the mechanism nailed down to that level. But I got it, and I read it, and that's the deal.

DR. MARKS: I know it's going to be tabled until tomorrow; but I think before we get to the end game on this ingredient, we ought to be -- I think we should be clear on both the needs that we had.

Ron Shank, I hear your discussant point; the short duration exposure should not be toxic. And therefore, don't need the pump and propellant hair spray.

DR. HILL: The industry has already voted, because they've taken it out of the aerosol and pump sprays. I mean, effectively, they've voted, they've taken it out.

DR. SHANK: If that's the case, it's no longer used in any available product.

DR. MARKS: Yes. And then you can say safe as used.

DR. SHANK: Then you can say safe as used. Because it isn't used in available --

DR. HILL: But there are a few potentially incidental inhalation, and you have to be sure you cover -- and I think we have more than adequately covered that. It was the pump sprays and the propellant sprays that are the insufficiency that he's asking about.

DR. MARKS: Well, we are. Because basically this is the panel's recommendations in terms of what we need to know to proceed with a safe. Ron and Tom, do you feel the same, that these two chemicals are similar enough that the toxicity would be overlapping in an inhalation?

DR. HILL: Let me send you the paper on the mechanism of the Korean issue. Because if you haven't read it, you have to, to understand why I'm saying that. Because my initial assertion was we have a biguanide versus a guanidinium moiety, there's no reason to assume that they're the same.

But then when you look at the mechanism of the fibrosis, which they've got nailed down about incontrovertibly as anything ever gets nailed down in science, there's a very, very high probability this would have the same exact affect. Their antimicrobial affects are actually by the same mechanism as much as anybody knows. And the fibrosis has actually a similar type of mechanism.

DR. MARKS: Is that paper referenced in this? If it isn't, it should be.

DR. HILL: It might be now. It wasn't originally.

DR. MARKS: Let's just make sure that gets in. So, tomorrow the action's going to be table. I don't think there will be much issue about that.

DR. SLAGA: If the other comes up, I do like what Ron was stating about adding that in the discussion. The fact that inhalation was brought up before; you know, to drop something without something in the document, I would like --

DR. SHANK: We have to handle it.

DR. MARKS: Oh, yeah.

DR. HILL: I think we do too.

DR. SLAGA: We have to handle it in the discussion in this report.

DR. MARKS: You had short duration exposure and -- that was the main issue. Solidifying --

DR. SLAGA: Yeah.

DR. SHANK: A few puffs is very different from the humidifier thing, which is a different chemical.

DR. MARKS: Right.

DR. SHANK: But we do have inhalation tox in animal studies. But these animals are exposed for six hours a day for five days a week. That's a very different exposure than the occasional puff, especially for fibrosis.

DR. HILL: And that mechanistic paper actually ties the significance of that accumulated exposure to the endpoint. It's very nice. I think it's very compellingly convincing; which I'm not an easy guy to convince.

DR. SLAGA: Did you say pump or puff?

DR. SHANK: I said puff.

DR. ANSELL: He's from California.

DR. SHANK: We're kind of strange.

DR. SLAGA: A couple puffs of a cigarette, actually -- if you believe in hormesis -- can actually help build detoxification. As long as you don't go over a few puffs a day, it may be beneficial, right? I would never say that --

DR. HILL: This particular one -- if you give me a few moments. We're going to break for lunch here in a moment and I can tell you.

DR. ANSELL: It might be a Korean office.

DR. HILL: It is. It is, but that group published like five or six papers. And actually, you might want them all, but there's a particular one that most --

DR. MARKS: Okay, I think that's really important. Obviously, extremely important. Bart, who's going to capture that for the next rendition of this draft? Because Wilbur was the author, right?

DR. HELDRETH: Yes.

DR. MARKS: And I'm coving it. And I think it'd be worthwhile to put it in now so that, you know, in another -- so the study's done in September. Are we going to see it next March? We're talking about year, nine months from now. I could just see us forgetting this discussion. I think capturing it is going to be really important.

Because I don't think we should end up with a -- assuming the HRIPT is negative, there's no sensitization, we're going to come with a safe conclusion. And I think we need to really address that inhalation; and to not wait until then and say, okay, we have to go another meeting to address that.

DR. HILL: But there were these large studies, not genetically controlled, that did show that there was sensitization at about .3.

DR. MARKS: Oh yeah, that's why we want the sensitization. We aren't giving that a ride. It's the second part I wanted to address, was the consumer use data. And there was what Ron said.

DR. HILL: On the inhalation.

DR. MARKS: Yeah. Okay.

DR. HELDRETH: Certainly, everything will be captured. You know, of course, we're going to have the transcripts. And we'll put that information into the next iteration of the document, as well as perform a literature search to make sure that we've captured everything that's potentially new.

DR. MARKS: Good. Okay. Sorry guys, I wanted to clarify that. I didn't want to wait until next year to say, okay, we got the HRIPT industry, now give us the pump data. We've been focusing on that.

Day 2 of the June 4-5, 2018 CIR Expert Panel Meeting – Full Panel

DR. BELSITO: At the September meeting, we issued a tentative conclusion stating that the available data were insufficient to make a determination about polyaminopropyl biguanide, which is actually polyhexamethylene biguanide hydrochloride, under the intended conditions of use. And we wanted a HRIPT involving a diverse population of 100 subjects, with a dose of 1,000 micrograms. We also recommended they may want to consider a slightly lower dose in case the 1,000 micrograms/cm2 was positive.

We wanted further data on consumer use data on pump and propellant hairsprays to determine extent of exposure from aerosolized use, given the reports of issues with a similar product in humidifiers in Korea. We received none of this, despite the fact that we were told that industry was going to be putting together a group to do the HRIPT. We got a memo, date June 4th, saying that the council had formed a taskforce with the objective of beginning this study in September, and perhaps we could table this.

After a rather lengthy discussion, our group decided not to table, but to go ahead with an insufficient conclusion, as previously stated. And that still gives industry two years to come up with what they promised six months ago, so that we can begin to move this ahead, particularly the respiratory issue.

DR. BERGFELD: Do you want to state your conclusion?

DR. BELSITO: It's the same conclusion we had before. It wasn't changed.

DR. BERGFELD: Okay. Well, just restate it.

DR. BELSITO: Okay. We're going ahead with an insufficient conclusion. We need to know a HRIPT, with a diverse population, so that you can read erythema of at least 100 subjects, with a dose of 1,000 micrograms/cm^2.

And we wanted to look at a margin of safety for consumer use data, on pump and propellant sprays, for use in determining the extent of exposer of polyaminopropyl biguanide during product use. And we thought that that could be determined, based upon the information in the current report, if we had current practices of use for pump and propellant hairsprays, which I'm told we do.

DR. BERGFELD: Is there a second or a comment, Dr. Marks' team? Dr. Marks?

DR. MARKS: We perhaps were a little bit more lenient. We felt we could table it since the HRIPT study has been scheduled to occur in September of this year, which means that we would probably see this ingredient back the beginning of next year. So, we didn't feel the same urgency concerning the HRIPT and coming to a final conclusion with that.

And then as far as the respiratory concerns, we did talk about that yesterday; and we thought that, in the discussion, it could be handled in cosmetics as short duration exposure, so it shouldn't be toxic. So, therefore, we weren't really needing further studies on the pump and propellant hairsprays. But the biggest issue is whether we go with issuing a final report with an insufficient data.

DR. BELSITO: We had quite a bit of discussion on the respiratory also, in terms of short versus long. And we're a bit divided about that. I'm not sure we know how long those children in Korea were exposed to the humidifier. And I don't know that we had that data that shows that short duration is any different from longer duration.

The reason for us deciding not to table, was not so much because of concerns about the HRIPT, but rather we want to start the two-year clock on the aerosol use; and we're told that if we come back and change the conclusion on skin, but not lung, that two-year clock will begin today, rather than beginning sometime in 2019 when we see these data again. And that was our reason for electing to go ahead and decide not to table the issue.

DR. BERGFELD: Comments from the Marks team? Ron Hill?

DR. HILL: Yeah, I just made note yesterday, and actually there's a series of papers; but one that we didn't get in either of the meetings and the dossier, but then I had requested from Wilbur and got in actually September, have very detailed and very compelling information about the mechanism. Grant you it's a different chemical because it's PHMG.

But the other part of that mechanistic information is there's a very high degree of certainty that pops out of all that research that suggest that PHMB, the chemical we're currently considering, would be mechanistically comparable in terms of the lung fibrosis. And part of that is that accumulated exposure; the lung can defend itself as long as the exposures aren't too long and too high.

So, I mean, we don't have exact in humans and that experiment would be unethical, but we also have information that industry has taken this ingredient out of aerosol sprays and pump sprays. They're no longer in use. So, the current practice of use is no pumps, no aerosol.

Then that takes us to what you just said; I'm not sure that information can even be available if in

current practice of use it's not. Then you're down to incidental inhalation and powders, which I think is a nonissue; but if anybody got concerns about that they can look at it more closely.

We got a lot of information in the most recent version of our inhalation. Resource document that talks about all of that, in terms of being able to come up with the margin of safety, if somebody wanted to do that I think you can get there.

But the point is, the mechanistic information, the Koreans clearly spent a lot of government funding so there's a series of, I think, eight or ten papers addressing this. But the 2016 paper, which is actually one of the ones mentioned in the Women Voices of Earth memo, we didn't have in our package. So, I had thought I read it and then after the meeting I looked and said I didn't read it because I didn't have it; and then I requested that day from Wilbur and he sent it that day.

I read that part on the way home and said, okay now I need to read some cross references, which aren't on my IPad, they're on my computer at my office at work. But the gist of it is, it's an accumulative effect, the lung can defend itself as long as it's not for an extended period of time, repeatedly, over and over, day after day, night after night, in the case of the vaporizer. There's very high probability this PHMB would cause the same effect at about the same concentration, based on that mechanism, because it's basically a membrane modification, based on the cationic nature of that.

And from chemical point of view the biguanide is not going to be significantly different from the guanidine in that mechanism. So that's the gist of everything I digested from all that study.

DR. BERGFELD: Any other comments? Dan?

DR. LIEBLER: No.

DR. BERGFELD: Paul? Curt?

DR. BELSITO: Ron, let me just get this clear. So, in your review of the literature, you found that brief intermittent exposures would have no effect, even if those exposures got to the alveolar area, because the lung would repair itself. It was only with continuous exposure, or relatively continuous exposures, that it became problematic?

DR. HILL: If it was going to stay in aerosol, and you have one of these obsessive individual who's spraying that aerosol around their head, multiple times a day, every single day, then the concern probably would exist. That's my take on it.

DR. BELSITO: Define multiple, and frequency.

DR. HILL: I can't fully define; but I would say three or four times a day, every single day, would probably put us in the range where we would begin to have concerns in. And again, I think industry, if what's in here is accurate, that they have taken it out of aerosols and pump sprays -- now that doesn't mean it's not still on the shelves out there somewhere. So, that would still be a concern, is what's still sitting on shelves in stores. But other than that, I think the problem will be solved from that point of view; then you're back to skin.

DR. BELSITO: My only concern is that industry, that has reported to Carol, has taken it out. We don't know what industry that has not reported to Carol, number one. Number two, you have to understand that although the EU has banned this, it does not affect companies who will sell products that are not in the EU. So as a good example, methylisothiazolinone has been banned from European Union, but still appears in products in the United State because we said it was safe if it passed the QRA.

So, you know, just because Europe has banned it, does not mean there will not be products in the U.S. that do contain it. And just because what Carol has said, that they're not reporting it, doesn't mean that it's not being used by some company that hasn't reported to CIR.

I think that because of this issue, we really need to make a statement about inhalation, whether or not we're told it's currently being used in the United States, in products.

DR. HILL: I think our conclusion should end up saying either unsafe or use not supported for pump sprays and aerosols. I'm not conflicted on that. I think ultimately, our conclusion has to say that.

You're now just saying, how fast do we need to get that out there? Do we go forward with the report so that that gets out there now and starts the clock, or can we afford to wait six months?

DR. KLAASSEN: I would like to see the margin of exposure calculated, and also if we can get information of why the European banned it. What was the evidence, or what was the scientific information? How did they come to that conclusion? Or was it just a kneejerk?

DR. BERGFELD: Ron Hill and then Ron Shank.

DR. HILL: I was just going to say some of the key -- that one paper that I was talking about was the 2016 publication; but there were several others in 2017 that came out and followed up. And so, actually the European decision, probably, couldn't take all that science yet into consideration, at that point, so that's just something to keep in mind.

DR. BERGFELD: Ron Shank, any comment?

DR. SHANK: Yes, the question about inhalation toxicity, in this case, depends very much, I think, on duration of exposure. The animal studies, which were on the ingredient, shows there is significant toxicity by the inhalation route. These are animal studies where the animals are exposed six hours a day, five days a week. That's very different from the cosmetic exposure, which is a matter of seconds.

The Korean study, which was a different chemical, showed inhalation toxicity, the mechanism may be similar. That was an additive to humidifier liquids, so the exposures were much longer than you would ever get with a cosmetic use.

I think we can take the concern out of the -- I don't think we have to delay the report, for more information, because I'm not too sure what information you're going to get. What are you going to ask for?

DR. BELSITO: Do we have a no-effect level for the respiratory endpoint? You're telling me that you see an effect at six hours, fine, that's excessive. You see an effect when someone aerosolizes a room, presumably overnight, and that has an effect. Can you tell me at what point there's no effect?

DR. SHANK: In the animal studies --

DR. BELSITO: In any study. I mean, do we have NOAEL?

DR. SHANK: I'd have to go back and read the details of the animal studies; but I would suspect there was a no-effect exposure. But that's not the point.

DR. BELSITO: I think the point always is to find a no-effect exposure.

DR. SHANK: Well, in the past, when the industry has said that they would provide the data that we're asking for, as long as the attempt is reasonable, we have honored that promise. I still think we're within the timeclock, industry apparently is moving ahead, according to yesterday's memo, I think we should give them the time to do the HRIPT study.

And we can handle the inhalation issue, if you accept -- and I do -- Dr. Hill's analysis. I agree with that. If you don't, then you can conclude, for inhalation use, this ingredient should not be used. I think we should honor industry's intention to do the sensitization study.

DR. SNYDER: The rats they did, did derive at .025 no-effect concentration level. And that was what was used to calculate the margins of safety.

So, we have a table that we have -- we're comfortable with margins of safety of 100 or more, but we have the pump, where we don't have a good -- we have a margin safety of 11. We need additional data on the pump, as related to consumer exposures, so that we can calculate a margin of safety. We don't have that.

And I don't think we should go out -- or we should ignore that, because we can't defend it. I don't think we should go out with the margin of safety of 11 and say that's acceptable. Because we do know this was used at .053, it's likely still being used, even though it's not reported; and so, I think we need to do our due diligence and know what margin of safety we are comfortable with.

DR. SHANK: Okay, that's fine. We can handle this in the discussion. We have the margin of safety calculations. But to say we're going to go insufficient because we need more data, while industry has promised to do the sensitization studies, I think is not fair to industry.

DR. SNYDER: The one issue that we discussed yesterday was we asked, in regard to -- when we table a document, there's no really mechanism for informing the stakeholders, the consumers, the manufacturers, the ingredient providers and things. And so, we were concerned, or at least we can factor that into our decision, to continue to move forward, because if we go out with the insufficient data announcement, then that's a formal document that goes out there.

If we table it, it just sits and there's no real information passed; and so now we've prolonged it, and -- as Donald alluded to yesterday -- we've had this happen before where HRIPT, yes, the protocol hasn't even been approved yet.

And so, they're trying to get it done in September. What if it gets delayed again until the beginning of 2019? And then now we're looking at 2020, and that report is just sitting there without relaying any information, that we felt was probably important for stakeholders to be aware of.

DR. BERGFELD: I got to call on Jay, who's been wanting to speak.

DR. ANSELL: We, of course, would defer to the Panel on the issues of inhalation, though we'd be extremely disappointed if this material were to -- if the report were not to be tabled. You had asked for additional data, we promised the data.

And to advance the report along, knowing that the data will be delivered, we think is an unnecessary burden on the staff and the Panel. We think it would be far more efficient of people's time to simply table it, wait for the report to come through, and then make a decision; rather than advancing it, pulling it back, and then re-advancing it.

DR. BERGFELD: Thank you. Ron Hill?

DR. HILL: I do have a question in regard to that particular issue. We've got some large studies that were, of course, not stratified by skin genotype, that suggest the overall sensitization rate to this stuff in the population is about .5 percent, somewhere consistently .3, .4, .5 percent. So, we already know that piece of information. Is that a low enough level to not worry about it, I guess, is what I'm asking from a dermatology point of view, or a dermal toxicology point of view.

DR. BERGFELD: Don?

DR. BELSITO: Well, the reason that I initially asked that this be moved up is because with your banning more and more and more preservatives, or limiting preservatives, there's a smaller and smaller pallet that's out there. And polyaminopropyl biguanide, up until now, has really been primarily two uses, very low concentration in contact lens solutions, and as an additive to pools, instead of chlorine, as an antiseptic in swimming pools. But what happens if industry starts using this at higher concentrations?

For example, chlorhexidine you almost never saw as a preservative in a cosmetic product. It's now appearing on the label of cosmetic products, not as an antiseptic, but because of limitations in the use of other preservatives. The whole marketplace is changing. The way this material has characteristically been used in times past could easily change.

DR. HILL: I'm pretty confident that chlorhexidine used in non-cosmetic application is also increasing. We'd have to get information from the FDA, but definitely dental swabs and -- that's one I'm directly familiar with, but there are other things. And there's at least a little whiff that there could be cross-reactivity here.

DR. BERGFELD: Tom, we haven't heard from you.

DR. SLAGA: Yeah, I agree with Ron Shank. I think we can deal with the respiratory in the discussion; and number two, I think this should be tabled since we do have a letter stating that this basically will be underway very shortly.

DR. BERGFELD: Curt, can I hear from you?

DR. KLAASSEN: Yeah, the two aspects, I think that we're talking about here -- and sometimes they get mixed up -- I'll just talk to the effect on the inhalation. I again, would ask that we do this exposure quite differently than the way it was done before. In the calculation, they only looked at concentration, they didn't take into effect time. And by my calculations, the margin of exposure it's probably closer to 70,000 rather than 10, because they were exposed for 70,000 or 7,000 times longer than the humans. And that's not been calculated in the margin of exposure.

Exposure is not the concentration, it's the concentration times time. And when one is exposed for 15 seconds, and the other a day, and the other for six hours a day, you've got to put that in there. That's 7,000 times different. I'm not sure there is an inhalation problem, other than a kneejerk.

DR. BELSITO: Curt, look at Table 12, it looks to me like they do have spray duration as part of their exposure; it's 14.4 seconds.

DR. HILL: Times how many times a day? Because that -- how many times a day, that's what matters.

DR. BELSITO: We don't know. I'm assuming they just did once a day. But do we know habits and practices for the times that a spray is used, a potential hairspray or a pump? And if we do, then that also needs to be factored in, rather than just the factor of one.

DR. KLAASSEN: I will agree. That's why I wanted -- as I said yesterday, both that paragraph, right at the end, right before the summary, talks about the so called risk assessment. And, in fact, it's even called, really a nice name if I could find it; I can't find it.

But the point is, is that we need to have a paragraph and a table so we really understand how this margin of exposure was calculated. I can't figure it out. I read it five times. And so, you know, let's do it right, and make it clear what was done. Maybe it was done right. I just can't figure it out.

DR. BERGFELD: Jay?

DR. ANSELL: And we agree that the 11-fold safety factor is concentration versus concentration, and it's not really a relevant assessment. In fact, we're in the midst of revising all of the inhalation boilerplate, to move away from a single criteria, for example, particle size alone, and recast it within the context of exposure and not any single parameter. We certainly agree with Curt's discussion that an 11-fold safety factor is a total misnomer, and should not be used for purposes of this assessment.

DR. BERGFELD: Jim, do you have a solution to this?

DR. MARKS: Yes.

DR. BERGFELD: Thank you.

DR. MARKS: I think we should table it for two reasons. One, is we promised the HRIPT and I

think we need to -- as Bart has said, if it's been purposed in good faith then we can table again.

And then the second is really our own issue, not from industry, is how do we interpret this inhalation. And it sounds like there're different opinions among the panel members and how to calculate that and come to a real margin of safety. And that's not something that I think we should move forward with a tentative conclusion. We can again table it to get the inhalation interpretation correct.

DR. BERGFELD: I think that Bart has to respond to what happens when an ingredient is tabled.

DR. HELDRETH: So, absolutely it's the Panel's purview to either table it or move the report forward. Certainly, if we do table it, the report essentially sits still, and changes like putting in a new calculation and thus forth, you know, don't move forward until the panel chooses to bring the report back online. So, those are just the options of how it works.

DR. MARKS: I would expect the next time we see the report -- and it's going to be the beginning of next year -- we'll have the HRIPT. And then there will be work done on calculating the inhalation margin of safety, taking into consideration what Curt said, what Ron Shank said and so on.

DR. BERGFELD: So, we have a motion without a second, and we have --

MR. GREMILLION: Can I --

DR. BERGFELD: Yes, Tom.

MR. GREMILLION: My understanding from yesterday's meeting was that industry is not even defending the use of this product in sprays and aerosol. So, we have a situation where there's been a promised study that's two year -- it's been six months -- it's two years to get this promised study on skin sensitization, and complete the report, and send the message, like Dr. Snyder pointed out, to manufacturers that this should not be in sprays and things that can be inhaled because these people died in Korea.

And I'm not really clear on they said that there are some thoughts that maybe the inhalation risk is being overblown, but I'm really surprised because the council doesn't seem to be advancing that notion that this isn't a problem and doesn't pose inhalation risks.

So, would just be really, strongly opposed to prolonging this more and not getting that message out, that this should not be in -- or, you know, there're products out there with a margin of safety that looks really suspect; and, you know, continuing to expose consumers to that.

DR. BERGFELD: So Tom, you're supporting an insufficient report.

MR. GREMILLION: Yes.

DR. LIEBLER: So, there are reported uses in sprays, which is why we're doing it. And what we still need is the use practices data for the uses in sprays, then we can do the margin of safety calculation properly. We were told that it will be forthcoming. Good.

We also need the HRIPT data. We are told that it'll be forthcoming, good. But we still need the data in both cases. So that's why I supported insufficient, because of our data needs. And I don't really see how the insufficient is more burdensome then tabling because our needs, our expectations are the same. We're going to get the same thing.

But I agree with Paul's point, about the insufficient report at least communicates to stakeholders what we are doing and why we are doing it; as opposed to just tabling it, where basically it looks like nothing is happening.

So, my view on this is our data needs are the same as currently articulated at the end of the discussion. Our current conclusion is currently articulated in this report before us. And until we have those pieces of information we can't do the proper calculation on inhalation, which I think will end up supporting the view that the inhalation exposure risk is not substantial. But if we can do a calculation, as opposed to play a hunch, we should do the calculation.

DR. BERGFELD: All right, any comments from the Marks team? We have a motion and we have not had a second.

DR. HILL: I just wonder what does the Consumer Commitment Code -- because once the 60-day comment period elapses on the final report, what does a Consumer Commitment Code impose for companies that are trying to honor that, with regard to an insufficient conclusion?

MS. KOWCZ: Again, we support the tabling because we have promise that we will do the data needs, we will deliver the data needs. We had a very lengthy discussion yesterday on the HRIPT. We cannot say any more -- I know Dr. Marks' team was not there.

But it's a standard protocol for HRIPT, diverse population as much as we can control that. It's done by an outside CRO, so it's not done internally, obviously, so they will determine the populations. So, you will have that data as soon as we get it.

We're not doing it in the summer, because it's a bad time. Every clinical research institute will

tell you, summertime is the worst time to do a study. Therefore, we had to get the funding. We had to get the approval from the member companies, that you will definitely have.

On the calculations, we can get that through a survey, correct Carol? Because we have a survey on hairspray usage.

DR. EISENMANN: That one's been done and published a long time ago.

MS. KOWCZ: Right.

DR. EISENMANN: And we've provided that to CIR.

MS. KOWCZ: Hasn't changed.

DR. EISENMANN: Hasn't changed. What I'm talking about is the amount -- they gave the product to consumer and they measured -- weighed the product before and after used so they could have daily amount of hairspray use.

DR. HILL: For pump sprays?

MS. KOWCZ: So those calculation can be viewed.

DR. EISENMANN: Pump and aerosol with daily grams per day. But that's not -- I mean, that's in a published paper.

DR. HILL: The reason I asked about the Consumer Commitment Code, which is the main thing, is because if we went out with the formal insufficient report, would that cause a company to pull the ingredient out to try to be honoring that code, and therefore lose a preservative that we know we might still need in everything but aerosol sprays?

MS. KOWCZ: Most of the companies do look at the insufficient data, and they will reformulate out; which to Dr. Belsito's point today, you're going with preservatives that are not even well known, not even well exercised, not having a lot of market exposure.

I think to table it is not an unreasonable request, knowing that we have habits and practices, we will have a HRIPT. I apologize that it's taken so long Dr. Belsito, but it does take a little bit of time to get all this together. So, we will have those three pieces of data probably by December; finally, by 2019 early.

DR. BERGFELD: Don, do you want to restate your motion? Do you want to go forward with your motion? You want to remove your motion?

DR. BELSITO: I mean, I'm hearing from Dan that we still feel that we should go ahead. I don't see how it changes anything, whether we table it or not; other than, if we table it nothing gets reported. It's simply close, and there's no report, other than in the minutes of this meeting, that there was any concern about aerosol use. And I think that what we're hearing from Dan, and from Paul, is that we like that concern to be brought out and made public.

DR. EISENMANN: There are also post meeting announcements that this would be recorded in. And I write CIR developments that we send out to -- we have a very large e-mail group that it gets sent out to anybody who wants it. So, it will be reported there.

DR. BERGFELD: What will be reported, the discussion or the main issues of the discussion?

DR. EISENMANN: The main issues of the discussion.

DR. BERGFELD: So, there will be some sub-activity.

DR. EISENMANN: Correct.

DR. BERGFELD: It will not be totally dead.

DR. LIEBLER: Even if it's tabled?

DR. BERGFELD: Even if it's tabled.

DR. LIEBLER: So, if it's tabled or insufficient, the process doesn't go any faster or slower.

DR. BERGFELD: Right.

DR. LIEBLER: Right?

DR. HELDRETH: The only thing that would change was Dr. Belsito's mentioning about how the clock would start, and the use not supported categorization of the spray uses would start. That's the only real difference.

DR. EISENMANN: And you'd have to issue a final report. So, you'd have to prepare the report --

DR. LIEBLER: That's right, that's what we're talking about.

DR. EISENMANN: -- and make some changes.

UNIDENTIFIED MALE: And you would have to petition to reopen.

DR. EISENMANN: And then we'd have to get it posted on the -- so, there're a number of things that would take staff time to do.

DR. BERGFELD: For the table, or for the insufficient?

DR. EISENMANN: To vote to make it a final report.

DR. BERGFELD: Okay.

DR. EISENMANN: And then, one example, the final report from the last meeting aren't up yet; so, you know, it does take them time to put the final reports out.

DR. HELDRETH: I don't think that should have anything to do with the panel's decision-making process. It's our job to put out reports. Your decision should be based on your opinions and the science, and how you think this should go forward. Whether or not the staff has to work on putting out final reports is irrelevant.

DR. HILL: I still think the potential risk to the public, of people starting to reformulate with something different versus let's give it time for the process to finish; get the calculations done, get the HRIPT, if possible, so that we know more about that; that tabling is better because of the potential for people beginning a reformulation process, which is not trivial to something that might be worst. That's how I was looking at this.

DR. BERGFELD: Any other comments from the Belsito team?

DR. LIEBLER: No. At this point, I really don't care. Table the damn thing or insufficient. We've beaten this to death, dug it up, kicked it around the cemetery, and then beaten it to death again and buried it. And now we're standing over the grave with shovels. This is enough.

DR. BERGFELD: All right, again. We have a motion and we have no second.

DR. BELSITO: I don't have to be the one that seconds it. Someone else can second it and we can vote on it.

DR. BERGFELD: All right. Anyone willing to --?

DR. HILL: The motion is still your motion to go forward?

DR. BELSITO: No, it's Jim's motion.

DR. HILL: Oh, okay. I'll second his motion.

DR. BERGFELD: It's Dr. Belsito's --

DR. HILL: It's not coming from your all's team, but --

DR. BERGFELD: It was your motion.

DR. BELSITO: It's my motion -- okay. Vote on my motion for -- okay. And he wanted to table it, right it's my motion. My motion, not to table.

DR. HILL: All right. So, then I withdraw my second.

DR. BERGFELD: Oh, withdraw your second. Okay. Any second on --

DR. MARKS: Now, hold it Don, it can't be a motion not to table. Your motion is to issue a tentative report with insufficient data.

DR. BELSITO: Yes. So that was my motion, it's up to someone to second; if no one seconds it, we move.

DR. BERGFELD: If no one seconds it, we stand for another motion.

DR. SNYDER: Dan seconded it.

DR. BERGFELD: You second it?

DR. SNYDER: No, Dan did.

DR. LIEBLER: Seconding without a microphone.

DR. BERGFELD: Okay. The motion has been seconded. We talked it, as you heard, up the kazoo. So, now call the question. All those in favor of the motion of insufficient, raise your hands.

So, the team from Belsito votes for it. And all those opposed? So, I am the one to make that decision. I'm opposed. I'm voting with the Marks team. So, at this time we'll entertain another motion.

DR. MARKS: Okay. I will move that we table this for both the HRIPT study, and also further clarification for the inhale toxicity of this ingredient.

DR. BERGFELD: Is there a second?

DR. HILL: Second.

DR. BERGFELD: Second. Discussion? None, hopefully. All those in favor of this motion to table? It is tabled. Opposed? Three opposing.

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DR. BELSITO: Okay. Polyaminopropyl biguanide. This is all my problem because I suggested it to be reviewed. At the December meeting, the draft final was tabled in response to a commitment for an HRIPT. November 2, we got a communication that it wouldn't be done -- it wasn't started until October 31 and wouldn't be finished until next week sometime.

Meanwhile, there was some information; exposure parameters with the inhalation risk that Dan had had questions about. We still don't have the HRIPT, but have your respiratory issues been answered, Dan?

DR. LIEBLER: I'm looking for it. I don't even remember that.

MR. JOHNSON: Wave 3.

DR. LIEBLER: Oh, Wave 3.

DR. BELSITO: You had queried, Wilber, and Dr. Zhu had responded.

DR. LIEBLER: Yes.

DR. BELSITO: So, you're comfortable with the inhalation safety, so we're just waiting for the HRIPT. So, I guess they're asking us to table it once again. Is that it?

DR. HILL: There's no need to do an action of tabling or not. It's still remained tabled. We wanted to bring -- there was two insufficiencies essentially: one for sensitization and one for this inhalation. So we thought, in the interim while we're waiting for the HRIPT to be completed and summarized, we would give you the opportunity to weigh in on where we stand for the inhalation insufficiency.

DR. BELSITO: So then what kind of discussion needs to go for the inhalation?

DR. SNYDER: Well, we had two of them, the margin of safety is less than a hundred: one was 63 and one was 11. For the pump spray. The margin of safety, they were received in Wave 3.

DR. BELSITO: Um hmm.

DR. SNYDER: So, was that okay? We wanted it to be above a hundred. We wanted to see it at a hundred, on insufficient data announcement.

DR. BELSITO: So, this is where the ConsExpo Web Model you're talking about?

DR. SNYDER: Wave 3, page 67.

DR. BELSITO: I just incorporated everything into -- I can go to Wave 3, page 67. Your page 66 is different from mine.

DR. SNYDER: I was on the wrong page. It's on Wave 3, I'm looking at the report.

DR. LIEBLER: Wave 3, page 68.

DR. SNYDER: Yeah.

DR. BELSITO: So, it was 200 for propellant hairspray, 11 for pump hairspray.

DR. SNYDER: And 100 --

DR. BELSITO: And 100 for a propellant deodorant spray. Which doesn't make sense because usually, I thought, a pump hairspray delivered a smaller --

DR. SNYDER: And it was 63 for pump spray using a larger droplet density -- larger droplet diameter.

DR. HELDRETH: Since we didn't have complete actual practices consumer data, for using these types of products, Jinqui used what may be overly conservative choices because it's all that we had. For example, constantly being exposed over a six-hour period, to the pump spray when we know that's not going to be how it's going to be used; but that was -- it was the information that we had available to calculate from.

DR. BELSITO: This comes from a Dutch -- he used a Dutch spray model, which some of it is in Dutch. The summary really is in English. It's a computer program to assess exposure of humans to a chemical substance in consumer products. It combines data on consumer products and mathematical exposure models. It was done in test chambers. But it is for consumer products, it's not for occupational. Just trying to see here where --

DR. HELDRETH: I'd also like to mention, that industry has commented to us, that they don't believe that this ingredient is used in spray products anymore. One potential option is to say that the data are insufficient for use in these types of products; and eventually, that will get transmuted into use not supported in spray products if you feel the data are still not useful there.

DR. BELSITO: These were ten-second sprayings, or squeezing, and they did full container versus an empty container.

DR. SNYDER: Where are you at? On what page?

DR. BELSITO: I'm actually looking -- it's not in Wave 3.

DR. SNYDER: Admin book?

DR. BELSITO: We, I think, got it in an email. It's the actual ConsExposure paper.
DR. SNYDER: Oh, okay.
DR. BELSITO: I downloaded it. I can send it to you if you want.
DR. SNYDER: I downloaded the email he sent us. Is that what it was in?
DR. BELSITO: Yeah. Do you see it?
DR. SNYDER: No. Oh, I have it.
DR. BELSITO: You got it?
DR. SNYDER: Somewhere. I got -- I just saw it.
DR. LIEBLER: Is this the email dated November 24?
DR. BELSITO: I don't know. I just copied it into the report from my tab. Give me your emails, I'll send it to you. Paul?
DR. SNYDER: klpath --
DR. BELSITO: Path -- oh, right. At Comcast. Dan?
DR. LIEBLER: Daniel.Liebler@vanderbilt.
DR. KLAASSEN: Klaassen.
DR. BELSITO: I thought you were corvette.
DR. KLAASSEN: Well, that's -- forget the Klaassen. Did you get it. So, two As, two Ss.
DR. BELSITO: Yeah. I may have you under Curt. I have you under CorvetteCurtisKlaassenPhD@gmail.
DR. KLAASSEN: Yeah, I got two of them. Either one.
DR. BELSITO: Try it a different way. I have to close down mine in order to do it. It's not letting me attach it for some reason. Dan, you're smarter than me. How do I do this? It's saying before that it was open. I just closed it all out. Attach file. There it is, okay. You should be getting it.
DR. KLAASSEN: There it is.
DR. BELSITO: Okay. Then this is the model that was used to calculate those margins of safety, correct?
DR. HELDRETH: Yes.
DR. BELSITO: But it still doesn't make sense to me why a pump had a lower margin of safety than a spray. I always thought it was just the other way around. And a DO. I thought DOs was supposed to be the supposed to be the worst.
DR. EISENMANN: Well, it looks to me like he used the same particle size for the aerosol as for the pump. So, the concentration in the pump must have been higher is all.
DR. BELSITO: So, there was a mistake in the calculation?
DR. EISENMANN: No, he just doesn't have data on pump particle size, so he just used aerosol particle size.
DR. LIEBLER: So, in Jinqui's calculation, yeah, he has airborne fraction for the propellant hairspray 0.2, for pump hairspray 0.02, and for propellant deodorant spray 0.9. Then he's got an asterisk on the pump value saying, "No default values are available, specifically for pump hairspray products. Spray parameter default values developed for pump toilet water sprays, assumed adequate for calculating conservative estimates of exposure for pump hairsprays."
And he also uses the median aerosol droplet diameter data, for propellant hairspray, for the pump hairspray. I thought the pump always has a larger particle diameter.
DR. HELDRETH: We just don't have the data.
DR. LIEBLER: That's one of the things that drives the favorable profile for pumps, and yet he used the propellant value in this calculation --
DR. HELDRETH: Because we didn't have any --
DR. LIEBLER: -- because you didn't have the pump value.
DR. HELDRETH: Right.
DR. LIEBLER: But we know, in general, pump values are bigger particle sizes. So, I'm not sure that's a valid -- it's certainly conservative. But I also think that, based on a lot of other things, we know it's not valid. That might be why the pump's coming out with a low margin of safety, Don.
DR. BELSITO: Right. I mean, that's what I'm saying, it makes no sense to me based upon what we've been told.
DR. LIEBLER: So, to come back to the issue that Bart raised a few minutes ago, if we don't have satisfactory data, to complete a calculation that we can justify, then we can still say we're in the situation of insufficient for sprays.

DR. BELSITO: Okay. We just heard that we're now being told it's not being used in sprays. In two years it goes to not used?

DR. HELDRETH: That's what we were told.

MR. JOHNSON: But it is used in the other fragrance preparation's product category based upon the FDA data. But we don't know whether or not that product is, in fact, a spray or not. We just know it's other fragrance preparation's category.

DR. BELSITO: If it's a spray, it would be insufficient.

DR. HELDRETH: That's right.

DR. LIEBLER: So, we've settled that.

DR. BELSITO: So, all of these calculations have not helped us with the respiratory issue.

DR. HELDRETH: That's right. And that's fine. We wanted to provide you with the best we could do, based on what we had and find out if that was enough. Or if we should continue the insufficiency, so that when we do finally get that HRIPT data, this will be an easy part of it.

DR. BELSITO: So, I mean, what we've said is continue the insufficiency, and if someone in industry wants to support an aerosolized use, they'll get us the data. Because right now, it clears propellants, it clears DOs, it just doesn't clear pumps.

DR. KLAASSEN: What was the number with the pumps that he came up with?

DR. LIEBLER: Eleven.

DR. BELSITO: Eleven.

DR. KLAASSEN: And we know that's wrong. We know it has to be greater than 100.

DR. LIEBLER: Right, but we just don't have a number, we can put in the calculation, that we can justify.

DR. KLAASSEN: Well, you take the aerosol number and you just tweak it.

DR. LIEBLER: Okay, just tweak it.

DR. EISENMANN: But the insufficient data is acceptable. I mean we tried to get them to help us do some calculations. They don't want to support inhalation use, so insufficient data is perfectly acceptable.

DR. BELSITO: So insufficient. Fine. So, we'll wait for the HRIPT, the inhalation will be insufficient.

DR. KLAASSEN: I guess I'd like to say that this so-called margin of safety of 100 is -- there's nothing magic about the number 100. Most over-the-counter drugs are three.

DR. BERGFELD: Number 3, not 300?

DR. KLAASSEN: No, three. Take triple the dose of acetaminophen, Tylenol for a week and see what happens. Take the highest dose of aspirin, that you're supposed to take, and triple it for a week and see how good you are. The number 100 is nothing magic, it's just a number. It's just super, super conservative.

DR. LIEBLER: And it's better than three.

DR. BELSITO: Okay. Any other comments?

DR. KLAASSEN: It's more conservative, I don't know if it's better.

DR. BELSITO: Okay. Fatty acids and fatty acid salts.

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DR. MARKS: The next ingredient I have is the Polyaminopropyl Biguanide.

DR. MARKS: And where is that?

DR. SHANK: Page 28, administration.

DR. MARKS: Well, thank you.

DR. SHANK: You're welcome.

DR. MARKS: In Wave 3 we have an inhalation risk memo, from Jinqiu, so we need to take that into consideration. Wilbur sent us a memo, dated November 9th, that we expect the final draft of this ingredient in April of next year. The HRIPT, we expect to be completed this month. And to me, the biggest questions -- I assume what we're going to do is table it until next year, in April.

And Rons and Tom, what about the inhalation safety, and particularly, the Wave 3 that Jinqiu sent out to us?

DR. SHANK: I think our panel should request consumer use data on pumps and propellant hairsprays, so we can actually get some quantitative data. Do you have that?

DR. ANSELL: No. We have an updated use, which shows that they're not used in either hairsprays or pumps. We had provided an updated use table, which were those uses.

DR. SHANK: Sorry, I missed that. Thank you.

MR. JOHNSON: But they are using a fragrance preparation, which could result in incidental inhalation exposure. So, that's why the data's still relevant, even though there are no uses in pump or propellant hairspray.

DR. SHANK: But it's fragrant is just an evaporation off the skin. It's not an aerosol in the spray.

MR. JOHNSON: Now that I don't know. This is based upon the FDA data, that's used in a fragrance preparation, so we don't know --

DR. HILL: Was the fragrance preparation the same as a perfume, or a cologne, or something like that? Is that a personal care product, is it a cosmetic ingredient, if it's a cologne?

MR. JOHNSON: It is.

DR. HILL: It is, all right. So, colognes do come in pump stray sometimes.

DR. MARKS: Any other comments, Ron, Ron, Tom? Ron Shank, you're okay, then, with that? And I think it's -- good, you're here Jinqiu. The Wave 3 is the memo from November 28. Correct?

DR. ZHU: Yeah.

DR. MARKS: Yeah. So, that has things like direction of spraying, et cetera. It's this memo here.

DR. ZHU: Yeah, we provided some additional summary of the relevant, you know, the default value we used in the model to calculate the inhalation exposure to Polyaminopropyl Biguanide. So, we built, based on this default, the parameters to calculate the exposure amount. But, you know, all these parameters are adjustable. It depends. So, like for pump hairspray, we do not have specific data on pump hairspray. So, we would use data from propellant hairspray, and pump toilet water spray, for pump hairspray.

One thing that you know, even we have the consumer use data available, and if the council provide such data, we still need to calculate the margin of safety, right? And based on the animal study as a point of departure. The current animal study we have is inhalation exposure data, you know, is -- the exposure scenario is 6 hours per day, 28 days, right? So, is that still okay? I mean, for -- even we have the consumer use data available, can we still -- based on the animal data to calculate the margin of safety, or any other alternative way when need to, you know, rely on to calculate the margin of safety? That's the thing.

DR. HILL: That related to a question I had, is that in your calculation you did not include a correction for exposure time, you kept it to the six hours per day.

DR. ZHU: That's correct because that's the only animal study we have for data.

DR. HILL: Well, right. But then you would say that the human exposure with the pump spray is maybe maximally 30 minutes a day. I mean, that would be ridiculous; in fact, 30 seconds times maybe 5, 6 times, if you obsessive, versus 6 hours a day. And because PHM -- because it's Polyaminopropyl Biguanide stuff, the toxicology that we're concerned about, mainly, is accumulative exposure in the lung, then exposure time matters greatly in this particular case. We would at least end up commenting that we know that humans aren't going to be exposed 6 hours a day, 28 days a month; that there's a lot bigger margin here.

DR. ZHU: Yeah. That's the thing, though, that we do not have other animal data available.

DR. HILL: The other thing that puzzled me, is there seems to be a big discrepancy about what we think we know about the particle size of the pump sprays.

Because my comment I had here is, why would the particles in a propellant spray be larger than a pump spray? That doesn't make any good sense. And then there's two different -- we've looked at two different -- because the council came back and said, well here's the actual particle size in pump sprays, but we were using a much smaller number that came from a European source, maybe? I forget where the other source was, but it's written in here somewhere. Anyway, I was puzzled.

Yeah, median aerosol, it's on Page 68 of the Wave 3. You had median aerosol droplet diameter for propellant was 46.5 micrometer, but pump was only 2.7, and propellant deodorant 8.3. So, I'm looking at why would propellant give 46.5, but pump give 2.7? That doesn't make any sense. And I realize those are not your numbers, they came from another source, and it's starred. Because that affects the mass generation rate.

DR. ZHU: That's the (inaudible) before (inaudible). We used that way in the model to calculate the initial --

DR. HILL: Right. So, that's what's in that internet that -- yeah. But it doesn't -- and then in other calculation, you did somewhere, the council came back and said, you really should have a droplet size of -- I forget what the number was, but it's significantly larger than that.

So, both exposure time and droplet size for pump spray if that comes in. And again, if it is in colognes, those do come in pump sprays.

DR. MARKS: Moving forward, how comfortable do you feel with the Wave 3? Because this, obviously, is going to end up in the document in terms of the safety. And then this also, I presume, is going to dovetail in with the aerosol and inhalation boilerplate we have, too. So, it all has to sort of merge and coincide. Ron?

DR. SHANK: We're still going to wait for the HRIPT at least?

DR. MARKS: Yes.

DR. HILL: Sure.

DR. MARKS: Oh, I know. I'm not thinking that we should have the inhalation toxicity totally finalized with this, but I'd hate in April for us to get the HRIPT, and then say, well, we need to go back and do more on the inhalation section of it. I'd kind of like to anticipate we're going to be comfortable with the inhalation section now, or what changes should Jinqiu give us to make us feel more comfortable with it?

And I heard you, Ron Hill, you didn't think the physicality of the particle size made sense between the two ways of aerosolizing.

DR. HILL: Well, one way of looking at it is, what he used to calculate gives a more conservative estimate, as well as ignoring the difference in exposure time, and it's still okay.

DR. MARKS: Okay.

DR. HILL: But I think we need to be very careful, mainly, because -- we don't -- no, it's not the same chemical, but the mechanism of toxicology is probably the same as the one that caused the deaths in the Korean situation. And so, that's where we need to be -- we clear this stuff, which I think it probably is safe, under pump spray uses and consumer uses in sprays in general, but if we come out and say so, we need to be sure that people can believe our margin calculations.

DR. ANSELL: Well, let me point out again that we do not support the use of this in a spray.

DR. HILL: Right.

DR. ANSELL: No one is using it as a spray. I'm not exactly sure why we continue to talk about the inhalation boilerplate for material which is not used in inhalation.

MR. JOHNSON: But the other fragrance preparation category FDA -- that product -- we don't know exactly what form that product is in, if it's an aerosolized product or not. Because we don't have that information from FDA.

DR. ANSELL: But the conclusion is predicated on the uses report; and we're not reporting any inhalation use. And to the extent that the conclusion points that out, we're fine with that.

DR. HILL: I would be comfortable that, too, but I remember -- it seems like, to me, the Women's Voices came and said, we don't care what you say, it is too being used in spray products.

DR. ANSELL: Yeah, but your conclusion --

DR. HILL: So, the conclusion would have to be written to capture that we think it's insufficient for use in sprays or the use is not -- how do you word that if we put that in a conclusion? But at a level, it's like the formaldehyde stuff that we worked on; if the science says it's safe, we should say it's -- you know, I don't know.

DR. MARKS: I get your point, Jay, is why we are going through all this margin of safety calculation and such if it's not being used in inhalation -- that there would be an inhalation exposure?

DR. ANSELL: And let me point out, it's not a margin of safety calculation, it's a margin of exposure -- a margin of concentration. As was pointed out, the fact that it's a calculation in terms of the

instantaneous concentrations does not count for actual exposure; because of respiration rate, duration, and the breathing zone, and so you come away with a much, much higher margin of safety.

But our position on this material is we do not support its use in spray products. And so, we would be happy with emphasizing that, particularly, since you're not going to get any more data about inhalation, because we do not support its use in inhalation.

DR. HILL: Well, and in fact, Lonza doesn't either, and they said so very clearly.

DR. MARKS: That would make it simpler.

DR. SHANK: Neat, clean.

DR. MARKS: Neat. Clean. So, Jinqiu, you won't have to do a lot of maneuvering and calculations. Again, in anticipation, would that be in the conclusion, or the conclusion is the present use and practices? And then it would be very clearly stated in the discussion, that it's not being used in spray products, and we expect there will be no inhalation exposures. I know we're kind of -- at this point --

DR. SHANK: I think the discussion is sufficient.

DR. MARKS: Yeah, okay.

DR. HELDRETH: Alternatively, you could have a conclusion that's based on safety, based on the HRIPT that we eventually get. And then also have the conclusion of use in spray products, or propellant sprays, that the data are insufficient. And so, ultimately, then, after a two-year clock, you would get a use not supported category. And that would seem to be in agreement with what everybody is saying, its use is not supported in sprays.

DR. ANSELL: Yeah, I think because of the history, that's a potential solution. But in none of these do we go through and say -- and we haven't reviewed all of the applications that it's not used in. So, you know, I think it would become a cumbersome conclusion to also cite all the products that it's not used in as well.

DR. HELDRETH: But, as Wilbur has pointed out, a few times, we have ECRP data suggesting that it's in some sort of fragrance product.

DR. HILL: Which we don't know if it's spray or not.

DR. ANSELL: And we don't do fragrances.

DR. HELDRETH: Right. But if it's not getting into the air and getting inhaled --

DR. HILL: If you just had a -- I know we haven't done this, specifically, before, but just in current practices of use, which does not include potentially inhaled products, or something along those lines. I mean, it would be different language than we've ever used in the conclusion, but fairly -- I mean, I'm just tossing that out there. So that you are specifically mentioning that we're not clearing this for potentially inhaled products, right, in the conclusions, in some manner, however, you want to cast it.

And again, this is not the same chemical as the one that caused the Korean meltdown. But all the evidence, and science now, suggests the mechanism would potentially be the same; but it's an accumulative exposure thing that we're nowhere near, so it probably in fact is perfectly fine to use in incidentally sprayed product. We just can't say so with a 1000 percent confidence.

DR. ANSELL: We would suggest that the discussion is the right place to amplify on all those elements.

DR. MARKS: And go in much more detail. I like the discussion.

DR. SHANK: For sure, in the discussion.

DR. HILL: I'm okay with it.

DR. MARKS: Yeah. Absolutely. The question is, do you also include it in the conclusion?

DR. SHANK: It had been used in aerosols and sprays in the past.

DR. MARKS: Right.

DR. SHANK: So, I think maybe putting that limitation in the conclusion, safe --

DR. MARKS: Insufficient for -- as Bart has suggested?

DR. SHANK: Or you can just say non-aerosolized. No, that's cumbersome. Insufficient for --

DR. HILL: Because a change in current reported practice doesn't necessarily affect what's still sitting out there on shelves in stores.

DR. SHANK: That's true.

DR. HILL: That's the other thing. Will, the consumers, be adequately alerted, if it's not in the conclusion? Given that it had been used, and that had been are art of use up until recently, and may still be, according to Women's Voices people, among others.

DR. MARKS: So, even though this isn't going to be the final run at this, I think at least give a heads up it's not being used in an inhalation exposure presently, not to be used in spray products. We'll discuss it in detail in the discussion. And in the conclusion we can have, insufficient for inhalation exposure as a conclusion. Then that way it alerts again. Does that sounds reasonable Ron, Ron, and Tom?

DR. SHANK: It is to me, yes.

DR. MARKS: As an anticipation; that obviously can change. Okay. Any other comments? Let's make the HRIPTs clean here, Wilbur.

MR. JOHNSON: Okay.

DR. MARKS: I don't want to have a long discussion on the sensitivity.

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DR. BERGFELD: Then we're moving onto Dr. Marks' discussion for the strategy for the Polyaminopropyl Biguanide.

DR. MARKS: Our team will move that this ingredient's report be tabled. We expect a final draft in April of next year. The HRIPT, that was requested, is proposed to be completed this month. Then we had, actually, a robust discussion about in Wave 3, Jinqiu's inhalation risk assessment/margin of exposure. In anticipation, our team thinks we're going to aim towards a conclusion that would not be used in inhalation exposure, not to be used in spray products, in the discussion and in the conclusion; thus, an insufficient for inhalation exposure. Just as a heads up, what we're thinking about. So, Don, your team knows, sort of, I see that as, actually, being the big issue, in April, is the inhalation.

DR. BERGFELD: So your motion is to table? Is there a second?

DR. MARKS: Yes.

DR. BELSITO: This was not really brought up as a material to vote on. My understanding was that it was brought up just to tell us where they were, and to get our feedback on the studies, that were presented, in terms of risk assessment for inhalation. And to give industry guidance as to where to go; so, it's already been tabled.

The HRIPT is not ready yet. Our team agreed with yours in terms of the respiration. One of the problems was we didn't have particle size for pump sprays, so the margin of safety came down to 11 for those, which seems surprising because particle size is said to be greater for pumps. We thought the respiratory data, at this point, was insufficient. And what we would need would be better data on pump size.

We were also told that industry is really not interested in using this in aerosolized products anyway. The bottom line is, right now it would be insufficient for products that could be inhaled, and we're awaiting the HRIPT. Industry is interested in using it in an aerosolized product, they need to provide us with more information on particle diameter size, so that the risk assessment can be reevaluated.

DR. HILL: We did talk about the idea that the estimate was really quite conservative, though, that he did, because it didn't take into account time of exposure among other factors.

DR. BERGFELD: Yeah.

DR. BELSITO: Well, it actually did, because the Dutch methodology actually looked at very limited times of exposures that mimic the actual use in sprays. So, it was very lifelike. It was Dutch -- Danish, okay.

DR. BERGFELD: I just checked with Bart. Excuse me. This particular item was brought up not only as an update, but an extension of the table. So, we could just agree to extend -- we don't have to exactly vote on it -- or we could vote. But if you nod your heads, we'll agree. And it looks like the inhalation continues to be a problem that we need to alert the industry about at this point in time. The hope is that it will be ready by April, but Bart says that may not be so?

DR. MARKS: I would suggest we vote. Because as I recall, there was a pretty robust discussion as to whether this should go as an insufficient tentative report, or be tabled, in one of our previous meetings. Is that correct?

DR. BERGFELD: We could do that as well.

DR. HELDRETH: Currently, the report stands as tabled. But there were two insufficiencies sitting for the panel to decide on. Industry has already committed to providing data to satiate the one insufficiency; but our intention was to bring this memo forward, so the panel, in the interim, waiting for that data, could decide on

whether or not this insufficiency could be squashed or needed to be upheld.

If you simply just want to show us that the consensus of the panel is that you feel that that would remain as sufficient, when we bring that report back, when the data comes in from industry for the sensitization, we'll include that as part of the conclusion.

DR. BERGFELD: I think that both team leaders have stated that's still an issue, the inhalation. I think that we can take that, and the fact that they are willing to table to wait for the patch testing. And we've had sort of a consensus agreement, with nod of head, that we can move on. I think that we will do that.

DR. GREMILLION: Sorry, what's the rationale for extending the table?

DR. BERGFELD: This is extending the table because of a request that they finish the testing. They're making analysis of the results, and they are due to report back to us in April. So, we're agreeing to extend the table.

DR. GREMILLION: So, what would happen if the table wasn't extended?

DR. BERGFELD: Well, we could go out as an insufficient at this point in time.

DR. GREMILLION: Right. I mean, we didn't need to bring the report here to make a decision on it at this point; we're just looking at the specific issue, of the report, while we're waiting for that data to come back. In very frank terms, we're not even really considering table, not table at this point. It is tabled. The panel agreed to table it, at the previous meeting, to wait for that data to come in.

DR. BERGFELD: Generally speaking, we put a time limit on a table, especially with our experience with promises. And so, this is an interim report and we're agreeing to extend, because there's been a statement saying that it's almost completed.

DR. GREMILLION: Yeah, I just wanted to clarify. I remember us talking about this before, and I guess -- and my concern is that it's an ingredient that was associated with a really terrible accident in Korea with a lot of people dying.

DR. BELSITO: It was not this material. It was a related material.

DR. GREMILLION: Yeah. I mean, that's also been a topic of a lot of discussion. I just want to call attention to this, and make sure that it's not being kind of kicking the can down the road; and definitely while maybe a potentially unsafe product is out there.

DR. HELDRETH: So, the concern about a safe product, I think, is mitigated by two facts: One, it doesn't appear that anybody's actually using this in an inhalable product in the US. That's what industry's telling us. Two, the panel just formed a consensus that the data are insufficient, to support its use, in those types of products. We don't think they're in use, and everybody here thinks there's not enough information to support their use in the future.

DR. GREMILLION: Well, I think that's great to go on and formalize that thinking.

DR. BELSITO: It will be in our minutes even though it's not a final conclusion, this report.

DR. BERGFELD: Yeah.

DR. HELDRETH: I'll put it in our post-meeting announcement as well.

DR. HILL: And clearly, watchdog groups are watching this evolve. And I will also say margin of safety estimates suggest that we probably do, even if they are still out there. It's not like there needs to be a recall; but that would be down to the FDA if that were the case.

DR. BERGFELD: Right.

DR. GREMILLION: I do think, though, that there's -- speaking of watchdog groups or whoever's using this information -- a decision that's in one of these documents that is triggering different interpretations than necessarily the minutes and what's said.

DR. HILL: I don't think that's the case. Also, the reason that there's been a delay on the study coming back from industry, is that the request was for a fairly complicated study in the sense of getting a distribution of skin types. And correct me if I'm wrong, but the ask was for actionable data, not a study that would result in ambiguity, when we got done, as much as science allows for that.

I understand your concern, but I was the one who raised the, yes, mechanistically, this compound might behave similarly to the one in South Korea. Honestly, our margin of safety estimates, using the time, are still pretty huge. And because this is a threshold effect, and what happened in Korea seems to be because substances being released in a vaporizer -- so, put into an aerosol form, and in an inhaled form, for essentially breathing in a room overnight -- was when the deaths occurred; night after night, probably, versus very brief exposures in a cologne or whatever these might still be out there on the shelves. But, again, FDA, that's their purview if they want to issue a recall. And consumer people can certainly exert their influence in that regard.

DR. BERGFELD: Thank you.

Safety Assessment of Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride) as Used in Cosmetics

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ABSTRACT: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride), which functions as a preservative in cosmetic products. The Panel reviewed relevant data relating to the safety of this ingredient and concluded that the available data are insufficient to make a determination that this ingredient is safe under the intended conditions of use in cosmetic formulations.

INTRODUCTION

The safety of the cosmetic ingredient identified by the International Nomenclature of Cosmetic Ingredients (INCI) name Polyaminopropyl Biguanide is reviewed in this assessment.[1] Polyaminopropyl Biguanide is reported to be used as a preservative in cosmetics, according to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI *Dicitionary*). The ***chemical name*** that corresponds to the cosmetic ingredient is polyhexamethylene biguanide hydrochloride (PHMB HCl), and it is the hydrochloride salt of an amino polymer comprising hexyl biguanide repeat units; it has a 6-carbon chain in each monomeric repeat unit, and is always supplied as the hydrochloride salt. INCI nomenclature often differs from standard chemical naming conventions; therefore, it should be noted that the substance identified by the ***chemical name*** polyaminopropyl biguanide is not a cosmetic ingredient.

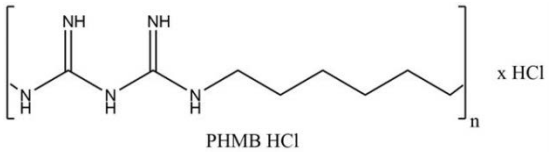
In CIR safety assessments, it is standard procedure to capitalize INCI names, but to use lower case for standard chemical names. Accordingly, throughout this report, when the INCI name Polyaminopropyl Biguanide is used (with appropriate capitalization), it is to be understood that it is referring to the chemical polyhexamethylene biguanide hydrochloride, and this is the ingredient with reported uses in cosmetics. Furthermore, most of the safety test data included in this report are on the chemical polyhexamethylene biguanide hydrochloride, as indicated by the use of the INCI name. The only exception to the exclusive use of the INCI name Polyaminopropyl Biguanide in this safety assessment relates to the summary of a cytotoxicity study, in which results for polyhexamethylene biguanide and polyaminopropyl biguanide are compared.

This safety assessment includes relevant published and unpublished data for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A list of the typical search engines and websites used, sources explored, and endpoints that CIR evaluates, is available 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.

CHEMISTRY

Definition and General Characterization

Polyaminopropyl Biguanide (CAS Numbers: 32289-58-0 [PHMB HCl]; [27083-27-8 (PHMB HCl)]; [28757-47-3 (PHMB)]) is the hydrochloride salt of an amino polymer comprising hexyl biguanide repeat units (PHMB HCl). According to the wINCI *Dictionary*, it is the organic compound that conforms to the formula depicted in Figure 1.[1]



PHMB HCl

Figure 1. Polyaminopropyl Biguanide (PHMB HCl)

Comments on the identity of Polyaminopropyl Biguanide were received from a chemical supplier, which stated that, effectively, all Polyaminopropyl Biguanide is polyhexamethylene biguanide HCl (i.e., C6 alkyl chains linked together by biguanide groups), and no propyl biguanide groups are present.[2] The INCI name is an artifact of arbitrarily choosing the middle of the C6 alkyl chains to identify the polymer repeating units of the ingredient.

Chemical and Physical Properties

Polyaminopropyl Biguanide is a polymer that, in its neat form, is a solid/powder with purity > 94.2%.[3] It is often marketed as an approximately 20% aqueous, pre-formulation solution. Chemical and physical properties are summarized in Table 1.

Method of Manufacture

One of the current methods for manufacturing Polyaminopropyl Biguanide is through the polycondensation of sodium dicyanamide and hexamethylenediamine.[4]

Scheme 1. Synthesis of Polyaminopropyl Biguanide via the polycondensation of hexamethylenediamine and dicyanamide.

Impurities

The following chemicals have been reported as possible impurities of Polyaminopropyl Biguanide: *N*-(6-aminohexyl)-*N*'-(6-(6-guanidinohexyl)guanidine, *N*-cyano-*N*'-(6-*N*-cyanoaminohexyl)guanidine, *N*-cyano-*N*'-(6-amnohexyl)guanidine), *N*-cyano-*N*'-6-(6-guanidinohexyl)guanidine hydrochloride, and 1,6-diguanidinohexane dihydrochloride.[3]

The trace metals content (in ppm, w/w) of 5 different batches of technical grade Polyaminopropyl Biguanide (solid) has been reported as follows: cadmium (< 0.25), chromium (< 0.25 - 0.7), cobalt (< 0.25), iron (14 - 40), lead (< 2), zinc (370 - 540), arsenic (< 2), and mercury (< 0.2).[3]

USE

Cosmetic

The safety of Polyaminopropyl Biguanide is evaluated based on data received from the U.S. Food and Drug Administration (FDA) and the cosmetics industry on the expected use of this ingredient in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database.[5] Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Council, of maximum reported use concentrations by product category.[6]

According to 2019 VCRP data, Polyaminopropyl Biguanide is being used in 147 cosmetic products, mostly leave-on products (Table 2).[5] The results of a concentration of use survey provided in 2017 indicate that Polyaminopropyl Biguanide is being used at concentrations up to 0.2% in leave-on products (eye lotions), and use in baby lotions, oils, and creams (leave-on products) at concentrations up to 0.1% is also being reported.[6] Polyaminopropyl Biguanide is also being used at concentrations up to 0.1% in rinse-off products, (i.e., hair dyes and colors and in skin cleansing products).

Cosmetic products containing Polyaminopropyl Biguanide may be applied to the skin and hair or may come in contact with the eyes (at maximum use concentrations up to 0.2 % in eye lotions) and mucous membranes (0.006% in other personal cleanliness products). Polyaminopropyl Biguanide is being used in a lipstick product, the application of which may result in incidental ingestion; no concentration data were reported for this use. It is also being used in baby lotions, oils, or creams at maximum use concentrations up to 0.1%. Products containing Polyaminopropyl Biguanide may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

According to FDA VCRP data, Polyaminopropyl Biguanide is used in a fragrance preparation, which may result in incidental inhalation exposure; concentration data were not reported for this use. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 µm, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm, compared with pump sprays.[7,8,9,10] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[7,8]

Polyaminopropyl Biguanide is currently listed in Annex V (entry 28) of the European Commission (EC) Regulation No. 1223/2009 (Cosmetic Regulation) as a preservative to be used in all cosmetic products at up to a maximum concentration of 0.3%.[11] Additionally, Polyaminopropyl Biguanide is classified as CMR 2 (Carc. 2) according to the Commission Regulation (EU) No. 944/2013. CMR substances are classified as carcinogenic, mutagenic, or toxic for reproduction. A substance is placed in carcinogen Category 2 (Carc. 2, suspected human carcinogens) when the evidence obtained from human and/or animal studies is not sufficiently convincing to place the substance in Category 1A (substances known to have carcinogenic potential for humans) or Category 1B (substances presumed to have carcinogenic potential for humans). The Carc. 2 classification was effective as of January 1, 2015 and, according to Article 15 (1) of the Cosmetics Regulation, the use of Polyaminopropyl Biguanide as a cosmetic ingredient is considered to be prohibited as of this date.[3] However, Article

15 (1) of the Cosmetics Regulation also states that a substance classified in Category 2 may be used in cosmetic products if the substance has been evaluated by the SCCS and found safe for use in cosmetic products. Conclusions on the safety of Polyaminopropyl Biguanide in cosmetics that have been issued by the SCCS are stated below.

The SCCS originally concluded that Polyaminopropyl Biguanide is not safe for consumers in all cosmetic products when used as a preservative up to the maximum concentration of 0.3%.[12] In 2017, the SCCS issued a final opinion stating that "the use of Polyaminopropyl Biguanide as a preservative in all cosmetic products at concentrations up to 0.1% is safe and that its use in sprayable formulations is not advised."[3]

Non-Cosmetic

Polyaminopropyl Biguanide is reported to be the most frequently used antiseptic in traumatic and orthopedic surgery.[13] According to another source, Polyaminopropyl Biguanide has the following uses: fungicide, algicide, sanitizer in swimming pools, preservative for cut flowers, materials preservative, bacteriostat in industrial processes, and water systems, and hard surface disinfectant (food and non-food contact surfaces).[14]

Polyaminopropyl Biguanide is a broad-spectrum antimicrobial agent used in a variety of products, including contact lens cleaning solutions, skin disinfectant solutions, and wound dressings.[15] Solid wound dressings are composed of various synthetic or naturally-derived materials, and typically contain added antimicrobials, such as silver, bismuth, chlorhexidine, bacitracin, or Polyaminopropyl Biguanide. Wound dressings are regulated by FDA as Class 1 medical devices (i.e., the device is exempt from premarket notification procedures). However, this classification does not apply to wound dressings that contain added drugs, such as antimicrobial agents.[16]

Additionally, Polyaminopropyl Biguanide has been reviewed by the United States Environmental Protection Agency (EPA). The EPA concluded that its use as a pesticide has very low aggregate risk of adverse health effects to the public or environment.[14]

In Australia, Polyaminopropyl Biguanide is listed in the Poisons Standard – the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) in Schedule 6.[17] Schedule 6 chemicals are described as "substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label." Schedule 6 chemicals are labeled "Poison." According to this standard, Polyaminopropyl Biguanide can be used in preparations containing concentrations of 5% or less and when packed and labeled for therapeutic use.

TOXICOKINETICS STUDIES

Dermal Penetration

The dermal penetration studies summarized below are presented in Table 3.

In Vitro

In one study, skin penetration experiments were performed using both rat (skin disks in solutions; 5-day equilibration phase) and human skin (receptor fluid in diffusion cell collected up to 15 days) in vitro.[12] At 0.4%, 1.4%, 5%, and 20% concentrations of Polyaminopropyl Biguanide, absorption rates through human epidermis were 8.13, 22.8, 350, and 1005 ng/cm^2/h, respectively. At 0.4%, 20% (early phase), and 20% (late phase) [^{14}C]-Polyaminopropyl Biguanide, absorption rates in rat whole skin were 131, 3695, and 11,940 ng/cm^2/h, respectively. Another study involved the application of Polyaminopropyl Biguanide (5% solution) to rat skin biopsies from newborn hairless rats and human epidermal skin in diffusion chambers. In rat skin, no absorption was detected up to day 5 of exposure. In human epidermal skin biopsies, a low rate of penetration (~ 0.09 %) was noted after 24 h. Polyaminopropyl Biguanide solutions (0.1% aqueous micellar solution, 0.1% oil-in-water emulsion, 0.3% aqueous micellar solution, and 0.3% oil-in-water emulsion) were applied to human split-thickness skin in a 2-part dermal penetration study.[3] In Part 1, penetration of the 0.1% aqueous micellar solution and 0.1% in oil-in-water emulsion was determined directly after the 24 h exposure period. In Part 2, 24 h exposure to the 0.3 % aqueous micellar solution and to 0.3% in an oil-in-water emulsion was followed by an additional 72 h period to determine whether the test compound that was absorbed into the skin during the previous 24 h period would move from the skin into the receptor fluid after the washout.

Absorption, Distribution, Metabolism, and Excretion (ADME)

The toxicokinetics studies (oral exposure) summarized below are presented in Table 4.

Animal

Oral

In rats, radiolabeled Polyaminopropyl Biguanide was excreted principally in the feces.[3] In one study, rats were dosed orally with 20 mg/kg/day for 10 days and elimination after dosing was described as follows: 5.6% ± 0.35% in urine, 93.1% ± 1.58% in feces and 0.2 % exhaled.[12,18] In another animal study (male Alderley Park rats) of the distribution of radioactivity after dosing, the greatest amounts of radioactivity were detected in adipose tissue, followed by the kidneys and liver. No radioactivity was detected in brain. Small amounts of Polyaminopropyl Biguanide oligomers with 2 cyano-guanidino-end groups were found in the urine, together with trace constituents, 3,3-dicyano-1,1-hexamethylenediguanidine and a compound considered to be 1-(6-aminohexyl)-3-cyanoguanidine. Absorption was not detected in a study in which mice received a single oral dose (2 ml) of [^{14}C]-Polyaminopropyl Biguanide.[12] The results from a study in which groups of Wistar Han rats received [^{14}C]-Polyaminopropyl Biguanide in drinking water or in the diet for 7 days, indicated that most was absorbed and that excretion was primarily via the urine.[19]

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Animal

The acute toxicity data summarized below are presented in Table 5 (dermal studies), Table 6 (oral studies), and Table 7 (inhalation studies).

Dermal

There was no mortality or other signs of systemic toxicity in rats that received a single dermal dosage of 5000 mg/kg aqueous Polyaminopropyl Biguanide, but hemorrhage of dermal capillaries at the application site was observed.[2,12] In an acute dermal toxicity study of 20% aqueous Polyaminopropyl Biguanide on rabbits, the LD_{50} was reported to be > 400 mg/kg.[12]

Oral

An LD_{50} of > 1000 mg/kg was reported for rats dosed orally with aqueous solutions of up to 25% Polyaminopropyl Biguanide.[20] A median lethal dosage of 25.6 mg/kg was reported for rats dosed orally with a 0.4% Polyaminopropyl Biguanide solution.[21]

Inhalation

LC_{50}s of > 0.36 mg/l and equal to 0.37 mg/l were reported in acute inhalation toxicity studies in which rats were exposed for 4 h to Polyaminopropyl Biguanide solutions at concentrations of 360 mg/m^3 in air and up to 300 mg/m^3 in air, respectively.[12] Dark/red lungs were observed at necropsy. A concentration-related depression of respiratory rate was reported in a study in which mice were exposed to Polyaminopropyl Biguanide at concentrations up to 208 mg/m^3.[12]

Human

Risk Assessment

The EPA conducted a screening-level acute dietary human health risk assessment for Polyaminopropyl Biguanide in food.[14] Risk estimates were calculated for females 13 to 50 years old, the only population subgroup with an acute toxicity endpoint (not stated) that was of concern. "Risk estimates for the use with the highest exposures were 9% of the acute Population Adjusted Dose (aPAD = 0.2 mg/kg/day) and, therefore, were not of concern." The EPA defines an aPAD as a dose at which an individual could be exposed on any given day and no adverse health effects would be expected.

Short-Term Toxicity Studies

The short-term dermal, oral, and inhalation toxicity studies summarized below are presented in Table 8.

Dermal

There were no mortalities or signs of systemic toxicity in rats that received dermal applications of Polyaminopropyl Biguanide at dosages up to 200 mg/kg daily over a 30-day period (21 applications total; no-observed adverse effect level (NOAEL) = 200 mg/kg/day).[12] In a 21-day dermal toxicity study involving rabbits, there was no evidence of toxic effects on the skin after 20% aqueous Polyaminopropyl Biguanide (12,000 ppm solution (1 ml)) was applied daily.

Oral

A lowest-observed-adverse-effect-level (LOAEL) of 0.1 mg/ml for Polyaminopropyl Biguanide was reported in 28-day oral toxicity studies involving rats and mice.[12] Rats (groups of 10) that received Polyaminopropyl Biguanide (in drinking water, doses up to 150 mg/kg) for 4 weeks experienced dehydration, clinical signs of rough coat and hunched posture, and body weight loss (all classified as severe).[19] Across the 3 dose groups, 10 rats had to be terminated due to severe weight loss, whereas, the remaining rats eventually adapted and began to gain weight. Absolute liver weights in all dose groups were similar to the control group. Mild centrilobular hypertrophy in liver observed in some of the rats (all dose groups). In the same study, Polyaminopropyl Biguanide administered (in the diet, 4000 mg/kg) to rats for 4 weeks caused a statistically significant decrease in body weight and absolute liver weight. In this dietary group, there was no evidence of centrilobular hypertrophy in the liver. Also, there was no evidence of necrosis or inflammatory lesions in the liver when Polyaminopropyl Biguanide was administered in drinking water or in the diet. In a 60-day oral toxicity study on Polyaminopropyl Biguanide involving rats, mild toxicity in the liver or kidneys was observed (by microscopic examination) at 2 mg/kg/day (dose equivalent to 0.2 mg/l of 0.4% solution of test substance), 8 mg/kg/day (dose equivalent to 0.4 mg/l of 0.4% solution of test substance), and 32 mg/kg/day (highest dose, equivalent to 1.2 mg/l of 0.4% solution of test substance). None of the animals died.[21]

Inhalation

In 21-day and 28-day inhalation toxicity studies on Polyaminopropyl Biguanide involving rats, no-observed-adverse-effect-concentrations (NOAECs) of 0.025 mg/m^3 and 0.0239 mg/m^3 were reported, respectively. [12] The animals were exposed (nose-only, concentrations up to 26 mg/m^3) to the test substance 5 days per week, 6 h/day. In the 28-day study, squamous metaplasia was observed in the larynx of males and females exposed to 0.25 mg/m^3 and 2.5 mg/m^3, and tracheal inflammation was observed in males and females exposed to 2.5 mg/m^3. Pneumonitis and bronchitis were observed in the lungs of males and females exposed to 2.5 mg/m^3. In the 21-day study, slightly-to-moderately severe pneumonitis was observed, at histopathological examination, in rats exposed to 0.25 mg/m^3. Moderate to severe pneumonitis was observed in rats exposed to 2.75 mg/m^3, and severe nasal irritation and dyspnea were observed at a concentration of 12.5 mg/m^3.

Subchronic Toxicity Studies

The subchronic oral toxicity studies summarized below are presented in Table 9.

Oral

The following results were reported in 90-day oral toxicity studies on Polyaminopropyl Biguanide involving rats: no mortalities, but iron pigment/deposits observed in Kupffer cells (at 12,500 ppm and 5000 ppm in diet) and a NOAEL of 1000 ppm.[12,20] There were no treatment-related macroscopic post-mortem findings in mice in a 90-day drinking water study of 20% aqueous Polyaminopropyl Biguanide (concentrations up to 0.3 mg/ml in drinking water),[3] and a NOAEL of 1000 ppm was reported for this ingredient in a 90-day feeding study in which mice received concentrations up to 4000 ppm in the diet.[12] A NOAEC of 5500 ppm was reported for Beagle dogs fed Polyaminopropyl Biguanide at concentrations up to 11,000 ppm in the diet for 90 days.[12,20]

Chronic Toxicity Studies

Animal

The chronic dermal and oral toxicity studies summarized below are presented in Table 10.

Dermal

In an 80-week chronic toxicity study involving mice (dermal applications 5 days/week), a mortality rate of 75% was reported for the highest dose group (10% Polyaminopropyl Biguanide; 30 mg dose).[20] The exophthalmos observed throughout the study was more severe in this group, compared with the other groups, but the results of histological examination of the eyes and gross and microscopic examination of the thyroids were negative. A NOAEL of 0.6 mg/mouse/day was reported.

Oral

In a 104-week oral toxicity study involving rats, a NOAEL of 2000 ppm (highest concentration tested in diet) was reported for Polyaminopropyl Biguanide.[12] This concentration corresponded to 36 mg/kg/day in male rats. A no-observed-effect-level (NOEL) of 200 ppm for histopathologic changes was reported in a 122-week oral toxicity study involving rats fed Polyaminopropyl Biguanide at concentrations up to 2000 ppm in the diet.[20] Increased adrenal weight was reported for males and females at concentrations of 1000 ppm and 2000 ppm in the diet. In a study involving mice, Polyaminopropyl Biguanide (concentrations up to 1000 ppm) in diet for 97 weeks did not cause any macroscopic changes in the spleen or liver. [12] In this study, the parents were treated and then the offspring were treated for 97 weeks after they were selected for the study. A NOAEL of 1500 ppm for Polyaminopropyl Biguanide was reported in a 1-year feeding study involving dogs; treatment-related histopathological findings in the liver and kidneys were reported at dietary concentrations of 3000 ppm/4500 ppm. In this study, groups of animals were fed test-substance concentrations of 300 ppm, 1500 ppm, and 4500 ppm for up to weeks 11/12. The 4500 ppm concentration was reduced to 3000 ppm for the remainder of the study because high dose males exhibited unexpected signs of toxicity, including marked reddening/peeling of scrotal skin, loss of appetite, body weight loss, and/or indications of liver impairment in the form of elevated plasma alanine transaminase and/or aspartate transaminase activities. In a 26-week feeding study involving dogs, dietary concentrations of 1500 ppm and 4500 ppm Polyaminopropyl Biguanide produced concentration-related hepatotoxicity and nephrosis.[20]

Human

Risk Assessment - Dermal

In this risk assessment, an NOAEL of 2000 ppm, derived in a 104 wk dietary study of Polyaminopropyl Biguanide (20.2% aqueous) in rats[12] (summarized in Table 10) was used in a margin of safety (MOS) calculation performed by the SCCS.[3] The following assumptions were used to calculate a MOS: all cosmetics contain 0.3% Polyaminopropyl Biguanide; the NOAEL is 3.1 mg/kg/day (takes into consideration 8.5% oral absorption); and dermal penetration is 4.09%. Dermal penetration was determined using the results of a dermal penetration study summarized earlier in the report in which 1.56% of applied dose was found in the dermis and 0.03% of the absorbed dose was recovered in the receptor fluid.[3] Then, based on SCCS Notes of Guidance, one standard deviation (2.5%) was added to the absorbed amount, yielding a calculated dermal absorption value of 4.09% (1.56% + 0.03% + 2.5% = 4.09%).[3,12] The MOS values (assuming dermal absorption = 4.09%) are 258 (based on cosmetic exposure estimate) and 227 (based on cosmetic exposure estimate + non-cosmetic exposure estimate). Thus, the MOS is lower when additional exposure from non-cosmetic use is incorporated.

The EPA assessed the human health risks associated with residential-handler and post-application pesticide exposure scenarios (including pesticides containing Polyaminopropyl Biguanide) using surrogate exposure data, maximum application rates (specified on the product labels), and standard assumptions.[14] The agency determined that all margins of exposure (MOEs) from dermal and inhalation exposure for residential handlers are above the 100 target and, therefore, were not concerning. For post-application dermal and incidental ingestion (oral exposures) scenarios, MOEs calculated based on an oral NOAEL of 20 mg/kg/day were also above the EPA's level of concern. Residential handler exposures may occur when individuals mix, load, or apply a pesticide. Individuals could incur post-application exposure either as bystanders affected by exposures during the application of the pesticide or when they enter a treated site after the application.

Chronic dietary risk estimates were provided for the general US population and all population subgroups.[14] These estimates were below EPA's level of concern for the general US population (i.e., < 10% of the chronic Population Adjusted Dose [cPAD]) and all population subgroups (i.e., < 37% of the cPAD for children). The cPAD is the level of exposure (mg/kg/day) that the EPA determines should not be exceeded.[14] Therefore, the chronic dietary risk is not of concern.

The aggregate risk assessment integrates the assessments that were conducted for dietary and residential exposure. Aggregate calculations were performed for adults and children using the Aggregate Risk Index (ARI) method. ARIs were greater than 1.2 for children and greater than 5.4 for adults, and these risks were determined not to warrant the EPA's concern.[14] As a general rule, an ARI of ≥ 1 is of little concern, but an ARI of < 1 suggests a risk that is of concern. Here, the ARIs are > 1, but the risks are below the EPA's level of concern.[22]

Risk Assessment - Inhalation

The most recent Council survey of maximum reported use concentrations by product category (update provided to CIR on July 18, 2017) indicates that Polyaminopropyl Biguanide is not being used in pump or propellant hair sprays.[23] However, products categorized as Tonics, Dressings, and Other Hair Grooming Aids that contain Polyaminopropyl Biguanide at maximum use concentrations of up to 0.1% are reported in the survey, and it is possible that products included

in this category are sprays. Furthermore, 2019 FDA VCRP data indicate that Polyaminopropyl Biguanide is being used in the Other Fragrance Preparations product category (use concentration data were not provided by industry for this use). Given the potential for inhalation exposure, CIR performed a risk assessment using the ConsExpo Web Spray Model (Consumer Exposure Model, Web version 1.0.1).[24,25,26,27,28] The maximum concentrations of use (0.0004% in propellant hair sprays and 0.053% in pump hair sprays) included in this risk assessment to estimate the inhalation exposure concentrations of Polyaminopropyl Biguanide during the use of cosmetic spray products were based on the results from a previous Council survey that were submitted to the CIR on April 11, 2017.[6]

The parameters used in this risk assessment are presented in Table 11. Conservative default values published by Rijksinstituut voor Volksgezondheid en Milieu (RIVM – the Dutch National Institute for Health and Environment) were used in all of the calculations.[26] One exception is that the room ventilation rate was assumed to be 0.2 room-air exchanges per hour, which is the default value specified in REACH guidance, rather than 2 exchanges per hour indicated by RIVM guidance for bathrooms.[28] The more conservative value (0.2/h) appears to be more appropriate to represent low-end air-exchange rates in homes in the US, in which ventilation fans may not be used routinely. No default values were available specifically for pump hair spray products. Thus, the spray duration assumed for propellant hair sprays (14.4 sec) and default values for pump toilet-water sprays were used in the calculations for pump hair sprays.

The use of conservative default values for multiple exposure parameters ensures that high-end, "reasonable worst-case" exposures are calculated.[26,28] Generally, the exposure concentrations predicted by the ConsExpo Model increase with increasing spray durations and decrease with increasing exposure durations/event (i.e., the time over which the exposure concentrations are averaged after each spraying event).

The average Polyaminopropyl Biguanide inhalation exposure concentrations over the 5-min default exposure duration/event were 0.00012 mg/m^3 for propellant hair sprays and 0.0022 mg/m^3 for pump hair sprays.

The NOAEC was approximately 0.024 mg/m^3 in a 28-day inhalation study in which rats were exposed, nose only, to Polyaminopropyl Biguanide in an aerosolized water solution, 6 h/day, 5 days/week.[3] MOSs were calculated by dividing the NOAEC by the average inhalation exposure concentrations/event estimated using the ConsExpo model. The MOSs were 200 for propellant hair sprays and 11 for pump hair sprays.

An MOS of 100 may be considered to be adequate to allow for the uncertainties associated with using the NOAEC from a short-term rat study to evaluate potential chronic human exposures (i.e., 10 for short-term to long-term exposure extrapolation x 10 for inter-species extrapolation = 100). Accordingly, the ConsExpo Web model was used to calculate concentrations of use that would yield an MOS of 100 for Polyaminopropyl Biguanide in pump and propellant hair spray products and propellant deodorant products. The results indicate that use concentrations of 0.0058% in pump hair sprays, 0.00084% in propellant hair sprays, and 0.000055% in propellant deodorant sprays would each be associated with an MOS of 100.

The daily exposure duration in the rat study (6 h) from which the NOAEC was derived (i.e., 6 h/day or 360 min/day) is 72 times greater than the exposure duration of a person using a hair spray once a day (1 event/day x 5 min/event = 5 min/day), 5 days per week, and 24 times greater than the exposure duration of a person using a hair spray 3 times a day 5 days/week.

The daily exposure duration in the rat study is about 7 times greater than the exposure duration would be for a beautician applying hair spray to customers an average of 10 times a day, 5 days/week. The beautician's occupational exposure may be reduced by workplace ventilation systems and larger room volumes, as well as the direction of the spraying (i.e., away from the beautician).

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

The developmental and reproductive toxicity studies summarized below are presented in Table 12.

NOAECs of 1000 ppm (after feeding in diet on gestation days 1 through 20)[12] and 1300 ppm (after feeding in diet during a 9-day pre-mating period and until the 3rd generation)[12,29] have been reported in oral reproductive and developmental toxicity studies on Polyaminopropyl Biguanide (in the diet) involving rats. In an inhalation study, degeneration of seminiferous tubules in the testis of 1 male rat was observed after exposure to 0.25 mg/m^3 (6 h/day, 5 days/week for 3 weeks), but this was not observed in any other group, including the group exposed to the highest concentration (26 mg/m^3).[12] An NOAEL of 10 mg/kg/day for developmental toxicity was reported in an oral dosing (by gavage on gestation days 6 through 15) study involving mice.[12,29] An NOAEL of 40 mg/kg/day for developmental toxicity has also been reported in an oral dosing (by gavage on gestation days 8 through 20) study involving rabbits.[12] Polyaminopropyl Biguanide has been classified as embryotoxic at oral dosage rates of 32 mg/kg/day (animal strain and dosing protocol not stated) and 100 mg/kg/day (rats; protocol not stated), and as teratogenic in rats at an intraperitoneal dosage rate of 10 mg/kg/day (dosing protocol not stated).[30]

GENOTOXICITY STUDIES

The genotoxicity studies (in vitro and in vivo) summarized below are presented in Table 13.

In an Ames test, Polyaminopropyl Biguanide was non-genotoxic at doses up to 5000 µg/plate with and without metabolic activation. [12] At the highest dose evaluated (333,300 µg/plate) in the Ames test, Polyaminopropyl Biguanide was weakly genotoxic in *Salmonella typhimurium* strain TA 1538 without metabolic activation. Polyaminopropyl Biguanide was non-genotoxic in a mouse lymphoma assay at concentrations up to 2000 µg/ml with and without metabolic activation, or in an in vitro micronucleus test (cultured human peripheral blood lymphocytes) at concentrations up to 50 µg/ml (without metabolic activation) and up to 250 µg/ml (with metabolic activation). In an in vivo micronucleus test, Polyaminopropyl Biguanide was non-clastogenic in polychromatic erythrocytes from mice that received single oral dosages up to 400 mg/kg. In an in vivo unscheduled DNA synthesis assay, there was no induction of unscheduled DNA synthesis in hepatocytes from rats that received single oral doses up to 1500 mg/kg.

CARCINOGENICITY STUDIES

The carcinogenicity studies (in vitro, dermal, and oral) summarized below are presented in Table 14.

In Vitro

Polyaminopropyl Biguanide was evaluated at concentrations up to 3000 µg/ml in the cell transformation assay (using baby hamster kidney fibroblasts); there was no difference in the number of transformed cell colonies between test and negative control cultures.[12] In another assay, RAW 264.7 mouse macrophages (a macrophage-like, Abelson leukemia virus transformed cell line derived from BALB/c mice) were co-cultured with SVEC-10 mouse liver endothelial cells in various experimental conditions: pre-activation of macrophages with Polyaminopropyl Biguanide or lipopolysaccharide (LPS) and/or co-culture in presence of Polyaminopropyl Biguanide. Polyaminopropyl Biguanide, tested at concentrations up to 1 ppm, had no direct effect on liver cell proliferation and did not potentiate cell proliferation induced by activated macrophages.[3]

Animal

Dermal

Polyaminopropyl Biguanide was classified as a hepatocarcinogen in mice at the highest dose tested in a study in which Polyaminopropyl Biguanide in ethanol was applied to the skin daily at doses up to 750 mg/kg/day (5 days/week) for 80 weeks.[20] The NOAEL was 0.6 mg/mouse/day (15 mg/kg/day). A variety of inflammatory hepatic changes was observed in all groups, including the controls. However, at 30 mg/mouse/day, severe hepatitis was observed in some of the animals. These hepatic changes appeared to have been mainly responsible for causing increased numbers of deaths in the high dose group. Additional study results are included in the 80-week chronic dermal toxicity study that is summarized earlier in this safety assessment. A scientific advisory panel advising the SCCS indicated that the hepatitis observed in this study may be attributable to the *Helicobacter hepaticus* infections, which may also be responsible for the increased incidence of hepatocellular neoplasms in these animals.

Oral

A statistically significant increase in the incidence of hemangiosarcomas and hemangiomas was reported in male mice (C57B1/10J/CD-1 strain) that received Polyaminopropyl Biguanide at a dietary concentration of 4000 ppm daily for 2 years.[12] In a 97-week study in which mice were fed Polyaminopropyl Biguanide at dietary concentrations up to 1000 ppm prior to and during mating, and their offspring were fed the same concentrations, there were no treatment-related (non-neoplastic or neoplastic) increases in histopathologic findings.[12,20] Hemangiosarcomas or hemangiomas in the liver or other sites and a high mortality incidence (80%) were reported by week 97. In a 124-week oral feeding study in which rats were fed Polyaminopropyl Biguanide at concentrations up to 2000 ppm, 80% mortality was also reported.[12] A low incidence of hemangiomas or hemangiosarcomas (mostly in lymph nodes) was observed in the groups of remaining animals (7 groups, with 8 to 21 rats/group; 1 animal with a hemangioma or hemangiosarcoma per group). When mice were fed Polyaminopropyl Biguanide at dietary concentrations up to 4000 ppm for up to 28 days, increased cell proliferation in a concentration-related manner was noted at 1200 ppm and 4000 ppm. [3] Polyaminopropyl Biguanide was classified as non-carcinogenic in rats fed dietary concentrations up to 2000 ppm for 122 weeks.[20] At 124 weeks, 80% mortality was reported. A low incidence of hemangioma (2 of 64 males; 2 of 64 females) and hemangiosarcoma (1 of 64 females) was reported in a study in which rats were fed Polyaminopropyl Biguanide at a dietary concentration of 2000 ppm for 2 years.[31] In another 2-year study, Polyaminopropyl Biguanide was administered (in drinking water or in diet) to groups of rats. Hepatocellular tumors were induced at concentrations of 1000 mg/l and 1500 mg/l, but not at a concentration of 500 mg/l. The hypothesized

mode of action (MOA) for liver tumors induced by Polyaminopropyl Biguanide in drinking water involves increased hepatocyte proliferation and induction of hepatocellular foci and tumors.[19]

OTHER RELEVANT STUDIES

Effect on Lung Cells

A study was performed to characterize the inflammatory responses, including the mechanism of action, induced in lung cells exposed to Polyaminopropyl Biguanide.[32] A549 cells that were exposed to Polyaminopropyl Biguanide showed concentration-dependent (0 to 80 µg/mL) decreased viability, significant reactive oxygen species (ROS) generation (at 20 µg/mL), inflammatory cytokine secretion (statistically significant increase in tumor necrosis factor alpha (TNF-α) release (at 20 µg/mL), and nuclear factor kappa B (NF-κB) activation (expression of IκB-α protein significantly degraded at concentrations > 10 µg/mL). Statistically significant cytotoxicity to A549 cells was observed at concentrations > 10 µg/mL. Polyaminopropyl Biguanide triggered inflammatory cytokine secretion and NF-κB activation by modulating the degradation of IκB-α and through the accumulation of nuclear p65. It was noted that TNF-α plays important roles in interleukin-8 (IL-8) expression as well as in NF-κB activation. IL-8 production induced by Polyaminopropyl Biguanide was completely suppressed by an NF-κB inhibitor, but not by an ROS scavenger. The authors suggested that Polyaminopropyl Biguanide induces inflammatory responses via the NF-κB signaling pathway.

Other Cellular Effects and Antimicrobial Activity

Polyaminopropyl Biguanide (polyhexamethylene biguanide; C6) was compared to the (structurally) closely related polyaminopropyl biguanide (C3) with respect to antiseptic efficacy and cytotoxicity in vitro.[33] Antimicrobial efficacy tests were performed via determination of the minimum bactericidal concentration (MBC). Polyaminopropyl Biguanide (polyhexamethylene biguanide; C6) exhibited high antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli* (minimal bactericidal concentration = < 0.05 mg/ml (0.005%)), whereas polyaminopropyl biguanide (C3) proved to be ineffective in bacterial eradication. These results suggest that even small differences in the chemical structure of related agents, such as Polyaminopropyl Biguanide (polyhexamethylene biguanide; C6) and polyaminopropyl biguanide (C3), can substantially affect their efficacy.

Cytotoxicity was evaluated in human keratinocytes (HaCaTs) and murine fibroblasts (L929). In fibroblast or keratinocyte cultures, concentrations for both test substances ranged from 0.005% to 1% v/v. Polyaminopropyl biguanide (C3) was also tested at concentrations ranging from 0.25% to 3% v/v. Cultures were incubated for up to 72 h. For all tested concentrations, Polyaminopropyl Biguanide (polyhexamethylene biguanide; C6) was highly cytotoxic to human HaCaT and L929 murine fibroblast cell after 24 and 72 h of incubation, never exceeding a survival rate of 27 %. Polyaminopropyl biguanide (C3) displayed significantly lower cytotoxicity at concentrations ranging from 0.005% to 0.1% v/v. At concentrations up to 0.1 %, no cytotoxic effect could be detected in L929 cells after 24 h, whereas, for HaCaT cells, moderate and high cytotoxicity was evident at 0.05% and 0.1% polyaminopropyl biguanide (C3). After 72 h, only a weak cytotoxic effect on L929 cell at 0.05% and 0.1% polyaminopropyl biguanide (C3) could be observed, while, for HaCaT cells, concentrations up to 0.1% were classified as non-cytotoxic. However, concentrations ≥ 0.25% polyaminopropyl biguanide (C3) were highly cytotoxic to cells of both cell lines after 24 h of incubation. When compared directly, polyaminopropyl biguanide (C3) consistently resulted in a significantly higher cell survival rate than Polyaminopropyl Biguanide (polyhexamethylene biguanide; C6), irrespective of concentration and incubation time ($P \leq 0.0006$).[33]

It has been hypothesized that exposures to Polyaminopropyl Biguanide may have epigenetic effects, including non-genotoxic DNA base modifications (e.g., changes in DNA-base methylation) and altered mitogenic cytokine production.[34] These effects have been assessed *in vitro* using 3 cell types,: Caco-2 cells (from a human colon adenocarcinoma) with a p53 non-functional gene (Δp53: mut p53), Neuro-2A (mouse neuroblastoma cells), and HepG2 cells (human hepatocellular carcinoma) with functional p53 genes. The studies focused mainly on Polyaminopropyl Biguanide effects on the liver, but also examined the gut and brain since these are also the target organs. At Polyaminopropyl Biguanide concentrations of 1µg/mL to 20µg/mL, neither a growth stimulatory effect nor a growth inhibitory effect was observed. Viability testing using neutral red resulted in an IC_{50} of 20–25 µg/mL after treatment with Polyaminopropyl Biguanide for 3 h, whereas the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) cell viability test led to IC_{50} of 80 µg/mL, 160 µg/mL and 160 µg/mL for HepG2 cells, Neuro-2A cells and Caco-2 cells, respectively. The neutral red test showed that the cell lines had similar sensitivity to Polyaminopropyl Biguanide at much lower concentrations than with the MTT assay, indicating that the cellular target is the membrane. (The principle of neutral red test is based on the integrity of the cellular, lysosomal and endosomal membrane, while the MTT test is an indicator of metabolic activity in living cells.) Polyaminopropyl Biguanide does not induce significant oxidative stress (as determined by measuring production of malondialdehyde (MDA) or lipoperoxidation, nor does it induce hydroxylation of DNA (8-hydroxy-2'-deoxyguanosine [8-OH-dG]) and/or its hypermethylation (5-methylcytosine [m5dC] content), the latter being strongly implicated in DNA replication and regulation and cell division.

Additional results from this study indicated that Polyaminopropyl Biguanide did not induce significant production of mitogenic cytokines, such as TNF-α (tumor necrosis factor-alpha), interleukins (IL-1 alpha), and NF-κB, which can cause either apoptosis or stimulate the growth of transformed cells or tumors. Instead, concentrations of 20 to 100 µg/mL Polyaminopropyl Biguanide killed cells of all types in less than 3 h. The expression of genes involved in the mechanisms of cell death induced by Polyaminopropyl Biguanide, including p53, the pro apoptotic gene bax and others, and the anti-apoptotic bcl-2 and caspase-3 genes, has been evaluated using reverse transcription polymerase chain reaction (RT-PCR) methodology. Results indicated that it does not appear that Polyaminopropyl Biguanide-induced cell death is the result of apoptosis, but, rather, is cytotoxic at the cell membrane level, resulting in necrotic cell death. Finally, there was no apparent inhibition of GAP-junctions (i.e., gap junctional intercellular communication (GJIC)) in the presence of Polyaminopropyl Biguanide. Taken together, the data indicate that Polyaminopropyl Biguanide did not exhibit clear or remarkable epigenetic effects, except for a slight increase in the levels of some cytokines and a transcription factor at concentrations that cause rapid cell lysis.[34]

DERMAL IRRITATION AND SENSITZATION STUDIES

The skin irritation, sensitization, and phototoxicity/photosensitization studies summarized below are presented in Table 15.

Irritation

Polyaminopropyl Biguanide (0.5 g, moistened with water; single 4-h application) was classified as a mild skin irritant in rabbits.[12] Single applications (24 h) of 20% aqueous Polyaminopropyl Biguanide to rabbits indicates that this compound is non-corrosive, but moderately irritating, to intact skin, and severely irritating to abraded skin. Repeated applications of Polyaminopropyl Biguanide (12,000 ppm; 1 ml per application) to the skin of rabbits for 21 days were not irritating.[12] Severe skin irritation was observed in all rats that received a single 24-h application of 25% aqueous Polyaminopropyl Biguanide at dosages of 2.5 ml/kg and 5 ml/kg.[20] Polyaminopropyl Biguanide (0.04%) was classified as a non-irritant when applied to the skin of rats for 24 h. Repeated applications of 20.2% aqueous Polyaminopropyl Biguanide to rats for 21 days resulted in slight skin irritation (at 60 mg/kg/day) and moderate irritation (at 200 mg/kg/day).[12] Slight to moderate erythema was observed in guinea pigs that received repeated applications of 25% aqueous Polyaminopropyl Biguanide for 3 days.[35] In a study involving mice, the highest dose of Polyaminopropyl Biguanide (10% concentration in ethanol, 30 mg dose) caused hyperkeratosis and, occasionally, ulceration extending into the dermis when applied repeatedly for 80 weeks.[20] Polyaminopropyl Biguanide (up to 1.5% active) was not classified as a primary skin irritant when applied for 24 h to the skin of human subjects (17 males and 28 females).[12]

Sensitization

Results were positive for Polyaminopropyl Biguanide in the local lymph node assay (LLNA).[36,37] In maximization tests on Polyaminopropyl Biguanide, moderate skin sensitization was observed in guinea pigs induced with 0.06% active ingredient (intradermal injection) and 20.2% active ingredient (occlusive application) and challenged with Polyaminopropyl Biguanide (20.2 % active ingredient) and a 30% solution of the ingredient (6% active ingredient) in deionized water, and moderate to strong sensitization was observed in guinea pigs induced with 0.2% active ingredient (intradermal injection) and 20.2% active ingredient (topical application) and challenged with Polyaminopropyl Biguanide (20.2% active ingredient).[12] In another guinea pig maximization test, sensitization was not observed in guinea pigs induced with 0.15% (intradermal injection) and 20% Polyaminopropyl Biguanide (topical application) and challenged with 10% or 20% Polyaminopropyl Biguanide. In one Buehler test on Polyaminopropyl Biguanide, guinea pigs were induced with 2% active ingredient (topical application), challenged with 2% active ingredient, and rechallenged with 0.2%, 2%, and 4% active ingredient. The initial challenge with 2% active ingredient and rechallenge with 2% and 4% active ingredient resulted in faint erythema; rechallenge with 0.2% active ingredient produced negative results. Polyaminopropyl Biguanide (2% active ingredient) was classified as a moderate sensitizer. In another Buehler test, it was determined that the threshold for eliciting sensitization in guinea pigs was ~ 1%. Induction concentrations ranged from 0.3% to 5% and challenge concentrations ranged from 0.075% to 15%. Results from a study evaluating the possible cross-reactivity of Polyaminopropyl Biguanide (challenge with 20%) with chlorhexidine (challenge with up to 4% chlorhexidine gluconate) in guinea pigs were negative.

In a human repeated insult patch test (HRIPT; 191 subjects), it was determined that 20% aqueous Polyaminopropyl Biguanide (2% active ingredient; effective concentration = 0.4%) was not capable of causing primary skin irritation, but was capable of causing sensitization.[3] When a leave-on product containing 20 % Polyaminopropyl Biguanide (tested at 0.5% , effect concentration 0.1% Polyaminopropyl Biguanide) was evaluated in an HRIPT involving 207 subjects, it was concluded that the product did not induce dermal sensitization.[38] In another HRIPT (115 subjects; any ethnicity, provided that their degree of skin pigmentation did not significantly interfere with evaluations) on a neck cream containing 0.2% Polyaminopropyl Biguanide, the product did not cause clinically meaningful irritation or sensitization.[39] In a study provided by the cosmetics industry, the skin sensitization potential of 20% Polyaminopropyl Biguanide (diluted with distilled water to

1% v/v prior to testing; effective concentration = 0.2%; dose per cm^2 not stated) was evaluated in an HRIPT involving 108 subjects (Asian (~2%), Bi-racial (~3%), Black (~ 23%), Caucasian (~ 33%), and Hispanic (~39%); Fitzpatrick skin types not stated).[40] The authors concluded that Polyaminopropyl Biguanide did not induce dermal sensitization in the subjects tested, and a NESIL of 750 µg/cm^2 was provided under separate cover.

Risk Assessment

A quantitative risk assessment (QRA) was performed by industry in response to the Panel's concerns about sensitization potential.[41] The QRA for contact dermatitis with Polyaminopropyl Biguanide in cosmetics yielded a no expected sensitization induction level (NESIL) of 1000 µg/cm^2, which supports the use of this ingredient at concentrations of ≤ 0.1%. Among the human data that were used to derive the NESIL was an HRIPT involving 26 subjects tested with 1% Polyaminopropyl Biguanide at a dose of 1000 µg/cm^2, the highest non-sensitizing dose in relation to all of the HRIPT data that were considered. The NESIL of 1000 µg/cm^2 was used to determine whether estimated exposure, using maximum use concentrations from a Council survey, could be considered safe. The ratio of AEL (Acceptable Exposure Level)/CEL (Consumer Exposure Level) was > 1, except for the product that contained 0.2% Polyaminopropyl Biguanide.

A second QRA, performed by industry, yielded a NESIL of 750 µg/cm^2. The human data that were used to derive the NESIL are from a more recent HRIPT , involving 108 subjects (Asian (~2%), Bi-racial (~3%), Black (~ 23%), Caucasian (~ 33%), and Hispanic (~39%))tested with 0.2% Polyaminopropyl Biguanide, that is summarized previously in this report.[42]

According to one source, the results from an initial risk assessment indicated that the use of Polyaminopropyl Biguanide at concentrations < 0.2% could be extended to include underarm deodorants.[43] Neither details relating to this risk assessment nor the reference is identified in the secondary source of this information. Additional information from this source is stated as follows: To consolidate the specific risk assessment supporting the use of Polyaminopropyl Biguanide in underarm deodorants, a strategy was also deployed to monitor the ongoing frequency of Polyaminopropyl Biguanide sensitization and to determine whether the use of Polyaminopropyl Biguanide in these products could be identified as a likely causal exposure in any sensitized individuals. Two studies (both summarized in Table 15) provided a baseline frequency of Polyaminopropyl Biguanide sensitization; 2 of 374 patients in a United Kingdom study and 6 of 1554 patients in a German study had positive patch test reactions to 2.5% aqueous Polyaminopropyl Biguanide. It was noted that this initial series of data suggested that the baseline frequency of Polyaminopropyl Biguanide sensitization was very low (0.5% and 0.4% in the United Kingdom and German studies, respectively). The majority of positive reactions were considered weak. It was noted that these data suggested that Polyaminopropyl Biguanide may not be a relevant contact allergen.

In a subsequent German multicenter study (summarized in Table 15) involving 1975 patients, 10 had positive reactions to 0.5% Polyaminopropyl Biguanide (20% aqueous Polyaminopropyl Biguanide tested at 2.5% concentration). The majority of the positive reactions were considered weak. When results of the 3 studies were considered together, it was noted that the frequency of sensitization reactions to Polyaminopropyl Biguanide remained low and stable, in spite of the use of Polyaminopropyl Biguanide in underarm deodorants.

Photosensitization/Phototoxicity

Animal

The photoirritation potential of 20% aqueous Polyaminopropyl Biguanide was studied using 10 male rats.[20] The following 2 concentrations of the test substance (in distilled water) were evaluated: 10% (effective concentration = 2%) and 25% (effective concentration = 5%). Each test concentration (0.1 ml) was applied to dorsal skin once daily for 4 days. The test site was irradiated with UVC (black lamp) for 3 h daily. Very strong irritation potential, but no significant photoirritancy, was reported in a study in which male rats were tested with Polyaminopropyl Biguanide at concentrations of 2% and 5%.

Human

A phototoxicity/photoallergenicity study on 20% aqueous Polyaminopropyl Biguanide was performed using 26 male and female subjects.[20] The test substance was diluted (1:20 in water; effective concentration = 1%) prior to application. Patches (20 mm x 20 mm square of Webril affixed to a 40 mm x 40 mm adhesive square) were moistened with 0.4 ml of the test substance (dose = 1 mg/cm^2) and applied to the upper arm for 24 h, 3 times per week for 4 successive weeks. Immediately after patch removal, the sites were exposed to direct rays of mid-day sun for 1 h. The challenge application occurred at week 6. Polyaminopropyl Biguanide was essentially non-irritating and did not induce sensitization, phototoxicity, or photoallergenicity. The dose (1 mg/cm^2) information used in this study was provided by the Cosmetics Europe Consortium in response to a CIR request for additional information.[44]

OCULAR IRRITATION STUDIES

The ocular irritation studies summarized below are presented in Table 16.

Undiluted Polyaminopropyl Biguanide was a severe ocular irritant/corrosive agent when instilled into the rabbit eye.[3] The instillation of 25% aqueous Polyaminopropyl Biguanide into the eyes of rabbits resulted in severe inflammation and corneal damage in unrinsed eyes and slight inflammation in rinsed eyes.[20] Moderate and mild ocular irritation were observed in unrinsed and rinsed rabbit eyes, respectively, after 20% aqueous Polyaminopropyl Biguanide was instilled.[3] In another study involving rabbits, the instillation of Polyaminopropyl Biguanide (25% aqueous) into the eyes induced slight inflammation, but no corneal ulceration.[20] Ocular irritation was not observed when Polyaminopropyl Biguanide (0.04% active ingredient) was instilled into the eyes of rabbits.[20] In a study in which 20% aqueous Polyaminopropyl Biguanide (100 µl) was instilled into human eyes (from cadavers) and the eyes of rabbits in a temperature-controlled chamber (32 - 36˚C), normal corneal morphology was observed at histological examination.[45]

CLINICAL STUDIES

The patient multicenter studies summarized below are presented in the Human Sensitization Studies section of Table 15. In another type of clinical study, no adverse effects were noted following the exposure of 29 patients to a pre-operative antiseptic for cataract surgery that contained 0.2 % Polyaminopropyl Biguanide.[46]

Retrospective and Multicenter Studies

In a multicenter study involving 374 patients patch tested with 2.5% aqueous Polyaminopropyl Biguanide, 2 sensitization reactions were reported. [43,47] Ten patients with sensitization reactions to 0.5% Polyaminopropyl Biguanide and 16 patients with sensitization reactions to 1% Polyaminopropyl Biguanide were identified in a multicenter study involving 1975 patients.[48] In a multicenter study involving 1554 patients, sensitization reactions were observed in 6 patients patch tested with 0.5% Polyaminopropyl Biguanide.[49]

Case Reports

An itchy rash on the hand was observed over a 2-year period in a non-atopic patient with a history of retinal detachment surgery.[50] The patient had regularly used a rinse-off contact lens cleaning solution containing 0.001% Polyaminopropyl Biguanide twice daily. A patch test chamber containing the undiluted contact lens cleaning solution was applied to the skin for 2 days, and doubtful results were reported on day 4. A patch test chamber containing a 10% dilution of the product (0.0001% Polyaminopropyl Biguanide tested) was subsequently applied to the skin, and positive results (+ reaction) were observed on day 7. Additionally, semi-open tests of the undiluted product yielded a weak positive reaction on day 7. In other tests, the individual ingredients (obtained from the manufacturer) of the contact lens cleaning solution were diluted to different concentrations in water. There were no reactions to 2% aqueous Polyaminopropyl Biguanide, but a weak, late reaction (1+ reaction) to 5% aqueous Polyaminopropyl Biguanide was observed on day 7. However, stronger and earlier reactions were observed after the application of 10% aqueous Polyaminopropyl Biguanide (+? reaction on day 2; 2+ reaction on days 5 and 7) and 20% aqueous Polyaminopropyl Biguanide (2+ reaction on day 2; 3+ reaction on days 5 and 7). Patch test results for 20% aqueous Polyaminopropyl Biguanide in 10 control subjects were negative.

In a case report on a non-atopic patient with a history of bilateral leg ulcers and multiple contact allergies, mild hand dermatitis was observed after repeated use of a wound irrigation solution that contained Polyaminopropyl Biguanide and a wound gel containing the same disinfectant.[51] The composition of the disinfectant (liquid and gel) was as follows: 0.1% Polyaminopropyl Biguanide, 0.1% undecylenamidopropyl betaine, and water; the gel also contained glycerol and hydroxyethyl cellulose. In a repeated open application test, a positive reaction was observed after the gel was applied twice daily (in elbow fold) for 10 days. The patient was also patch tested (patch test chamber) with 5% aqueous Polyaminopropyl Biguanide (a dilution of a 20% aqueous solution). The solution was applied to the upper arm for 2 days; reactions, scored according to International Contact Dermatitis Research Group (ICDRG) guidelines were negative on day 2, but were positive on day 4. The patch test (same procedure) was repeated at concentrations of 2.5% and 5% aqueous Polyaminopropyl Biguanide. Positive reactions to the 5% concentration were observed on day 2 (+) and day 4 (++, with partially pustular morphology). Results for the gel and liquid were negative in patch tests.

A chronic, recurrent and itchy dermatitis was observed in a male patient who used wet wipes.[52] Polyaminopropyl Biguanide, an ingredient of the product, was tested at different concentrations (20%, 2%, and 0.2% aqueous). Scoring was performed in accordance with ICDRG guidelines. On day 2 and day 4, respectively, + and ++ reactions to 20% Polyaminopropyl Biguanide (with a papulovesicular reaction, extending outside of the test chamber) were observed; +? and + reactions to 2% Polyaminopropyl Biguanide were observed on days 2 and 4, respectively. No reactions to 0.2% Polyaminopropyl Biguanide were observed.

A non-atopic patient with a history of Crohn's disease presented with a dermatitis eruption in the area around where the gastrostomy tube had been inserted. Polyaminopropyl Biguanide was a component of the antimicrobial foam dressing that was used. The patient was patch tested with Polyaminopropyl Biguanide (5% aqueous) at 2 separate sites on the upper back. At 96 h, + reactions were observed at both sites. Negative results were reported for the 10 control subjects who were patch tested.[53]

Contact Urticaria

A female patient experienced grade III anaphylaxis (IgE-mediated mechanism confirmed) with palmar pruritus, flush, swelling of lips, swallowing difficulties, hypotension, and loss of consciousness while using a new brand of wet toilet paper containing Polyaminopropyl Biguanide as a disinfectant.[17,54] The detailed allergy history of the patient indicated 3 prior anaphylactic episodes (grade II) during wound care of a leg ulcer. One of the episodes occurred after the use of a wound dressing that contained Polyaminopropyl Biguanide. The other 2 episodes occurred after wound cleansing with 2 different Polyaminopropyl Biguanide disinfectants, one of which contained Polyaminopropyl Biguanide, polyethylene glycol (PEG) 4000, and no other additives. The composition of the other disinfectant that contained Polyaminopropyl Biguanide was not detailed. However, according to another publication, the composition of that disinfectant (liquid and gel) is as follows: 0.1% Polyaminopropyl Biguanide, 0.1% undecylenamiopropyl betaine, and water; the gel also contains glycerol and hydroxyethyl cellulose.[51] The patient had no known allergies or atopic diseases. Skin prick tests were positive for the disinfectant of known composition, which was tested in a 1:10 dilution, corresponding to 20 µg/ml Polyaminopropyl Biguanide. Positive skin prick test results were also reported for chlorhexidine in different commercial preparations. Skin prick test results for PEG 4000 were negative, and the same was true for the 5 healthy volunteers who were prick tested with the disinfectant of known composition. Whether or not the other disinfectant containing Polyaminopropyl Biguanide was evaluated in prick tests was not mentioned. Other results reported in this case report indicated that there was limited in vitro cross-reactivity between Polyaminopropyl Biguanide and chlorhexidine. The author noted that patients with known chlorhexidine allergy could be at risk for anaphylactic reactions to Polyaminopropyl Biguanide.

A male patient (atopic and diabetic) had a history of angioedema and pruritus after using wet wipes.[13] Patch test results for an ingredient of the wipes, Polyaminopropyl Biguanide (tested at 1:10 in water), and the wipe itself were negative. However, prick tests resulted in strong positive reactions to the wipe and this ingredient after 15 minutes, and the reactions continued to increase in intensity during the following 2 h.

The prick test (protocol and test concentration not specified) was used to diagnose immediate contact urticarial reactions in 44 patients with eczematous dermatitis. A positive reaction to Polyaminopropyl Biguanide was observed in 1 patient.[55]

Two cases of severe anaphylaxis were reported following contact of a surgical wound with a hospital disinfectant containing 0.2 % Polyaminopropyl Biguanide.[56] Immediate-type hypersensitivity to Polyaminopropyl Biguanide was suggested by positive skin prick tests in both patients and by negative skin tests in control individuals. Skin tests involving chlorhexidine were negative.

The case of a 77-year-old female patient who suffered from severe anaphylaxis during wound (leg ulcer) care was presented.[57] The results of an allergologic evaluation indicated specific IgE antibodies to chlorhexidine (a biguanide antiseptic), but anaphylaxis to chlorhexidine was not congruent with the patient history and dermal provocation tests. However, skin prick tests were indicative of sensitization to Polyaminopropyl Biguanide. These results were supported by the detection of specific IgE antibodies to Polyaminopropyl Biguanide, the results of basophil activation tests, and IgE inhibition analysis. In an assay to assess cross-reactivity, varying concentrations of Polyaminopropyl Biguanide and chlorhexidine (0.1 to 100 µg/ml) were added to the patient's serum. The results of this assay suggested a cross-reaction between Polyaminopropyl Biguanide and chlorhexidine. The authors presumed cross-reactive IgE antibodies binding to both biguanide antiseptics and identified Polyaminopropyl Biguanide as the likely cause of the anaphylactic reaction. Polyaminopropyl Biguanide was recognized as an emerging allergen that has to be considered as a cause of anaphylaxis.

Other Clinical Reports

Based on medical surveillance information obtained between 2004 and 2007 on employees who came in contact with Polyaminopropyl Biguanide in the workplace, no cases of skin sensitization to this chemical were reported.[12] All manufacturing and laboratory employees were offered complete medical evaluations on a regular basis depending on their age. These were conducted every one to two years.

In a clinical trial (106 dialysis patients) in which patients were treated for infections, Polyaminopropyl Biguanide was well-tolerated and there were only two cases of transient local skin erythema.[58] Four of 28 patients were excluded from a cohort study because of adverse effects related to a Polyaminopropyl Biguanide dressing.[59]

Reportedly, the application of very high doses (doses not stated) of Polyaminopropyl Biguanide can trigger fever and a generalized exanthema.[30]

Polyhexamethylene Guanidine Phosphate (PHMG)

Beginning in 2006, epidemics of a fatal lung injury were observed in Korea every spring.[60] It was subsequently demonstrated that this type of children's interstitial lung disease (chILD), characterized by rapid progression and high mortality, was associated with humidifier disinfectant use. These disinfectants contain oligo (2- [2-ethoxy] ethoxyethyl) guanidium chloride, polyhexamethyleneguanidine (PHMG), 5-chloro-2-methylisothiazol-3 (2H)-one/2-methylisothiazol-3-one, and didecyldimethylammonium chloride. PHMG (not the ingredient that is under review in this safety assessment) has some chemical similarity with Polyaminopropyl Biguanide. The 2 chemical structures are presented below. PHMG contains guanidine as part of its chemical structure, whereas Polyaminopropyl Biguanide contains biguanide.

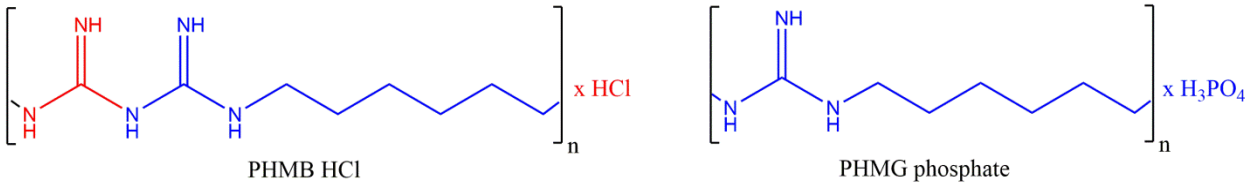


Figure 2. Polyaminopropyl Biguanide (PHMB HCl) vs PHMG phosphate.

The clinical characteristics of suspected cases between 2006 and 2011 were determined by a nationwide retrospective epidemiological study. The potential causal relationship with humidifier disinfectants was examined by a prospective surveillance study after humidifier disinfectant sales were suspended. One-hundred thirty-eight children (average age = 30.4 months) were diagnosed with chILD. The annual incidence increased in 2011 and then decreased to zero in 2012. At the time of hospital admission, the most frequent symptoms were cough and dyspnea. Disease progression resulted in spontaneous air leak and 80 children (58%) died. No new cases were found 2 years after the sale of humidifier disinfectants was suspended. The authors noted that the results of this study suggest that humidifier disinfectant inhalation causes an idiopathic type of chILD that is characterized by spontaneous air leak, rapid progression, lack of response to treatment, and high mortality.

A case-control study, with community-dwelling controls, was performed to validate the preceding study's findings and to confirm the exposure-response relationship between humidifier disinfectant and lung injury.[61] This study was based on re-examination of lung CAT scans and medical records at a hospital in Korea where many of the cases appeared. The purpose of the re-examination was to identify all cases of lung injury that fit certain criteria (i.e., criteria for the type of lung injury that was associated with the use of humidifier disinfectants in the previous studies). Each case of lung injury was matched with 4 community-dwelling controls, according to age (±3 years), sex, residence, and history of childbirth since 2006 (for women). Using a questionnaire, environmental risk factors, which included the humidifier (type and use) and the humidifier disinfectant, were investigated in August of 2011. Exposure to the humidifier disinfectant was calculated for both cases and controls, and the corresponding risks of lung injury were compared. Sixteen patients who were among the 28 eligible cases agreed to participate. Sixty matched controls (selected from the community that the hospital serves) were considered eligible for participation in the study.

Study results indicated a statistically significant, exposure-response relationship between humidifier disinfectant exposure and lung injury. The cases were significantly more likely to have been exposed to humidifier disinfectants, compared to controls (odds ratio (OR): 116.1; 95% confidence interval (CI): 6.5 to 2,063.7). The OR for an association between use of a humidifier disinfectant in which the active ingredient was specifically PHMG and lung injury was even greater (OR: 203.8; 95% CI: 11.1 to 3,724.1), suggesting that the lung injuries observed in people who used humidifier disinfectants were attributable to the use of humidifier disinfectants containing PHMG. All cases used several liquid humidifier disinfectant formulations that contained the same proportion of PHMG phosphate. The concentration of PHMG phosphate in the humidifier mist was not stated. Further examination of associations between exposure (number of bottles of disinfectant used per month x duration of exposure as number of months used x volume per bottle of disinfectant/days/ month) and lung injury indicated a clear relationship between the magnitude of daily exposure to disinfectants containing PHMG and the magnitude of the ORs. There was no association between lung injury and use of humidifier disinfectants in

which the active ingredient was a combination of isothiazolinone derivatives (5-chloro-2-methyl-4-isothiazolin-3-one/2-methyl-4-isothiazolin-3-one [MCI/MI]) or a guanidinium derivative (oligo(2-(2-ethoxy)ethoxyethyl guanidinium chloride [PHG]).[61]

An analysis of patients and fatalities attributed to inhalation exposure to PHMG indicates that this chemical mainly causes lung diseases, such as pulmonary fibrosis.[62] Of the known main components of the humidifier disinfectants, PHMG has been identified as the chemical substance that caused the most deaths. In surveys conducted to identify victims of the humidifier disinfectant, 22% of the research participants answered that they had used the humidifier disinfectant, and 21% complained of side effects.

In a refined risk assessment,[63] the time-weighted average (TWA) PHMG concentration in the bedroom air was 0.06 mg/m^3 (calculated value, which is 250 times greater than the exposure concentration of Polyaminopropyl Biguanide at 0.00024 mg/m^3, which is derived from a MOS of 100) for this scenario, averaged over 8 hours [The 28-day inhalation study on Polyaminopropyl Biguanide, summarized earlier in this safety assessment, was used as a comparison for the PHMG humidifier exposures.[12]]. This concentration in air is 27 times greater than the 0.0022 mg/m^3 (the exposure concentration of Polyaminopropyl Biguanide that yields a MOS of 11) inhalation exposure concentration of Polyaminopropyl Biguanide estimated for the use of a pump hair spray containing the highest maximum reported concentration of use (0.053%) Polyaminopropyl Biguanide (See Table 11 in the safety assessment report). Further, the exposure duration of 8 h for PHMG in the humidifier use scenario is 96 times greater than the conservative 5-min exposure duration/event assumed for Polyaminopropyl Biguanide in the consumer spray scenarios evaluated in the safety assessment.

SUMMARY

The safety of Polyaminopropyl Biguanide, which is used as a preservative in cosmetics, is reviewed in this assessment. Polyaminopropyl Biguanide is an INCI name; it refers to the hydrochloride salt of an amino polymer comprising hexyl biguanide repeat units (***chemical name***, polyhexamethylene biguanide hydrochloride (PHMB HCl)). It is not synonymous with the substance identified by the ***chemical name*** polyaminopropyl biguanide.

Polyaminopropyl Biguanide, in its neat form, represents a solid/powder of > 94.2 % purity, and is usually marketed as an approximately 20% aqueous, pre-formulation solution. One method for manufacturing Polyaminopropyl Biguanide is via the polycondensation of sodium dicyanamide and hexamethylenediamine.

The following chemicals have been reported as possible impurities of Polyaminopropyl Biguanide: *N*-(6-aminohexyl)-*N*'-(6-(6-guanidinohexyl)guanidine, *N*-cyano-*N*'-(6-*N*-cyanoaminohexyl)guanidine, *N*-cyano-*N*'-(6-amnohexyl)guanidine), *N*-cyano-*N*'-6-(6-guanidinohexyl)guanidine hydrochloride, and 1,6-diguanidinohexane dihydrochloride.

According to 2019 VCRP data, Polyaminopropyl Biguanide is being used in 147 cosmetic products, mostly leave-on products. The results of a concentration of use survey provided in 2017 indicate that Polyaminopropyl Biguanide is being used at concentrations up to 0.2% in leave-on products (eye lotions), and use in baby lotions, oils, and creams (leave-on products) at concentrations up to 0.1% is also being reported. The highest maximum use concentration that is being reported for Polyaminopropyl Biguanide in rinse-off products is 0.1% in hair dyes and colors and in skin cleansing products. Polyaminopropyl Biguanide in reported to be used in aerosolized products according to VCRP data, but this type of use was not reported in the concentration of use survey.

In 2017, the SCCS issued a final opinion stating that the use of Polyaminopropyl Biguanide as a preservative in all cosmetic products at concentrations up to 0.1% is safe and that its use in sprayable formulations is not advised.

The safety of Polyaminopropyl Biguanide has been reviewed by the US EPA, and the Agency concluded that this pesticide has very low aggregate risk of adverse health effects to the public or environment.

The results of a dermal penetration study on Polyaminopropyl Biguanide indicated that absorption through the skin equaled 1.56% (dermis contained 1.56% of applied dose) + 0.03% (receptor fluid contained 0.03% of applied dose). Based on SCCS Notes of Guidance, one standard deviation (2.5%) was added to the absorbed amount, yielding a calculated dermal absorption value of 4.09% (1.56% + 0.03% + 2.5% = 4.09%).

The principal route of excretion of radioactivity from orally administered Polyaminopropyl Biguanide (radiolabeled) was in the feces in the majority of the rat studies. However, in one rat study, most of the [^{14}C]-Polyaminopropyl Biguanide administered in drinking water or in the diet was absorbed, and the majority was excreted in the urine, with lesser amounts excreted in the feces. The following components have been detected in the urine of rats fed Polyaminopropyl Biguanide in

the diet: oligomers with 2 cyanoguanidino end groups, as well as the trace constituents, 3,3-dicyano-1,1-hexamethylenediguanidine and a compound that was considered to be 1-(6-aminohexyl)-3-cyanoguanidine.

There was no incidence of mortality or systemic toxicity in rats that received a single dermal dose of 5000 mg/kg aqueous Polyaminopropyl Biguanide; but, hemorrhage of dermal capillaries at the application site was observed. In an acute dermal toxicity study on 20% aqueous Polyaminopropyl Biguanide involving rabbits, an LD_{50} > 400 mg/kg was reported.

The LD_{50} was reported to be > 1000 mg/kg for rats dosed orally with aqueous solutions (up to 25% aqueous) of Polyaminopropyl Biguanide. A median lethal dose of 25.6 mg/kg was reported for rats dosed orally with a solution of 0.4% Polyaminopropyl Biguanide.

An LC_{50} of > 0.36 mg/l was reported in acute inhalation toxicity studies in which rats were exposed to Polyaminopropyl Biguanide solutions (concentrations up to 360 mg/m^3). Dark/red lungs were observed at necropsy. A dose-related depression of respiratory rate was reported in a study in which mice were exposed to Polyaminopropyl Biguanide at concentrations up to 208 mg/m^3.

There were no mortalities or signs of systemic toxicity in rats that received dermal applications of Polyaminopropyl Biguanide at doses up to 200 mg/kg daily over a 30-day period (21 applications total; NOAEL = 200 mg/kg). In a 21-day dermal toxicity study involving rabbits, there was no evidence of toxic effects on the skin after 20% aqueous Polyaminopropyl Biguanide was applied.

A LOAEL of 0.1 mg/ml (lowest concentration in drinking water) for Polyaminopropyl Biguanide was reported in the two 28-day oral toxicity studies involving rats and mice, respectively.

In 21-day and 28-day inhalation toxicity studies on Polyaminopropyl Biguanide involving rats, NOAEL values of 0.025 mg/m^3 and 0.0239 mg/m^3, respectively, were reported.

Rats (groups of 10) that received Polyaminopropyl Biguanide (in drinking water, doses up to 150 mg/kg) for 4 weeks experienced dehydration, clinical signs of rough coat and hunched posture, and body weight loss (all classified as severe). Across the 3 dose groups, 10 rats had to be terminated due to severe weight loss, whereas, the remaining rats eventually adapted and began to gain weight. Absolute liver weights in all dose groups were similar to the control group. Mild centrilobular hypertrophy in liver observed in some of the rats (all dose groups). In the same study, Polyaminopropyl Biguanide administered (in the diet, 4000 mg/kg) to rats for 4 weeks caused a statistically significant decrease in body weight and absolute liver weight. In this dietary group, there was no evidence of centrilobular hypertrophy in the liver. Also, there was no evidence of necrosis or inflammatory lesions in the liver when Polyaminopropyl Biguanide was administered in drinking water or in the diet. In a 60-day oral toxicity study on Polyaminopropyl Biguanide involving rats, mild toxicity in the liver or kidneys (at microscopic examination) was observed at daily doses of 2 mg/kg (equivalent to 0.2 mg/l of 0.4% solution of test substance), 8 mg/kg (equivalent to 0.4 mg/l of 0.4% solution of test substance), and 32 mg/kg (highest dose equivalent to 1.2 mg/l of 0.4% solution of test substance). None of the animals died.

In 90-day toxicity studies on rats and mice, 4000 to 5000 ppm Polyaminopropyl Biguanide or more in the diet was associated with iron pigment deposits in Kupffer cells in the rats, but no mortalities; the NOAEL was 1000 ppm in both species. In a 90-day study, 20% Polyaminopropyl Biguanide in drinking water yielded no treatment-related macroscopic findings in rats. A NOAEL of 5500 ppm was reported for Beagle dogs fed up to11000 ppm Polyaminopropyl Biguanide in the diet for 90 days.

In an 80-week chronic toxicity study (dermal applications 5 days/week), a mortality rate of 75% was reported for the highest dose group (10% Polyaminopropyl Biguanide, 30 mg dose). The exophthalmos observed throughout the study was more severe in this group, but the results of histological examination of the eyes and gross and microscopic examination of the thyroids were negative.

In a 104-week oral toxicity study involving rats, a NOAEL of 2000 ppm (highest concentration fed in diet) was reported for Polyaminopropyl Biguanide. This concentration corresponded to a NOAEL of 36 mg/kg/day in male rats, used to calculate a MOS. MOS calculations were performed, assuming that all cosmetics contain 0.1% Polyaminopropyl Biguanide and a dermal absorption value of 4.09%, and using the NOAEL of 36 mg/kg/day and a SED of 0.012 mg/kg/day; MOS values of 258 (based on cosmetic exposure estimate) and 227 (based on cosmetic exposure estimate + non-cosmetic exposure estimate) were determined. The SCCS performed the margin of safety calculations. It should be noted that the NOAEL of 36 mg/kg/day was corrected based on 8.5% oral absorption, and a NOAEL of 3.1 mg/kg/day was used for the MOS calculation.

A NOEL (for histopathologic changes) of 200 ppm was reported in a 122-week oral toxicity study involving rats fed Polyaminopropyl Biguanide at concentrations up to 2000 ppm in the diet. In a study involving mice, feeding with Polyaminopropyl Biguanide (concentrations up to1000 ppm in diet) for 97 weeks did not cause any macroscopic changes in tissues examined. A NOAEL of 1500 ppm for Polyaminopropyl Biguanide was reported in a 1-year feeding study involving dogs, though treatment-related histopathological findings in the liver and kidneys were reported at dietary concentrations of 3000 ppm and 4500 ppm. In a 26-week feeding study involving dogs, dietary concentrations of 1500 ppm and 4500 ppm Polyaminopropyl Biguanide produced dose-related hepatotoxicity and nephrosis.

In oral reproductive and developmental toxicity studies on Polyaminopropyl Biguanide involving rats, NOAEL values of 1000 ppm and 1300 ppm have been reported. In an inhalation study, degeneration of seminiferous tubules in the testis of 1 male rat was observed at a concentration of 0.25 mg/m^3, but this toxic effect was not observed at any other concentration, including the highest concentration (26 mg/m^3). A NOAEL of 10 mg/kg/day for developmental toxicity was reported in the only study (oral dosing) involving mice. A NOAEL of 40 mg/kg/day for developmental toxicity was reported in a study involving rabbits. Polyaminopropyl Biguanide has been classified as embryotoxic at oral dosage rates of 32 mg/kg/day (animal strain not stated) and 100 mg/kg/day (rats), and as teratogenic in rats at an intraperitoneal dosage rate of 10 mg/kg/day

In the Ames test, Polyaminopropyl Biguanide was non-genotoxic at doses up to 5000 µg/plate with and without metabolic activation. At the highest dose evaluated (333,300 µg/plate) in the Ames test, Polyaminopropyl Biguanide was weakly genotoxic in strain 1538 without metabolic activation. Polyaminopropyl Biguanide was non-genotoxic in the mouse lymphoma assay at concentrations up to 2000 µg/ml with and without metabolic activation, and in the in vitro micronucleus test (cultured human peripheral blood lymphocytes) at concentrations up to 50 µg/ml (without metabolic activation) and up to 250 µg/ml (with metabolic activation). In the in vivo micronucleus test, Polyaminopropyl Biguanide was non-clastogenic in polychromatic erythrocytes from mice that received single oral dosages up to 400 mg/kg. In the in vivo unscheduled DNA synthesis assay, there was no induction of unscheduled DNA synthesis in hepatocytes from rats that received single oral doses up to 1500 mg/kg.

Polyaminopropyl Biguanide was evaluated at concentrations up to 3000 µg/ml in the cell transformation assay (using baby hamster kidney fibroblasts), and there was no difference in the number of transformed cell colonies between test and negative control cultures. In another assay, RAW 264.7 mouse macrophages (a macrophage-like, Abelson leukemia virus transformed cell line derived from BALB/c mice) were co-cultured with SVEC-10 mouse liver endothelial cells in various experimental conditions: pre-activation of macrophages with Polyaminopropyl Biguanide or lipopolysaccharide (LPS) and/or co-culture in presence of Polyaminopropyl Biguanide. Polyaminopropyl Biguanide, tested at concentrations up to 1 ppm, had no direct effect on liver cell proliferation and did not potentiate cell proliferation induced by activated macrophages.

Polyaminopropyl Biguanide was classified as a hepatocarcinogen in mice, i.e., at the highest dose (30 mg of 10% Polyaminopropyl Biguanide (in ethanol) that was applied to the skin daily (5 days/week) for 80 weeks. An increase in the incidence of liver tumors was observed at the 30 mg/day dose; the increase was statistically significant only for liver tumors of endothelial origin. High mortality (76 to 78% of animals died) was noted in this group

A statistically significant increase in the incidence of hemangiosarcomas and hemangiomas was reported for only male mice that received Polyaminopropyl Biguanide at a dietary concentration of 4000 ppm daily for 2 years. In a 97-week study in which mice were fed Polyaminopropyl Biguanide at dietary concentrations up to 1000 ppm prior to and during mating and their offspring were fed the same concentrations, there were no treatment-related (non-neoplastic or neoplastic) increases in histopathologic findings. Hemangiosarcomas or hemangiomas in the liver or other sites were reported in this study along with the high mortality incidence (80%) by week 97. In a 124-week oral feeding study in which rats were fed Polyaminopropyl Biguanide at concentrations up to 2000 ppm, 80% mortality was also reported. A low incidence of hemangiomas or hemangiosarcomas (mostly in lymph nodes) was observed in the groups of remaining animals (7 groups, with 8 to 21 rats/group; 1 animal with a hemangioma or hemangiosarcoma per group). When mice were fed Polyaminopropyl Biguanide at dietary concentrations up to 4000 ppm for up to 28 days, increased cell proliferation in a concentration-related manner was noted at 1200 ppm and 4000 ppm. Polyaminopropyl Biguanide was classified as non-carcinogenic in rats fed dietary concentrations up to 2000 ppm for 122 weeks. At 124 weeks, 80% mortality overall was reported. A low incidence of hemangiomas and hemangiosarcomas was reported in a study in which rats were fed Polyaminopropyl Biguanide at a dietary concentration of 2000 ppm for 2 years. In another 2-year study, Polyaminopropyl Biguanide was administered (in drinking water or in diet) to groups of rats. Hepatocellular tumors were induced at concentrations of 1000 mg/l and 1500 mg/l, but not at a concentration of 500 mg/l. The hypothesized mode of action (MOA) for liver tumors induced by Polyaminopropyl Biguanide in drinking water involves increased hepatocyte proliferation and induction of hepatocellular foci and tumors.

In a study involving A549 lung cells in vitro, it was noted that Polyaminopropyl Biguanide induces inflammatory responses via the NF-κB signaling pathway.

Except for a slight increase in some cytokines and transcription factor at concentrations at which cell lysis occurs rapidly, Polyaminopropyl Biguanide did not exhibit clear and remarkable epigenetic properties at 20 to 100 µg/mL.

Polyaminopropyl Biguanide (polyhexamethylene biguanide) exhibited high antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli*, whereas, though chemically closely related, polyaminopropyl biguanide proved to be ineffective in bacterial eradication. When compared to Polyaminopropyl Biguanide (polyhexamethylene biguanide), polyaminopropyl biguanide displayed significantly lower cytotoxicity at concentrations ranging from 0.005% to 0.1% v/v; both chemicals were cytotoxic.

The results of animal studies indicate that the skin irritation potential of Polyaminopropyl Biguanide may be concentration-dependent as well as dependent upon the duration of application. For example, the skin irritation potential of Polyaminopropyl Biguanide (single 4-h application) was classified as a mildly irritating in rabbits. Single applications (24 h) of 20% aqueous Polyaminopropyl Biguanide to rabbits were non-corrosive, moderately irritating to intact skin, and severely irritating to abraded skin. Repeated applications of Polyaminopropyl Biguanide (12,000 ppm) to the skin of rabbits for 21 days were classified as non-irritating. Polyaminopropyl Biguanide (up to 1.5% active) was not classified as a primary skin irritant when applied for 24 h to the skin of human subjects.

Positive results were reported for Polyaminopropyl Biguanide in the local lymph node assay. In maximization tests on Polyaminopropyl Biguanide, moderate skin sensitization was observed in guinea pigs induced with 0.06% active ingredient (intradermal injection) and 20.2% active ingredient (occlusive application) and challenged with Polyaminopropyl Biguanide (20.2 % active ingredient) and a 30% solution of the ingredient (6% active ingredient) in deionized water, and moderate to strong sensitization was observed in guinea pigs induced with 0.2% active ingredient (intradermal injection) and 20.2% active ingredient (topical application) and challenged with Polyaminopropyl Biguanide (20.2% active ingredient). In another guinea pig maximization test, sensitization was not observed in guinea pigs induced with 0.15% Polyaminopropyl Biguanide (intradermal injection) and 20% (topical application) and challenged with Polyaminopropyl Biguanide (10% or 20%). In one Buehler test on Polyaminopropyl Biguanide, guinea pigs were induced with 2% active ingredient (topical application), challenged with 2% active ingredient, and rechallenged with 0.2%, 2%, and 4% active ingredient. The initial challenge with 2% active ingredient, and rechallenge with 2% and 4% active ingredient, resulted in faint erythema; rechallenge with 0.2% active ingredient produced negative results. Polyaminopropyl Biguanide (2% active ingredient) was classified as a moderate sensitizer. In another Buehler test, it was determined that the threshold for eliciting sensitization in guinea pigs was ~ 1%. Induction concentrations ranged from 0.3% to 5% and challenge concentrations ranged from 0.075% to 15%.

Very strong irritation potential, but no significant photoirritancy, was reported in a study in which male rats were tested (dermal application) with Polyaminopropyl Biguanide at concentrations of 2% and 5%. When tested at a concentration of 1%, in 26 subjects, Polyaminopropyl Biguanide was essentially non-irritating and did not induce sensitization, phototoxicity, or photoallergenicity.

In a human repeated insult patch test (HRIPT, 191 subjects), it was determined that Polyaminopropyl Biguanide (2% active ingredient) was not capable of causing primary skin irritation, but was capable of causing sensitization. In an HRIPT (115 subjects) on a neck cream containing 0.2% Polyaminopropyl Biguanide (dose/unit area = 100 µg/cm^2), results were negative for clinically relevant skin irritation and there was no evidence of allergenicity. When a leave-on product containing 0.1 % Polyaminopropyl Biguanide (dose/unit area = 25 µg/cm^2) was evaluated in an HRIPT involving 207 subjects, it was concluded that the product did not induce dermal sensitization. In an HRIPT provided by the cosmetics industry, the skin sensitization potential of a 20% Polyaminopropyl Biguanide solution (diluted with distilled water to 1% v/v prior to testing; effective concentration = 0.2%) was evaluated in an HRIPT involving 108 subjects (Asian (~2%), Bi-racial (~3%), Black (~ 23%), Caucasian (~ 33%), and Hispanic (~39%); Fitzpatrick skin types not stated). The authors concluded that Polyaminopropyl Biguanide did not induce dermal sensitization in the subjects tested. Using the results from this study, a QRA, performed by industry, yielded a NESIL of 750 µg/cm^2.

Case reports with sensitization reactions to Polyaminopropyl Biguanide (reported as an ingredient of wet wipes, contact lens cleansing solutions, wound irrigation solutions, pre-operative antiseptics, and antimicrobial foam dressings) have been reported. The prick test was used to diagnose immediate contact urticarial reactions in 44 patients with eczematous dermatitis. A positive reaction was observed in 1 patient.

Undiluted and 25% aqueous Polyaminopropyl Biguanide were severe ocular irritants when instilled into unrinsed rabbit eyes. Polyaminopropyl Biguanide (20% aqueous) induced slight inflammation, and Polyaminopropyl Biguanide (0.04% active ingredient) was non-irritating to the eyes of rabbits. In a study in which 20% aqueous Polyaminopropyl

Biguanide was instilled into human eyes and the eyes of rabbits in a temperature-controlled chamber, normal corneal morphology was observed at histological examination.

DISCUSSION

The safety of Polyaminopropyl Biguanide for use as a preservative in cosmetics is reviewed in this safety assessment. Polyaminopropyl Biguanide is an INCI name; it refers to the hydrochloride salt of an amino polymer comprising hexyl biguanide repeat units (polyhexamethylene biguanide hydrochloride (PHMB HCl)). This ingredient does not actually contain the chemical polyaminopropyl biguanide, which has a 3-carbon chain in each monomeric repeat unit. Rather, the INCI name, Polyaminopropyl Biguanide, applies exclusively to chemical polyhexamethylene biguanide, which has a 6-carbon chain in each monomeric repeat unit, and is always supplied as the hydrochloride salt. The chemical polyamino-propyl biguanide is not a cosmetic ingredient.

There was no evidence of systemic toxicity following dermal exposure to 0.4% Polyaminopropyl Biguanide, which is greater than the 0.2 % maximum reported cosmetic use concentration of this ingredient. Furthermore, the Panel noted that the dermal penetration of Polyaminopropyl Biguanide is minimal, considering that most of the compound remains in the epidermis and its distribution systemically is not a concern.

Overall, the available in vivo and in vitro genotoxicity data on Polyaminopropyl Biguanide in bacterial and mammalian cells are negative. The Panel noted that in vitro genotoxicity assays are difficult to interpret for microbial toxins such as the cytotoxic preservative Polyaminopropyl Biguanide. However, after reviewing the available data, the Panel determined that genotoxicity is not a concern. A low incidence of hemangiomas and hemangiosarcomas was reported in a study in which rats were fed Polyaminopropyl Biguanide at a dietary concentration of 2000 ppm for 2 years. The Panel noted that the vascular tumors observed in rats and mice were likely attributable to sustained hepatotoxicity (i.e., a non-genotoxic mechanism), from high exposures (i.e., doses above the maximum tolerated dose) that the Panel considered not toxicologically relevant to cosmetic use. Furthermore, the carcinogenicity study results reviewed are equivocal.

Results were classified as positive for Polyaminopropyl Biguanide in the local lymph node assay. However, interpreting the study results is hampered by the absence of a reported EC3. Additionally, the Panel noted that Polyaminopropyl Biguanide is a sensitizer at 2%, and that elicitation occurs at a much lower concentration (0.2%) in animal studies. Based on the results of these studies, the Panel expressed concerns about sensitization potential. In response, industry performed a quantitative risk assessment (QRA).

The QRA for contact dermatitis with Polyaminopropyl Biguanide in cosmetics yielded a NESIL of 1000 µg/cm^2, which supports the use of this ingredient at concentrations of ≤ 0.1%. Among the human data that were used to derive the NESIL was an HRIPT involving 26 subjects tested with 1% Polyaminopropyl Biguanide at a dose of 1000 µg/cm^2, the highest non-sensitizing dose in relation to all of the HRIPT data that were considered. However, the Panel noted the small subject population in this HRIPT (a test population of ≥ 100 subjects is usually preferred). Furthermore, in an HRIPT on a neck cream containing 0.2% Polyaminopropyl Biguanide (dose = 100 µg/cm^2) that involved more than 100 subjects, faint, pink reactions were observed at various times during challenge or during induction in some subjects, but the skin types evaluated were not sufficiently diverse. Based on these observations, the Panel suggested that the NESIL of 1000 µg/cm^2 may not be correct and determined that an HRIPT (with at least 100 subjects with a range of Fitzpatrick skin types) on Polyaminopropyl Biguanide at doses of 500 and 1000 µg/cm^2 is needed. A second QRA, performed by industry, yielded a NESIL of 750 µg/cm^2. The human data that were used to derive the NESIL are from an HRIPT involving 108 subjects (Asian (~2%), Bi-racial (~3%), Black (~ 23%), Caucasian (~ 33%), and Hispanic (~39%); Fitzpatrick skin types not stated) tested with 0.2% Polyaminopropyl Biguanide.

In addition to concerns relating to sensitization potential, the Panel also expressed concern over the existence of case reports of contact urticaria attributable to the use of Polyaminopropyl Biguanide in wound dressings. However, it was determined that contact urticaria would not be an issue in relation to cosmetic product applications after considering that this reaction was observed under the conditions of burn dressings on severely damaged skin. The Panel also determined that skin irritation potential at cosmetic use concentrations is not a concern, considering that Polyaminopropyl Biguanide (up to 1.5% active) was not classified as a primary skin irritant when applied for 24 h to the skin of human subjects.

The Panel noted the availability of clinical studies relating to child deaths in South Korea that were associated with inhalation exposure from humidifiers that had been disinfected with a humidifier disinfectant containing polyhexamethylene guanidine phosphate (often referred to as polyhexamethylene guanidine; PHMG). PHMG is not the same chemical as the cosmetic ingredient Polyaminopropyl Biguanide. However, in an abundance of caution, the Panel requested MOS calcula-tions for Polyaminopropyl Biguanide inhalation exposure from cosmetic products that are sprayed.

The most recent Council survey of maximum reported use concentrations by product category indicates that Polyaminopropyl Biguanide is no longer being used in pump or propellant hair sprays. However, products categorized as "Tonics, Dressings, and Other Hair Grooming " that contain Polyaminopropyl Biguanide at maximum use concentrations of up to 0.1% are reported in the survey, and it is possible that products included in this category are sprays. Furthermore, 2019 FDA VCRP data indicate that Polyaminopropyl Biguanide is being used in the Other Fragrance Preparations product category (use concentration data unavailable). Given the potential for inhalation exposure, CIR performed a risk assessment using the ConsExpo Web Spray Model (Consumer Exposure Model, Web version 1.0.1) The maximum concentrations of use (0.0004% in propellant hair sprays and 0.053% in pump hair sprays) included in this risk assessment to estimate the inhalation exposure concentrations of Polyaminopropyl Biguanide during the use of cosmetic spray products were based on results from a previous Council survey that were submitted (April 11, 2017) to the CIR. The ConsExpo Web Spray Model and a no observed adverse effect concentration (NOAEC) (from a 28-day inhalation study in which rats were exposed, nose only, to Polyaminopropyl Biguanide in an aerosolized water solution for 6 h/day, 5 days/week) were used in the MOS calculations for inhalation exposure. MOS values for pump hair sprays (MOS = 11) and propellant hair sprays (MOS = 200) were calculated. Exposure concentrations that would yield an MOS of 100 for propellant and pump hair sprays were also calculated.

After reviewing this risk assessment, the Panel noted that the exposure scenario in the 28-day inhalation study is not representative of consumer pump and propellant hair spray product use, and determined that data more relevant to consumer use are needed. The Panel also noted that there are potential safety issues relating to chronic ingredient inhalation exposure, potentially experienced by hairdressers, but acknowledged that evaluation of occupational safety is not within the purview of the Panel.

The Panel originally determined that the following additional data are needed in order to evaluate the safety of Polyaminopropyl Biguanide in cosmetic products:

- HRIPT on Polyaminopropyl Biguanide involving a diverse population (i.e., with a range of Fitzpatrick skin types) of 100 subjects tested with a dose of 1000 μg/cm^2 (and recommend to test at 500 μg/cm^2 as well), and
- Consumer use data on pump and propellant hair sprays, for use in determining the extent of exposure to Polyaminopropyl Biguanide during product use.

The draft final report on Polyaminopropyl Biguanide was tabled at the June 2018 Panel meeting, pending the completion and subsequent availability of the human repeated insult patch test that the Council agreed to provide. The HRIPT was provided and has been reviewed by the Panel. However, an additional insufficiency that was determined by the Panel remains:

- Consumer use data on pump and propellant hair sprays, for use in determining the extent of exposure to Polyaminopropyl Biguanide during product use.

Thus, a strategy memorandum was issued at the June 2018 Panel meeting to provide the Panel with an opportunity to review, in detail, the exposure parameters that are associated with pump and propellant spray use with this ingredient. Upon completion of this review, the Panel confirmed that the consumer use data are yet insufficient to accurately calculate an inhalation margin of safety.

CONCLUSION

The CIR Expert Panel concluded that the available data are insufficient to make a determination that Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride) is safe under the intended conditions of use in cosmetic formulations.

TABLES

Table 1. Physical and Chemical Properties of Polyaminopropyl Biguanide

Property	Value	Reference
physical form (at 20°C and 101.3 kilopascals (kPa)) and/or color	pale yellow powder	3
average molecular weight (Daltons (Da))	3686 - 4216. Molecular weight distribution in commercially used mixture: 6% is < 500, 14.1% is between 500 and 1000, and 75.8% is > 1000	3
water solubility (g/100 ml)	41 ± 1	3
other solubility (g/100 ml)	ethanol: 0.5 ± 0.08 methanol: 41 ± 1	3
relative density (at 20 ± 0.5°C)	1.20 ± 0.0025	3
melting point (°C)	78.9 - 136.3	3
boiling point (°C)	decomposes at 205-210, before boiling	3
vapor pressure (Pa at 20°C)	1.32×10^{-7}	3
log P_{ow} (at 25 ± 1°C)	-2.3	3
UV absorption (λ) (nm)	236	3

Table 2. Frequency (2019) and concentration (2017) of use according to duration and type of exposure

	# of Uses[5]	*Max Conc of Use (%)*[6]
	Polyaminopropyl Biguanide	
Totals*	**147**	*0.00001-0.2*
Duration of Use		
Leave-On	*100*	*0.00001-0.2*
Rinse-Off	*47*	*0.00025-0.1*
Diluted for (Bath) Use	*NR*	
Exposure Type		
Eye Area	27	0.01-0.2
Incidental Ingestion	1	NR
Incidental Inhalation-Spray	1; 26[a]; 30[b]	NR; 0.000023-0.1[a]
Incidental Inhalation-Powder	30[b]	NR
Dermal Contact	94	0.00001-0.2
Deodorant (underarm)	NR	0.003
Hair - Non-Coloring	12	0.000023-0.1
Hair-Coloring	NR	0.1
Nail	4	NR
Mucous Membrane	11	0.006
Baby Products	1	0.1

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may or 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 these products are sprays or powders, but it is possible the use can be as a spray or 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 – not reported

Table 3. Dermal Penetration Studies

Ingredient	Animals/Protocol	Results
[^{14}C]- Polyaminopropyl Biguanide (20.2% aqueous; specific activity = 0.88 mCi/ml)	Various concentrations applied to human skin (epidermis from abdominal skin) in diffusion cell. (dose volume = 1 ml; receptor fluid; sterile physiological saline). Receptor fluid samples collected daily for up to 15 days. Also, uptake experiment whereby 2 cm^2 rat skin disks (whole skin from flank and dorsum of male and female Wistar-derived, Alderley-Park rats) bathed in different concentrations; 5-day equilibration phase.	At concentrations of 0.4%, 1.4%, 5%, and 20%, absorption rates ($ng/cm^2/h$) through human epidermis were 8.13, 22.8, 350, and 1005, respectively. At concentrations of 0.4%, 20% (early phase - not defined), and 20% (late phase - not defined) [^{14}C]- Polyaminopropyl Biguanide, absorption rates ($ng/cm^2/h$) through rat whole skin were 131, 3695, and 11940, respectively.[12]
[^{14}C]- Polyaminopropyl Biguanide (5% solution)	Applied to skin biopsies of newborn, hairless rats and to human epidermal skin in diffusion chamber (receptor fluid not stated).	For rat skin biopsies, no skin absorption was detected up to day 5 of exposure. For human epidermal skin biopsies, low rate of penetration of ~0.09 % was noted after 24 h, and this penetration rate was from 0.11 % up to 0.81 % after adding dimethylsulfoxide (DMSO) to dosing solution.[12]
[^{14}C]-Polyaminopropyl Biguanide (0.1% w/w in aqueous micellar solution); [^{14}C]- Polyaminopropyl Biguanide (0.1 % w/w in oil-in-water emulsion)	0.1% in aqueous micellar solution and 0.1% in oil-in-water emulsion, respectively, applied (24-h exposure study) to human split-thickness skin from 4 donors (dose = 200 $\mu l/cm^2$; $\approx$ 2 mg/cm^2) in diffusion cell (receptor fluid: phosphate-buffered saline with sodium azide (0.01% w/v)). Penetration was determined directly after exposure.	Total dislodgeable dose (skin wash + tissue swab + pipette tip + donor chamber wash): 48.43% (for test substance in aqueous micellar solution) and 52.35% (for test substance in oil-in-water emulsion) of radioactivity removed during skin washing. At 24 h post-dosing, absorbed (fractionof applied dose that was measured in receptor fluid) dose was 0.03% (for test substance in aqueous micellar solution) and 0.04% (for test substance in oil-in-water emulsion). The epidermis + lower layers of stratum corneum contained 11.47% (for test substance in aqueous micellar solution) and 14.20% (for test substance in oil-in-water emulsion) of the applied dose. The dermis contained 1.56% (for test substance in aqueous micellar solution) and 1.02% (for test substance in oil-in-water emulsion) of the applied dose. Mass balance was complete: 90.93% (for test substance in aqueous micellar solution) and 98.96% (for test substance in oil-in-water emulsion) of the applied dose. Based on SCCS Notes of Guidance, one standard deviation (2.5%) was added to the absorbed amount, yielding a calculated dermal absorption value of 4.09% (1.56% + 0.03% + 2.5% = 4.09%).[3]
[^{14}C]-Polyaminopropyl Biguanide (0.3 % w/w in aqueous micellar solution); [^{14}C]- Polyaminopropyl Biguanide (0.3 % w/w in oil-in-water emulsion)	Polyaminopropyl Biguanide solutions applied to human split-thickness skin from 4 donors (dose volume = 200 $\mu l/cm^2$; application rate $\approx$ 2 mg/cm^2) in diffusion cell (receptor fluid: phosphate-buffered saline with sodium azide (0.01% w/v)). In Part 1, penetration of the 0.1% aqueous micellar solution and 0.1% in oil-in-water emulsion determined directly after 24 h exposure period. In Part 2, 24 h exposure to 0.3 % aqueous micellar solution and to 0.3% in oil-in-water emulsion followed by additional 72 h period to determine whether test compound absorbed into the skin during previous 24 h period would move from skin into the receptor fluid after the washout. All samples analyzed by liquid scintillation counting.	In 24-h study, 48.43% (from aqueous solution) and 52.35% (from oil/water emulsion) of [^{14}C]- Polyaminopropyl Biguanide-derived radioactivity removed during washing procedure (dislodgeable dose at 24 h). At 24 h post dose, absorbed (fraction of applied dose measured in receptor fluid) dose was 0.03% (0.58 ng equiv/cm^2, from aqueous solution) and 0.04% (0.72 ng equiv/cm^2, from oil/water emulsion) of the applied dose. Epidermis + lower layers of stratum corneum contained 11.47% (238 ng equiv/cm^2, from aqueous solution) and 14.20% (291 ng equiv/cm^2, from oil/water emulsion) of applied dose. Dermis contained 1.56% (32.3 ng equiv/cm^2, from aqueous solution) and 1.02% (20.9 ng equiv/cm^2, from oil/water emulsion) of applied dose. In the 72-h study, 53.33% (from aqueous solution) and 58.10% (from oil/water emulsion) of [^{14}C]- Polyaminopropyl Biguanide-derived radioactivy removed during washing procedure. At 72 h post dose, absorbed dose was 0.02% (1.29 ng equiv/cm^2, from aqueous solution) and 0.03% (1.94 ng equiv/cm^2, from oil/water emulsion) of applied dose. Epidermis + lower layers of stratum corneum contained 14.54% (972 ng equiv/cm^2, from aqueous solution) and 14.45% (921 ng equiv/cm^2, from oil/water emulsion) of applied dose. Dermis contained 1.23% (82.0 ng equiv/cm^2, from aqueous solution) and 1.46% (93.4 ng equiv/cm^2, from oil/water emulsion) of the applied dose. Absorption through skin = 1.56% (dermis contained 1.56% of applied dose) + 0.03% (absorbed dose = 0.03% of applied dose). Based on SCCS Notes of Guidance, one standard deviation (2.5%) added to absorbed amount, yielding calculated dermal absorption value of 4.09% (1.56% + 0.03% + 2.5% = 4.09%).[3]
[^{14}C]-Polyaminopropyl Biguanide (19.2% aqueous; specific activity = 38.9 mCi/g; tested at 0.3% w/w in representive cosmetic formulation)	Polyaminopropyl Biguanide formulation applied to human split-thickness skin from 5 donors in diffusion cell (receptor fluid: phosphate-buffered saline). Application up to 24 h.	At 24 h, the absorbed dose (mean: 0.17 %) was the sum of the receptor fluid (0.171 %) and the receptor wash (definition not provided, 0.01 %). Dermal delivery (3.49 %) was the sum of the absorbed dose and the portion in the epidermis (3.18 %) and the dermis (0.14 %).[12]

Table 3. Dermal Penetration Studies

Ingredient	Animals/Protocol	Results
[^{14}C]-Polyaminopropyl Biguanide (20.2% aqueous; specific activity = 1.85 GBq/732 mg)	Applied to human skin epidermal membranes in diffusion cell (receptor fluid: distilled water). Nominal concentrations up to ~200 g/l applied (not occluded) at 10 µl/cm^2. ~200 g/l also applied (occluded) at 200 µl/cm^2.	At ~200 g active ingredient/l (occluded), absorption rate 0.110 ± 0.044 µg/cm^2/h (n = 4) and absorption percentage 0.001% over 24-h. At 197 g active ingredient/l (unoccluded), absorption rate 0.009 ± 0.003 µg/cm^2/h (n = 5) and absorption percentage 0.012% over 24-h .[12]
20.2% aqueous Polyaminopropyl Biguanide (20.2% aqueous; specific activity = 1.4 MBq/mg)	Test substance warmed to 40°C and nominal concentrations up to 200 g/l applied (at volume of 10 µl/cm^2, unocluded and occluded) to human skin epidermal membranes in diffusion cell (receptor fluid: distilled water).	At a concentration of 200 g active ingredient/l (occluded for 0.5 h then unoccluded for 23.5 h), absorption rate was < 0.002 ± < 0.001 µg/cm^2/h (n = 6) and absorption percentage was < the limit of quantitation over a 24-h period. Other data for a dose of 200 g active ingredient/l (occluded) indicated an absorption rate of 0.118 ± 0.012 µg/cm^2/h (n = 5) and an absorption percentage of 0.007% over a 24-h period.[12]

Table 4. Toxicokinetics Studies

Ingredient	Animals/Protocol	Results
Polyaminopropyl Biguanide (in drinking water or in diet)	Total of 6 groups in study. Four groups of 4 male Wistar Han rats treated with ^{14}C-Polyaminopropyl Biguanide at doses of 500, 1000, 1500 mg/l (in drinking water) and 4000 mg/kg (in diet) for seven days. Additionally, a recovery study included 2 groups of 4 rats treated with ^{14}C-Polyaminopropyl Biguanide at doses of 1500 mg/l (in drinking water) and 4000 mg/kg (in diet) for five days. Dosing was followed by withdrawal of treatment for 5 days. At ~ 24 h prior to termination, 24 h urine and feces collected in metabolism cages. At necropsy, blood collected from the abdominal aorta, and the liver, kidneys, stomach and testes were removed.	Most of the ^{14}C-Polyaminopropyl Biguanide administered in the drinking water or in the diet was absorbed, and the majority was excreted in the urine, with small amounts excreted in the feces. For the 3 groups that received test substance in drinking water, ^{14}C-Polyamino-propyl Biguanide levels in feces and urine conformed to a clear dose response. The data indicated that total DPM (disintegrations per minute) consumed considerably more in rats that received Polyaminopropyl Biguanide in the diet when compared to drinking water. Low levels of radioactivity present in whole blood, with even lower levels in the plasma, liver, kidneys, stomach, and testes. DPM significantly lower in urine and feces of recovery groups. Recovery groups also had reduced amounts of radioactivity in whole blood and low levels of radiolabel remained in tissues, particularly in the kidneys. Thus, most of the Polyaminopropyl Biguanide administered in drinking water or in the dietwas absorbed, and the majority was excreted in the urine, with lesser amounts excreted in the feces.[19]
[^{14}C]-Polyaminopropyl Biguanide (20% aqueous in double deionized water; specific activity = 1.85 GBq/4 mmol)	Groups of Alpk:APfSD (Wistar-derived) rats (3 to 5/sex/group). Single oral dosage (20 mg/kg) administered by gavage. Labelled and unlabeled test substances fractionated into low, medium and high molecular weight (MW) fractions by centrifugation and also administered orally.	In bioavailability experiment (3 groups of 4 males), following single oral doses of low, medium and high MW fraction of Poyaminopropuyl Biguanide, 94.9%, 101.4%, and 96% of radioactivity, respectively, was eliminated via feces and 5.2%, 0.2%, and 0.2 % of the radioactivity, respectively, was excreted via urine. In biliary excretion experiment (3 rats), single oral dose of unfractionated test substance administered: Most of radioactivity excreted via feces over 48 h (96.8% in males; 98.9 % in females), < 3 % excreted in urine, and < 0.2% excreted in bile. In excretion and tissue retention experiments (5 males, 5 females), single oral dose of low MW fraction: Males excreted 7.8 % via urine and 94.1 % via feces; females excreted 2.6% via urine and 93.5% via feces. In tissues, highest amounts of radioactivity found in livers (0.18% of dose in males; 0.19 % of dose in females) and kidneys (0.03% of dose in males; 0.04 % of dose in females). Lower concentrations found in all other tissues investigated. Residual carcasses contained 0.22 and 0.28% of administered dose. It was noted that up to 8.5% of applied radioactivity might be considered bioavailable (sum of urinary excretion and radioactivity in tissues and residual carcass at study termination).[3]

Table 4. Toxicokinetics Studies

Ingredient	Animals/Protocol	Results
[^{14}C]- Polyaminopropyl Biguanide (20% aqueous in double deionized water; specific activity = 1.85 GBq/4 mmol)	Groups of Alpk:APfSD (Wistar-derived) rats (5/sex/group) fed diets containing either 200 ppm or 2000 ppm unlabeled ingredient for 14 days. Groups then fed single oral dose of diet incorporating [^{14}C]-labeled ingredient as 9 % suspension (4 ml/kg). High dose corresponded to 0.8 mg [^{14}C]-labeled ingredient /kg (2 MBq/kg) and, low dose, to 0.08 mg [^{14}C]-labeled ingredient/kg (0.2 MBq/kg).	Principal route of excretion of radioactivity was feces. At 200 ppm, fecal excretion of radioactivity amounted to 105 % and 109 % of administered dose for male and female rats, respectively. At 2000 ppm, percentages of fecal excretion were 106 % and 105% in male and female animals. Urinary excretion accounted for 2.1% and 2.2% of dose in males and females at the low dose and for 2.3 % and 1.8 % in males and females at the high dose. Conclusion: At 200 ppm, 4.7 % and 3.9 % of administered doses bioavailable in males and females, respectively. Bioavailability 3.0 % and 2.6 % in high dose males and females, respectively. The major parts of radioactivity were excreted during the first 24 h and excretion was virtually complete within 72 h.[12]
Radiolabeled Polyaminopropyl Biguanide	5 male Alderley Park rats. Oral dosage (dosing method not stated) rate 20 mg/kg/day over 10 days.	5.6% ± 0.35 % excreted in urine, 93.1% ± 1.58% excreted via feces and 0.2 % was exhaled.[12,18]
Radiolabeled Polyaminopropyl Biguanide	Male Alderley Park rats fed diet containing 20 ppm.	Greatest amounts of radioactivity detected in adipose tissue, followed by kidneys and livers. No radioactivity detected in brain. Urinary polymer-related material consisted of small amounts of Polyaminopropyl Biguanide oligomers with 2 cyanoguanidino end groups, as well as the trace constituents 3,3-dicyano-1,1-hexamethylenediguanidine and compound that was considered to be 1-(6-aminohexyl)-3-cyanoguanidine.[12,18]
[^{14}C]-20% Polyaminopropyl Biguanide (4.6 µCi)	5 male rats (strain not stated). Feeding with dosages of 100 mg/kg in the diet	93% of radioactivity excreted in feces within 5 days. Six percent of radioactivity found in urine, 0.6% found in bile, and 0.2% found in expired air. Findings suggested to the authors that test substance was poorly absorbed from gut and no evidence of enterohepatic recirculation.[20]
[^{14}C]-20% Polyaminopropyl Biguanide	Groups of 3 male rats (strain not stated) maintained on diet that contained 100 ppm test substance	Concentration in abdominal fat peaked at 1.2 ppm after 3 weeks and was maintained at this level for another 2 weeks on diet. After returning to normal diet, concentrations in the abdominal fat reduced to 0.3 ppm after 5 weeks. Concentration in the liver did not exceed 0.6 ppm after 5 weeks of feeding, and was reduced to undetectable levels within 3 weeks of return to normal diet. Comparable concentrations (maximum) in the kidney and heart were 0.8 ppm and 0.1 ppm. Radioactivity not detected in brain.[20]
[^{14}C]-Polyaminopropyl Biguanide	10 NMRI mice received single oral dose of 2.0 mL by gavage and were then frozen in acetone at up to 48 h post-dosing. Whole body autoradiography subsequently performed (additional details not provided).	No absorption detected[12]

Table 5. Acute Dermal Toxicity Studies

Ingredient	Animals	Protocol	Results
Polyaminopropyl Biguanide (in distilled water)	10 Sprague-Dawley rats (5 males, 5 females).	OECD Guideline 402. Clipped skin of trunk treated with single dose of 5000 mg/kg. Application site covered with semi-occlusive dressing for 24 h. 14-day observation period.	No mortalities or systemic toxicity. Hemorrhage of dermal capillaries noted at treatment sites of 8 animals one and two days after dosing. [2,12]
Polyaminopropyl Biguanide (20% aqueous)	2 groups of 20 (10 males, 10 females/group) specific pathogen free (SPF) albino rats.	Topical application of test substance at doses of 2.5 ml/kg and 5 ml/kg, respectively. Test substance applied to intact skin and spread over area of ~1 $inch^2$. Site covered with patch for 24 h. 7-day observation period. Necropsy not performed.	No mortalities.[20]
Polyaminopropyl Biguanide (20% aqueous)	4 New Zealand White rabbits (2 males, 2 females).	OECD Guideline 402. Test substance (2 ml) applied to shaved area (~150 x 130 mm) of dorso-lumbar region and held in place with occlusive dressing for 24 h. 14-day observation period.	Dermal LD_{50} > 2 ml/kg , i.e., greater than 400 mg/kg (active ingredient).[12]

Table 6. Acute Oral Toxicity Studies

Ingredient	Animals	Protocol	Results
Polyaminopropyl Biguanide (in distilled water)	6 female Sprague-Dawley rats	OECD Guideline 425. Dosed by gavage with 550 or 2000 mg/kg (dose volume = 20 ml/kg).	All 3 rats dosed with 2000 mg/kg died. No deaths at dose of 550 mg/kg. Signs of systemic toxicity in 1 animal dosed with 2000 mg/kg, but not at 550 mg/kg. Abnormalities noted at necropsy of rats that died were: hemorrhagic or abnormally red lung, dark liver, dark kidneys, hemorrhage or sloughing of the gastric mucosa, sloughing of the non-glandular epithelium of the stomach and hemorrhage of the small intestine. No abnormalities at necropsy of rats that survived 14-day observation period. LD_{50} = 1049 mg/kg.[12]
25% aqueous Polyaminopropyl Biguanide	6 rats (3 males, 3 females; strain not stated)	Single oral dose of 4000 mg/kg (equivalent to 1000 mg/kg Polyaminopropyl Biguanide) by stomach tube. 7-day observation period.	1 female rat died. Necropsy findings included generalized congestion with gastric distention and hemorrhage, and lympholysis. LD_{50} > 1000 mg/kg Polyaminopropyl Biguanide.[20]
25% aqueous Polyaminopropyl Biguanide	3 female rats (strain not stated)	Single oral dose (2 g/kg), followed by 7-day observation period.	No deaths and all organs appeared normal at necropsy.[20]
25% aqueous Polyaminopropyl Biguanide	6 rats (3 males, 3 females; strain not specified)	Single oral dose of 40000 mg/kg	1 male rat died. Severe generalized congestion with dilatation of the stomach and mucosal hemorrhage were observed at necropsy. Microscopic examination revealed gastric inflammation, ulceration, and thymic lympholysis, but no other specific lesions.[20]
20% aqueous Polyaminopropyl Biguanide	groups of Alderley Park rats (5 /sex/dose)	OECD Guideline 401. Doses up to 5000 mg/kg (dose volume = 10 ml/kg) administered by stomach tube. 14-day observation period. Necropsy not performed.	Signs of toxicity did not persist beyond day 7 or 8. LD_{50} of 2747 mg/kg (males) and 2504 mg/kg (females), corresponding to ~ 549 and ~501 mg/kg (active ingredient), respectively.[12]
Polyaminopropyl Biguanide (in deionized water)	Groups of 10 Sprague-Dawley rats	Single dose by gavage (stomach tube). Dosages ranged from 2 mg/kg to 40 mg/kg.	Administration of 25.6 mg/kg dose, i.e. 1.6 mL of 0.4% Polyaminopropyl Biguanide solution (equivalent to 6.4 x 10^3 mg/l of 0.1% solution) resulted in 50% mortality. LD_{50} = 25.6 mg/kg. Following signs observed at LD_{50}: inactivity, ataxia, diarrhea, hyperreflexia, and convulsive twitching. No histopathological lesions in heart and kidney samples. 30% of animals tested had mild hydropic changes in zone 1 of liver samples.[21]

Table 7. Acute Inhalation Toxicity Studies

Ingredient	Animals/Protocol	Results
Polyaminopropyl Biguanide (purity 99.6%) in aqueous solution	Wistar CRL:(WI) rats (groups of 10; 5/sex/test concentration). OECD Guideline 403-compliant study. Exposure levels (nose-only): 0.1, 0.3 and 0.5 mg/l (100, 300, and 50 mg/m^3) for 4 h. Mass medium aerodynamic diameters: 1.49-2.20 μm, with GSD in 1.84-2.29 μm range.	Note: In preliminary test, 2 rats exposed to 1 mg/l died. At 0.1 mg/l, no deaths, but main clinical signs observed on day 0 and included: slight to moderately labored respiration, rhonchus, decreased activity, hunched back, and increased respiratory rate. At 0.3 mg/l, all animals with slight-to-moderately labored respiration. Slight-to -severe decreased activity also observed; moderate ataxia in one animal. At 0.5 mg/l, main clinical signs included: moderately -to-severely labored respiration with noisy respiration up to gasping, increased respiratory rate, and decreased activity. At necropsy, enlargement of dark/red discolored lungs and/or dark/red discoloration of the fur at the perinasal and/or white foamy material in the trachea in all animals found dead (only in 0.3 and 0.5 mg/l groups). LC_{50} = 0.37 mg/l (370 mg/m^3)for males and females combined.[12]
20.6% w/w Polyaminopropyl Biguanide	Alpk:APfSC rats (10 rats; 5/sex). Exposed (nose-only) for 4 h to single dose of 1.76 mg/l (1760 mg/m^3) of formulation (corresponds to 0.36 mg/l (360 mg/m^3) of Polyaminopropyl Biguanide (mass medium aerodynamic diameters: 1.8-2.0 μm, with a geometric standard deviation [GSD] of 2 μm))	1 male died 3 h after exposure. Respiratory distress in all females and most males. Red mottled lungs in dead male and 2 other males on day 15. LC_{50} estimated at > 0.36 mg/l (360 mg/m^3) for Polyaminopropyl Biguanide.[12]
Polyaminopropyl Biguanide (20% aqueous in spa water)	Groups of 5 mice of the Alpk:APfCD-1 strain exposed (duration not stated) to aerosol. target concentrations of 5, 50 and 200 mg/m^3, corresponding to analyzed concentrations 11.7, 62.9 and 208 mg/m^3, respectively; median aerosol sizes (MMAD) 2.52, 3.08 and 4.31 μm.	Mean respiratory rate depression was 12% ± 4%, 20% ± 7 % and 40 ± 15% for target concentrations of 5, 50 and 200 mg/m³, respectively, and RD_{50} (concentration causing 50 % depression in respiratory rate) 264 mg/m³ (no sensory irritation) calculated.[12] The SCCS noted that this RD_{50} is outside of investigated concentration range and is of questionable reliability. SSCS also stated that the results of this study indicate that test substance should be considered a respiratory irritant.[12]

Table 8. Short-Term Toxicity Studies

Ingredient	Animals	Protocol	Results
Dermal Studies			
25% aqueous Polyaminopropyl Biguanide	3 female rats (strain not specified).	Test substance applied (amount per cm^2 not specified) to intact skin of the back, under occlusive dressing, for 3 alternating 24-h periods; i.e., each application period followed by 24-h non-treatment period.	No specific systemic effects were observed.[20]
20.2% aqueous Polyaminopropyl Biguanide	Groups of 10 (5 males, 5 females per group) rats of the Alpk:APfSD (Wistar-derived) strain	Three groups received applications (occlusive, on back) of 0 mg/kg, 20 mg/kg, 60 mg/kg, and 200 mg/kg, respectively, 6 h per day for 30 days (21 applications total). Fourth group served as the control.	No mortalities and no overt clinical signs of toxicity up to the highest dose tested. No substance-related effects on body weight, food consumption, organ weights, hematology or clinical chemistry. Gross pathology and histopathology revealed no evidence of systemic toxicity. NOAEL for systemic toxicity = 200 mg/kg/ day.[12]
20% Polyaminopropyl Biguanide (diluted with water to 0.04% active ingredient)	5 female rats of Alderley Park strain.	0.04% applied (0.1 ml) to back on alternate days for total of 6 applications. No covering or test site covered with polyethylene secured with an adhesive plaster for 24 h.	No evidence of systemic toxicity (with or without covering).[20]
20% aqueous Polyaminopropyl Biguanide	6 female albino rabbits	12,000 ppm solution (1 ml) applied (unoccluded) to the back for 23 h. Re-applied, beginning at 1 h later, for total of 21 daily applications.	No evidence of toxic effects on the skin.[12]
Oral Studies			
25% aqueous Polyaminopropyl Biguanide	14 rats (7 males, 7 females; strain not specified)	Administered orally for 21 days, initially at 1 g/kg and subsequently at 0.5 g/kg doses.	4 males and 2 females survived 21 days of dosing; toxic signs not reported. Necropsy findings: gastrointestinal irritation, severe gastric hemorrhage, ulceration, peritonitis, thymic atrophy, and generalized congestion. At microscopic examination of major organs, non-specific changes consistent with gastrointestinal inflammation.[20]
20% aqueous Polyaminopropyl Biguanide	Groups of 16 (8 males, 8 females per group) rats of the Alpk:APfSD strain.	Four groups received concentrations of 0.1, 0.5, 1, and 2 mg/ml, respectively, in drinking water for 28 days.	Dose-related loss in bodyweight/body weight gain and reduced water and/or food consumption occurring predominantly during the first days of treatment (considered a palatability effect). Increased liver weight at 1 mg/ml, decreased liver weight at 2 mg/ml, and dose-related increase in kidney weight at all dose levels. NOAEL could not be derived. LOAEL = 0.1 mg/ml.[12]
20% aqueous Polyaminopropyl Biguanide	Groups of 20 (10 males, 10 females per group) mice of the C57Bl/10JfAP/alpk strain	Four groups received concentrations of 0.1, 0.3, 0.6, and 1.2 mg/ml, respectively, in drinking water for 28 days.	One male in 0.3 mg/ml group found dead on day 13. Dose-related initial loss of body weight, reduction in food and water consumption, and continued reduction in body weight and water consumption (considered a palatability effect). Treatment-related decrease in liver weight for males given 0.6 and 1.2 mg/ml, probably associated with poor nutritional status. Because effects on body weight and water consumption at all dose levels, NOAEL could not be derived. LOAEL = 0.1 mg/ml.[12]

Table 8. Short-Term Toxicity Studies

Ingredient	Animals	Protocol	Results
Polyaminopropyl Biguanide (in drinking water and in diet)	Groups of 10 male Wistar Han [Crl:WI(Han)] rats	Three groups received Polyaminopropyl Biguanide (in drinking water) at doses of 500, 1000, and 1500 mg/l, respectively (~ 50, 100, and 150 mg/kg, respectively) for 4 weeks. A fourth group received Polyaminopropyl Biguanide (in powdered diet) at a dose of 4000 mg/kg for 4 weeks, and another group served as the control (no test substance exposure). Animals were killed at end of study and necropsied. Liver sections prepared for histopathology	Polyaminopropyl Biguanide (in drinking water) caused dehydration, clinical signs of rough coat and hunched posture, and body weight loss (all classified as severe). Across the 3 dose groups, 10 rats terminated due to severe weight loss. Remaining rats eventually adapted and began to gain weight. Absolute liver weights in all dose groups were similar to control group. Mild cetrilobular hypertrophy in liver observed in some of the rats (all dose groups). Test substance administered in diet caused statistically significant decrease in body weight and absolute liver weight. No evidence of cetrilobular hypertrophy in liver. Also, no evidence of necrosis or inflammatory lesions in the liver after dosing with test substance (in drinking water or in diet).[19]
Polyaminopropyl Biguanide (in deionized water)	Groups of 6 Sprague-Dawley rats	60-day study. Dosage (by gavage) rates: Group 1: 2 mg/kg (equivalent to 0.2 mg/l of 0.4% solution of test substance); Group 2: 8 mg/kg/day (equivalent to 0.4 mg/l of 0.4% solution of test substance); and Group 3: 32 mg/kg/day (equivalent to 1.2 mg/l of 0.4% solution of test substance). Control group received deionized water	No mortalities. Signs of systemic toxicity noted 2 days after dosing in 1 animal dosed with 32 mg/kg, exhibiting lethargy, ataxia, decreased respiratory rate, labored respiration, ptosis and tiptoe gait. 50% of rats dosed with 32 mg/kg had either mild hepatocyte cytolysis or feathery degeneration with or without increased lymphocyte infiltration. No visible gross pathological changes in heart, liver and kidney samples. At 2 and 8 mg/kg, mild toxicity in 50% of liver samples and 50% of kidney samples examined microscopically. At 32 mg/kg, mild toxicity in 50% of liver samples examined microscopically (mild kidney toxicity in 1 rat). In control group, mild toxicity (at microscopic examination) in kidneys of 30% of animals.[21]
Inhalation Studies			
19.2% aqueous Polyaminopropyl Biguanide	Groups of 10 (5 males, 5 females per group) rats of the Alpk:APfSD (Wistar-derived) strain	Three groups were exposed (nose-only) to concentrations of 0.025mg/m^3, 0.25 mg/m^3, and 2.5 mg/m^3, respectively, 6 h per day (5 days per week; 28 days total). For satellite groups (0, 0.025, and 2.5 mg/m^3) the recovery period was 13 weeks. Target air concentrations of aqueous Polyaminopropyl Biguanide were 0.0239 mg/m³ (MMAD range: 0.32-1.30 μm), 0.257 mg/m³ (MMAD range: 0.48-5.06 μm) and 2.47 mg/m³ (MMAD range: 0.67-1.67 μm)	No treatment-related deaths or clinical signs up to 2.5 mg/m³. No toxicologically significant changes in hematology or blood clinical chemistry parameters. Lung weights slightly elevated for males and females exposed to 2.5 mg/m³; thymus weights elevated in males only at 2.5 mg/m³. No macroscopic treatment-related findings observed at post-mortem examination. Squamous metaplasia seen in the larynx of males and females at 0.25 and 2.5 mg/m³, and tracheal inflammation in males and females at 2.5 mg/m³. Pneumonitis and bronchitis in the lung in males and females exposed to 2.5 mg/m³, at end of exposure period and recovery period. NOAEC = 0.0239 mg/m³.[12]

Table 8. Short-Term Toxicity Studies

Ingredient	Animals	Protocol	Results
20% aqueous Polyaminopropyl Biguanide	Groups of 8 (4 males, 4 females per group) SPF albino rats of the Alderley Park strain.	Five groups exposed (nose-only) to 0.025mg/m^3, 0.25 mg/m^3, and 2.75 mg/m^3, 12.5 mg/m^3, and 26 mg/m^3, respectively, 6 h per day (5 days per week; 3 weeks total). Exposure to atmospheres of respirable particles (MMAD < 7 μm)	At 0.25 mg/m^3: 1 rat died and signs of moderate nasal irritation and tachypnea in this group. Histopathological examination revealed: slightly-to-moderately severe pneumonitis; thymus glands of 3 male and 3 female rats with reduction in cortical thickness and depletion of lymphocytes. Patchy loss of cilia in tracheal epithelium of 3 rats. At 2.75 mg/m^3, signs of nasal irritation and dyspnea. Histopathological examination revealed a moderate to severe pneumonitis. Thymus glands with severe depletion of lymphocytes and loss of normal architecture. At 12.5 and 26 mg/m^3, all rats died. Severe nasal irritation and dyspnea at 12.5 mg/m^3. NOAEC = 0.025 mg/m^3.[12]

Table 9. Subchronic Toxicity Studies

Ingredient	Animals	Protocol	Results
		Oral Studies	
25% Polyaminopropyl Biguanide	Young adult SPF Wistar rats (25 males, 25 females/group)	90-day dietary study. Concentrations of 0 ppm, 2500 ppm, and 5000 ppm in diet.	No deaths during the 90-day feeding period. No gross abnormalities or abnormalities in hematological parameters. No remarkable changes in organ/body weight ratios. Microscopic examination revealed unusual degree of iron pigment in liver cells and in Kupffer cells for females fed 5000 ppm in the diet. Iron pigment not observed in liver of rats fed 2500 ppm in the diet (detailed histopathological results not included). Not possible to establish NOAEL.[20]
25% aqueous Polyaminopropyl Biguanide	Alderley Park Wistar Rats (number of animals not stated)	90-day dietary study. Concentrations of 0, 625 and 1250 ppm active ingredient	No mortalities. At 1250 ppm, deposits of an iron-pigment in liver (in hepatocytes and Kupffer cells) observed in female rats. No toxicity findings after feeding with 625 ppm.[12]
25% aqueous Polyaminopropyl Biguanide	Three groups of Beagle dogs (inbred strain from Alderley Park, Cheshire; 4 males, 4 females per group)	90-day dietary study. Concentrations in diet of 0 ppm, 5500 ppm (1375 ppm active ingredient as dietary admixture), and 11000 ppm (2750 ppm active ingredient as dietary admixture)	No mortalities or signs of systemic toxicity or other adverse effects in treated or control animals. Results for hematological parameters and clinical blood chemistries unremarkable. Liver function test (for bromsulphthalein [BSP] retention) results indicated no test substance-related effect. No significant treatment-related variations in organ/body weight ratios or test substance-related gross pathology. Microscopic examination revealed slight hemosiderin deposits in 2 of 4 males fed 11000 ppm. NOAEL = 5500 ppm.[12,20]
20.2% aqueous Polyaminopropyl Biguanide	Wistar -derived rats (Alpk:APfSD strain), 4 rats/sex/group	90-day dietary study. Concentrations: 0, 1000, 2000, 4000, and 6000 ppm active ingredient (corresponding to approximately 0, 83.9, 171.5, 373.0, 556.1 mg/kg/ day active ingredient in males and 92.3, 192.9, 409.8, 617.4 mg/kg /day active ingredient in females).	Beginning at 2000 ppm, increased hemoglobin and hematocrit in males. Kidney was target organ. Renal functional change in form of decreased urine volume and increased specific gravity at 2000, 4000 or 6000 ppm animals (more marked in males). Treatment-related increase in kidney weight apparent for males at 4000 ppm or 6000 ppm (toxicological significance not determined). NOAEL = 1000 ppm (corresponding to 83.9 mg/kg bw/day in male rats and 92.3 mg/kg /day in female rats).[12]
20.2% aqueous Polyaminopropyl Biguanide	C57Bl/10JfCD-1 mice, 4 mice/sex/group	90-day dietary study. Concentrations: 0, 1000, 2000, 4000 ppm active ingredient (corresponding to about 0, 162, 328, 736 mg/kg/day active ingredient in males and 0, 224, 445, 963 mg/kg/day active ingredient in females) and 6000 ppm active ingredient (mg/kg/day dose not stated)	The exposure of mice to 6000 ppm was terminated due to high mortality. Marked effects on body weight gain and marked toxicity (specific effects not stated) at 4000 ppm. No treatment-related effects on liver and kidney weights and no gross or histopathological findings. NOAEL = 1000 ppm (corresponding to 162 mg/kg/day in male mice and 224 mg/kg/day in female mice) as NOAEL.[12]
20% aqueous Polyaminopropyl Biguanide	Mice of the C57BL/10JfAP/Alpk strain. 2 groups of 10 males and 10 females (1 test and 1 control)	90-day drinking water study. Test group dosed with 0.1 mg/ml during 1st week, 0.3 mg/ml during 2nd week, and 0.3 mg/ml from 3rd week until study termination.	Reduction in body weight gain and dose-related reduction in water consumption. No treatment-related macroscopic post-mortem findings.[3]

Table 10. Chronic Toxicity Studies

Ingredient	Animals	Protocol	Results
		Dermal Study	
Polyaminopropyl Biguanide	Four groups of SPF Alderley Park mice (50 males, 50 females/group)	Test substance (0.3 ml) administered daily at following doses 5 days per week for 80 weeks: 0 (in ethanol), 0.6 mg (0.2% test substance in ethanol), 6.0 mg (20% test substance) and 30 mg (10% test substance in ethanol).	High mortality rate (75% in males and females) in 30 mg/day group at the end of the study, compared to ~ 30% in other groups. Exophthalmos observed throughout study; more severe in 30 mg group. Keratitis in many of affected animals. At week 80, exophthalmos incidence of 10% (6% for males and 13% for females). Clinical and histological examination of eyes and orbital contents revealed no evidence of pathological abnormalities. Gross and microscopic examinations of the thyroids normal in large majority of cases. Tissues from other organs were also examined microscopically. The SCCS noted that the highest dose administered in this study exceeded the maximum tolerated dose, and that the NOAEL was 0.6 mg/mouse/day (15 mg/kg/day).[3,20]
		Oral Studies	
20.2% aqueous Polyaminopropyl Biguanide	Groups of 128 rats of the Alpk:APfSD (Wistar-derived) strain (64 males, 64 females per group)	Test substance administered in diet daily (for 104 weeks) at concentrations of 0 ppm, 200 ppm, 600 ppm, and 2000 ppm (corresponding to 0, ~12.1, ~36.3, and ~126.1 mg/kg/day (males) and 0, ~14.9, ~45.3, and ~162.3 mg/kg/day (females)	No treatment-related clinical signs, ophthalmoscopic findings, or effects on any hematological or urinalysis parameters throughout study. Slightly raised plasma alkaline phosphatase activity, predominantly in females receiving 2000 ppm, and a slightly increased incidence of hepatocyte fat and spongiosis hepatitis in males (at 2000 ppm). NOAEL = 2000 ppm., corresponding to 36 and 45 mg/kg/day for males and females, respectively. [12]
20% Polyaminopropyl Biguanide	Four groups of adult Beagle dogs (4 males, 4 females per group)	26-week study. Dietary concentrations of 0, 500, 1500, and 4500 ppm, respectively.	Treatment-related histopathological changes reported for sections of the liver and kidneys from dogs fed 4500 ppm: bile stasis, focal hepatocellular degeneration and necrosis, and focal proximal tubular nephrosis. Thus, feeding with dietary concentrations of 1500 ppm and 4500 ppm produced concentration-related hepatotoxicity and nephrosis.[20]
20.2% aqueous Polyaminopropyl Biguanide	Groups of 8 Beagle dogs (4 males, 4 females per group)	Test substance administered daily (for 1 year) at dietary concentrations of 0 ppm, 300 ppm, 1500 ppm, and 4500 ppm (corresponding to 0, ~11, ~54, and ~169 or ~108 mg/kg/day) up to weeks 11 or 12, and the concentration was reduced to 3000 ppm thereafter.	Males dosed with 4500 ppm had marked reddening/peeling of scrotal skin, loss of appetite, body weight loss and/or indications of liver impairment in the form of elevated plasma alanine transaminase and/or aspartate transaminase activities. Low testes weight apparent in male survivor in 3000 ppm group. Treatment-related histopathological findings in skin (dermatitis of scrotum, chin and limbs) as well as in the liver, kidney (males only) and testes of animals that received 4500/3000 ppm. No treatment-related histopathological changes in dogs of 300 or 1500 ppm group. NOAEL = 1500 ppm.[12]

Table 10. Chronic Toxicity Studies

Ingredient	Animals	Protocol	Results
20% Polyaminopropyl Biguanide	Groups of 30 male and 60 female SPF mice of the Alderley Park strain	Lifetime feeding study. 4 groups fed dietary concentrations of 0 ppm, 100 ppm, 200 ppm, and 1000 ppm, respectively, for 1 week prior to pairing and during mating. Feeding of females continued throughout pregnancy and lactation. All offspring were weaned at 3 weeks of age, and at 5 weeks of age, 50 males and 50 females were selected from each group. Offspring fed same diets as parents throughout study. Study terminated at 97 weeks after selection of the offspring, i.e., when the overall mortality had reached 80%.	After 18 months, mortalities in all groups comparable, though higher in males than in females. Increased liver weight in males and females fed 1000 ppm. For males fed 1000 ppm, mean spleen weight significantly higher when compared to controls; based on macroscopic examination of tissues, finding not test substance-related. Other non-neoplastic findings (specific findings not stated) also not test substance-related.[20]
20% Polyaminopropyl Biguanide	Four groups of SPF rats of the Alderley Park strain (60 males, 60 females per group)	122-week study. Dietary concentrations of 0 ppm, 200 ppm, 1000 ppm, and 2000 ppm, respectively. Study terminated at 124 weeks, i.e., when 80% mortality occurred in control group and in experiment overall	Cumulative mortality comparable between control and treatment groups. Slight anemia at 104 weeks in female rats of 2000 ppm group. Other hematological parameters comparable among groups. At 52 weeks, females fed 2000 ppm had increased kidney weight. Increased adrenal weight reported for males and females of 1000 ppm and 2000 ppm groups. No treatment-related findings at necropsy. At 52 weeks, 104 weeks, and study termination, microsocpic examination revealed increase in incidence of histiocyte conglomerates in mesenteric lymph nodes of female rats fed 1000 ppm and 2000 ppm. The NOEL (for histopathologic changes) = 200 ppm.[20]
Polyaminopropyl Biguanide	Strain not specified	Chronic toxicity study (protocol not described).	NOEL = 200 mg/kg/day.[30]
Polyaminopropyl Biguanide	Strain not specified	2-year chronic toxicity study (protocol not detailed). Dosage weight: 100 mg/kg/day	No adverse effects.[30]

Table 11. Exposure Concentrations and Margins of Safety (MOSs) for Hair Spray Products Calculated using the ConsExpo Web Model (ver. 1.0.1).[25]

Exposure Scenario Assumptions (spraying towards person) and Spray Parameters not Specific to Spray Type[a]			
Direction of spraying:	Towards exposed person	Room ventilation rate:	0.2/hr[b]
Exposure duration/event:	5 min	Cloud Volume:	0.0625 m^3
Room volume:	10 m^3	Density non-volatile:	1.5 g/cm^3
Room height:	2.5 m	Inhalation cut-off diameter:	15 µm

Spray Parameters and estimates of Exposure Concentrations and MOSs Specific for Spray type							
Cosmetic spray type	Spray duration (sec)	Weight fraction of Polyaminopropyl Biguanide (%)	Mass generation rate (g/sec)[e]	Airborne fraction (g/g)[e]	Initial median aerosol droplet diameter (µm) (Coefficient of Variation)[e]	Mean event Polyaminopropyl Biguanide exposure concentration (mg/m^3)[g]	MOS (NOEC[g]/Mean event exposure concentration)[h]
Propellant hair spray	14.4[a]	0.0004[d]	0.4	0.2	46.5 (2.1)	0.00012	200
	14.4[a]	0.00084	0.4	0.2	46.5 (2.1)	0.00024	100
Pump spray	14.4[c]	0.053[d]	0.1[f]	0.02[f]	2.7 (0.73)[f]	0.0022	11
	14.4[c]	0.0058	0.1[f]	0.02[f]	2.7 (0.73)[f]	0.00024	100
Propellant deodorant spray	10.2[a]	0.000055	0.45	0.9	8.3 (0.84)	0.00024	100

[a]default assumptions and values published by RIVM (Rijksinstituut voor Volksgezondheid en Milieu – Dutch National Institute for Health and Environment.[26,28]

[b]default room ventilation rate specified in REACH guidance (Chapter R.15 Consumer exposure estimation, ECHA 2012), as noted in RIVM report.[28]

[c]spray duration for pump hair sprays assumed to be the same as the default for propellant hair sprays

[d]concentrations of use reported in PCPC Industry survey dated 11 April 2017.[6]

[e]mass generation rate, airborne fraction, and initial aerosol droplet diameters default assumptions published by RIVM.[24]

[f]spray parameter default values developed for pump toilet water sprays assumed adequate for calculating conservative estimates of exposures from pump hair sprays

[g]exposure concentration averaged over the exposure duration

[h]no observed adverse effect concentration (NOEC) = 0.024 mg/m^3 from study; rats exposed 6 h/day, 5 day/week for 28 days to aqueous aerosols (mass median aerodynamic diameter [MMAD] = 0.32-1.30 µm.[3]

Table 12. Developmental and Reproductive Toxicity Studies

Ingredient	Animals	Protocol	Results
20.2% aqueous Polyaminopropyl Biguanide	Groups of 52 rats (26 males, 26 females) of the Alpk:APfSD (Wistar-derived) strain.	Four groups received dietary concentrations of 0, 200, 600, and 2000 ppm (corresponding to 0, ~23-24, ~70-71, and ~239-249 mg/kg/day in (males), and to 0, ~25-26, ~77-79, ~258-270 mg/kg/day (females) through 2 successive generations (including a 10-week pre-mating period).	No evidence of an effect on reproductive parameters or on offspring growth and development at concentrations up to 2000 ppm. Systemic, parental NOAEL = 600 ppm. NOAEL for reproductive and offspring effects = 2000 ppm.[12]
20.2% aqueous Polyaminopropyl Biguanide	Groups of 20 female New Zealand White rabbits	Four groups received oral dosages (by gavage) of 0, 10, 20, and 40 mg/kg/day on gestation days 8 through 20.	No effect on the number of fetuses, growth or survival in utero, except a slight increase in pre-implantation loss observed at 40 mg/kg/day (21.8 ± 25.6 vs 13.1 ± 15.2 in controls) and a significant increase in postimplantation loss at 20 mg/kg/day (11.4 ± 19.7 % vs 6.1 ± 8.4 % in controls) attributed to an increase in early intrauterine deaths. No evidence of teratogenicity. Percentage of fetuses with unossified 5th sternebrae or with fused 4th and 5th sternebrae increased at 40/mg/kg/day, but results not considered test substance-related. Maternal NOAEL = 20 mg/kg/day. Developmental NOAEL = 40 mg/kg/day.[12]
20% aqueous Polyaminopropyl Biguanide	Groups of 30 Sprague-Dawley rats (10 males, 20 females per group).	Four groups received dietary concentrations of 0, 200, 650, and 1300 ppm (dietary levels adjusted for 20% active ingredient) during the 9-week pre-mating period and until the 3rd generation.	Evaluations of the various reproductive indices, sex ratios, and body weight data of fetuses taken by Caesarean section and the offspring maintained through weaning revealed no meaningful differences between the control and treated groups. Necropsy of weanlings did not reveal any compound-related gross pathology. No findings indicative of embryotoxicity or teratogenicity. NOAEC = 1300 ppm.[12,20]
20% aqueous Polyaminopropyl Biguanide	Groups of 20 rats of the Alderley Park strain	Four groups received dietary concentrations of 0, 200, 1000, and 2000 ppm (expressed as active ingredient; corresponding to approximately 0, 13, 54, and 112 mg/kg /day) on gestation days 1 through 20 (mating day considered gestation day 0).	No mortalities and no adverse clinical effects in any group. No dose-related effects observed on fetal or litter weights. Increase in extra ribs at 2000 ppm considered consequence of maternal toxicity. No further test substance-related effect on fetal morphology, including ossification of the skeleton, in any of the test groups. Maternal NOAEC = 200 ppm. Developmental NOAEC = 1000 ppm.[12]
20% aqueous Polyaminopropyl Biguanide (in 0.5% aqueous polyoxyethylene(20)sorbitan monooleate)	Groups of 47 to 49 SPF mice of the Alderley Park strain mated (matings yielded groups of 21 pregnant mice). Group of 25 mice served as the control. Because of the poor fertility rate, the mating of more than 40 mice per group occurred in order to yield at least 21 pregnant mice per group.	Four groups received (by gavage) 10, 20, or 40 mg/kg/day (expressed as active ingredient) on gestation days 6 through 15 (mating day considered gestation day 0). Total volume administered = 0.1 ml per 10 g of body weight.	No mortalities or test substance-related adverse clinical signs. Gestational parameters such as implantation sites, pre- and post implantation loss, litter size and weight, resorptions not influenced by test substance at any dose. 21 fetuses with external abnormalities that were not test substance-related. Indications of slight retardation of ossification from examination of forelimb and hindlimb digits and numbers of caudal vertebrae at 20 and 40 mg/kg/day. Maternal NOAEL = 40 mg/kg/day. Developmental NOAEL = 10 mg/kg/day.[12,29]
0.04% Polyaminopropyl Biguanide	Animal strain not specified.	Oral dosing (test protocol not included)	Embryotoxic at 32 mg/kg/day.[30]
Polyaminopropyl Biguanide	Rats (number and strain not specified)	Rats dosed orally with 100 mg/kg/day	Embryotoxic.[30]
Polyaminopropyl Biguanide	Rats (number and strain not specified)	Rats dosed intraperitoneally with 10 mg/kg/day	Teratogenic.[30]
20% aqueous Polyaminopropyl Biguanide	Groups of 8 (4 males, 4 females per group) SPF albino rats of the Alderley Park strain	In short-term toxicity study, 5 groups exposed (nose-only) to concentrations of 0.025, 0.25, 2.75, 12.5, and 26 mg/m^3, respectively, 6 h per day (5 days per week; 3 weeks total).	At 0.25 mg/m^3, degeneration of a few seminiferous tubules in testis of 1 male rat.[12]

Table 13. Genotoxicity Studies

Ingredient	Strain/cell type	Assay	Dose/Concentration	Results
		In Vitro		
20% aqueous Polyaminopropyl Biguanide	*Salmonella typhimurium* strains: TA98, TA100, TA1535, TA1537, and TA1538	Ames test, with and without metabolic activation	333.3 mg (333,300 µg) per plate	Toxic at 333.3 mg per plate, particularly in strains TA98, TA100, and TA1535. Weakly genotoxic in strain TA1538 without metabolic activation.[12]
20% aqueous Polyaminopropyl Biguanide	*Salmonella typhimurium* strains: TA98, TA100, TA1535, TA1537, and TA1538	Ames test, with and without metabolic activation	Doses up to 500µg/plate	Non-genotoxic.[12]
19.6% aqueous Polyaminopropyl Biguanide (in DMSO)	*Salmonella typhimurium* strains: TA98, TA100, TA1535, TA1537, and TA1538.	Ames test, with and without metabolic activation	Doses up to 5000 µg/plate	Non-genotoxic, with or without metabolic activation in all but one strain. In strain TA98, negative results without metabolic activation, but slight responses (2.1 x background) observed with metabolic activation. Non-genotoxic.[12]
20% aqueous Polyaminopropyl Biguanide	L5178Y TK+/- mouse lymphoma cells	Mouse lymphoma assay, with and without metabolic activation	Concentrations up to 100 µg/ml	At 50 and 100 µg/ml, cytotoxicity higher than that of positive controls. Non-genotoxic.[12]
20% aqueous Polyaminopropyl Biguanide	P388 (*tk*+/-) mouse lymphoma cell line	Mouse lymphoma assay, with and without metabolic activation	Concentrations up to 2000 µg/ml	2000 µg/ml was cytolethal and clear cytotoxicity noted at 1000 µg/ml, with and without metabolic activation. Non-genotoxic.[12]
19.6% aqueous Polyaminopropyl Biguanide	Cultured human peripheral blood lymphocytes from 2 volunteers	Micronucleus test	Concentrations up to 50 µg/ml without metabolic activation and concentrations up to 250 µg/ml with metabolic activation.	No chromosomal aberrations. Non-genotoxic.[12]
		In Vivo		
19.6% aqueous Polyaminopropyl Biguanide	1000 polychromatic erythrocytes (from C57BL/6JfCD-1/Alpk mice) scored for presence of micronuclei	Micronucleus test.	Groups of 10 mice. Test substance administered (single dose, by gavage) at 0, 250, and 400 mg/kg (dosage volume = 10 ml/kg).	Non-clastogenic.[12]
19.6% aqueous Polyaminopropyl Biguanide	Alpk:APfSD (Wistar-derived) rat hepatocyte cultures exposed to [^{3}H]-thymidine	Unscheduled DNA synthesis assay	Test substance administered (single dose, by gavage) to 2 - 3 males per dose at 0, 750, and 1500 mg/kg (dosage volume = 10 ml/kg) for 4 h or 12 h.	No induction of unscheduled DNA synthesis.[12]

Table 14. Carcinogenicity Studies

Ingredient	Animals/Cells	Protocol	Results
		In Vitro Studies	
20% aqueous Polyaminopropyl Biguanide (in DMSO)	Baby hamster kidney fibroblasts (BHK21/C13)	Cell transformation assay, with metabolic activation. Test substances dose range of 0.25 - 2500 µg/ml and 25 -3000 µg/ml in separate experiments.	Cytotoxicity at 250 µg/ml and greater. No difference in number of transformed cell colonies between test and negative control cultures. Test substance did not induce cell transformation.[12]
Polyaminopropyl Biguanide (up to 1 ppm)	RAW 264.7 mouse macrophages co-cultured with SVEC4-10 mouse endothelial cells.	Experiment 1: Preactivaton of macrophages with Polyaminopropyl Biguanide (0, 0.75, and 1 ppm) or lipopolysaccharide (LPS) and/or co-culture in the presence of Polyaminopropyl Biguanide. Endothelial proliferation analyzed by incorporation of bromodeoxyuridine (BrdU). Experiment 2 summarized below.	Polyaminopropyl Biguanide had no direct effect on liver endothelial cell proliferation and did not potentiate cell proliferation induced by LPS-activated macrophages.[3]
Polyaminopropyl Biguanide (up to 1 ppm)	RAW 264.7 mouse macrophages	Reactive oxygen species (ROS) assay. Macrophages cultured with Polyaminopropyl Biguanide (0, 0.75, and 1 ppm). Production of ROS in macrophages detected by measurement of fluorescence intensity after addition of dihydrorhodamine and by evaluation of tumor necrosis factor (TNF) α and interleukin (IL)-6 in cell culture medium, as quantified by the enzyme-linked immunosorbent assay (ELISA).	No activation of macrophages.[3]
		Dermal Studies	
Polyaminopropyl Biguanide (up to 20% aqueous)	Four groups of SPF mice (50 males, 50 females/group) of the Alderley Park strain (Alpk:APfCD-1strain)	Test substance (0.3 ml) was administered dermally (non-occluded) at the following doses 5 days per week for 80 weeks: 0 (in ethanol), 0.6 mg (0.2% Polyaminopropyl Biguanide in ethanol), 6.0 mg (20% Polyaminopropyl Biguanide and 30 mg (10% Polyaminopropyl Biguanide in ethanol). The 0, 0.6, 6, and 30 mg doses corresponded to 0, ~15, ~150, and ~750 mg/kg/day.	Incidence of clinically-observed skin tumors: control (1 male), 6 mg of 20% concentration (2 males), and 30 mg/day of 10% concentration (1 male and 2 females). Liver + kidney tumors contributed more than 50% of total for the 30 mg/day group. Total number of kidney + liver tumors: control (5 males, 2 females), 0.6 mg/day group (4 males, 4 females), 6 mg/day group (5 males, 4 females), and 30 mg dose group (16 males, 7 females). Statistically significant increase in incidence of liver tumors (4 in controls and 10 in 30 mg/day group; statistically significant (Chi square, 1% level) only in case of liver tumors of endothelial origin (both benign and malignant; 2 in controls and 6 in 30 mg/day group). Many growths observed microscopically classified as moderate to severe hepatitis at histopathologic examination. Liver necrosis in all dose groups. Test substance classified as hepatocarcinogen in mice dosed with 30 mg/day.[20]
		Oral Studies	
20.2% aqueous Polyaminopropyl Biguanide	Groups of 110 mice (55 males, 55 females) of the C57Bl/10J/CD-1 Alpk strain.	4 groups received dietary concentrations of 0, 400, 1200, and 4000 ppm (0, ~55, ~167, and ~715 mg/kg/day, respectively) for 2 years	Mortalities increased in the 3000 ppm group; hemangiosarcoma was most frequent factor causing death. At 4000 ppm, increases in squamous cell carcinomas of the recto-anal junction (5 males and 8 females); also, in 1 male, 1 adenocarcinoma at same site and a squamous cell carcinoma of the skin adjacent to the anus. Gall bladder papillomas in males at 4000 ppm. Highest incidence of treatment-related tumors at 4000 ppm was in neoplasms of vascular origin (i.e., hemangiosarcomas, common tumor in C57Bl/10J/CD-1 Alpk mice). Hemangiosarcoma and hemangioma incidences (in liver and other sites) at 4000 ppm were above control incidence; findings statistically significant in male mice only. Small increased incidence of hemangiosarcomas in 1200 ppm group. Some evidence of carcinogenicity.[12]

Table 14. Carcinogenicity Studies

Ingredient	Animals/Cells	Protocol	Results
20.2% aqueous Polyaminopropyl Biguanide	Groups of 30 male and 60 female SPF mice of the Alderley Park strain	Four groups fed diets containing 0, 500, 1000 or 5000 ppm (equivalent to 0, 100, 200 and 1000 ppm active ingredient, respectively) for 1 week prior to pairing and during mating. Offspring fed same diets as parents throughout experiment	Study terminated when overall mortality reached 80 % at 97 weeks (dosing time after selection of offspring). High mortality due to fighting of males. No treatment-related (non-neoplastic or neoplastic) increases in histopathologic findings. However, regarding vascular tumors of concern, there were some animals with hemangiomas or hemangio-sarcomas in the liver or at other sites. Number of tumor-bearing animals: control (39 [18 males, 21 females]), 100 ppm (36 [16 males, 36 females]), 200 ppm (42 [17 males, 25 females]), and 1000 ppm (44 [23 males, 21 females]). Liver neoplasms observed only in male mice and incidence was: control (2/39 =5.1%), 100 ppm (2/36 = 5.5%), 200 ppm (5/42 = 11.9%), and 1000 ppm (9/44 = 20.9%). Dose-related tumor incidence in liver.[20] According to the SCCS, these data were considered to be of low reliability due to high mortality.[12]
20.2% aqueous Polyaminopropyl Biguanide	Groups of 60 male and 60 female rats of unspecified strain	4 groups fed at concentrations of 0, 200, 1000 and 2000 ppm	Study terminated at 124 weeks, due to 80% mortality. 2 outbreaks of infection noted. Long-term exposure unrelated to carcinogenic and other effects. Hemangiomas at week 52 in 1/12 male rats (mesenteric lymph nodes) fed 200 ppm and 1/12 male rats fed 200 ppm (cervical lymph nodes). Hemangiomas at week 104 in 2/12 males fed 1000 ppm (mesenteric lymph nodes) and in 1/8 females fed 200 ppm (uterus). Hemangiosarcoma at week 104 in 1/21 males fed 2000 ppm (mesenteric lymph nodes). Hemangiomas at week 124 (end of study) in 1/20 males fed 1000 ppm (mesenteric lymph nodes) and in 1/19 males fed 2000 ppm (spleen). No vascular tumors in controls. Study of questionable reliability due to infections and < 50% survival at end of study.[12]
20.2% aqueous Polyaminopropyl Biguanide	Wistar rats (20 males, 20 females)	Oral dosage rates 100 mg/kg/day for 25 months	No findings of clinically apparent tumors. Testicular tumor in 1 male. Mammary tumor (benign adenofibroma) in 1 female. Classified as inadequate study for various reasons, including that only 20 rats per sex, no controls, and only 1 dose tested.[20]
20% Polyaminopropyl Biguanide	SPF rats (60 males, 60 females per group) of the Alderley Park strain	Four groups fed dietary concentrations of 0, 200, 1000, and 2000 ppm, for 122 weeks.	Study terminated at 124 weeks, i.e., due to 80% mortality overall. Accumulative incidence of animals with suspected mammary tumors was comparable between control and treatment groups. Same was true for the number of tumor-bearing animals and the site and incidence of tumors. Non-oncogenic.[20]
Polyaminopropyl Biguanide	Groups of 5 male C57BI mice	Concentrations of 0, 100, 200, 400, 1200, and 4000 ppm in diet for 7, 14, or 28 days. Immunohistochemical detection of BrdUin mouse liver used to quantify cell proliferation in liver endothelial cells. Liver hepatotoxicity assessed by measuring alanine aminotransferase and aspartate aminotransferase in plasma of animals killed	Polyaminopropyl Biguanide increased cell proliferation in concentration-related manner at 1200 ppm and 4000 ppm. Cell proliferation also increased at 1200 ppm after feeding for 14 days. Plasma endotoxin, known activator of macrophages, increased at 1200 and 4000 ppm (after feeding for 28 days) and at 100 and 200 ppm (after feeding for 14 days).[3]
Polyaminopropyl Biguanide	Groups of Wistar- derived Alpk:ApfSD rats	Concentrations of 0, 200, 600 or 2000 ppm (approximately equivalent to 0, 12.1, 36.3 and 126.1 mg/kg/day in males and 0, 14.9, 45.3 and 162.3 mg/kg/ day in females) in diet for 2 years.	Hemangioma (2/64 males and 2/64 females) and hemangiosarcoma (1/64 females) in the liver of one animal fed 2000 ppm.[31]

Table 14. Carcinogenicity Studies

Ingredient	Animals/Cells	Protocol	Results
Polyaminopropyl Biguanide (in drinking water or in the diet)	Groups of rats (strain and number per group not stated).	In a 2-year study, Polyaminopropyl Biguanide (in drinking water) administered to groups of rats (strain and number per group not stated) at concentrations of 500 mg/l, 1000 mg/l, and 1500 mg/l. Test substance also administered (in diet) to group of rats at a dose of 4000 mg/kg.	Liver identified as main target organ for Polyaminopropyl Biguanide. Hepatocellular tumors induced at concen-trations of 1000 mg/l and 1500 mg/l, but not at a concentration of 500 mg/l. Tumor incidence greater in male rats than in female rats. Tumors had prominent vascular changes (changes in test and control rats) that resulted in initial misclassification as vascular tumors. Vascular changes in tumors later classified as ectasia. All tumors reclassified as hepatocellular foci, adenomas, and carcinomas. Administration of Polyaminopropyl Biguanide in diet did not cause increase in hepatocellular tumors.[19] The following experiments performed to determine the mode of action (MOA) of Polyaminopropyl Biguanide.
Polyaminopropyl Biguanide (in drinking water and in diet)	Groups of 10 male Wistar Han [Crl:WI(Han)] rats	Three groups received Polyaminopropyl Biguanide (in drinking water) at doses of 500, 1000, and 1500 mg/l, respectively (~ 50, 100, and 150 mg/kg, respectively) for 4 weeks. A fourth group received Polyaminopropyl Biguanide (in powdered diet) at a dose of 4000 mg/kg for 4 weeks, and another group served as the control (no test substance exposure). Animals were killed at end of study and necropsied. Liver sections prepared for histopathology and immunohistochemistry was performed on additional liver sections and a section of the duodenum. To determine the mode of action (MOA) for liver tumor induction (i.e., in 2-year carcinogenicity study above[19]) tumor formation in preceding carcinogenicity study) observed in , the potential for increased proliferation of hepatocytes and endothelial cells in the liver evaluated using endogenous marker for DNA synthesis (Ki-67). Double-labeling method identifying endothelial cells (CD-31) utilized. Monoclonal mouse anti-rat CD31 antigen and monoclonal anti-rat-Ki-67 were used. Endothelial cell proliferation determined by the number of Ki-67 positive cells in ~ 1000 CD-31 positive cells in liver tissue.	Dose responsive increase in endothelial cell labeling index. Increase was statistically significant in 150 mg/kg dose (in drinking water) group and in the 4000 mg/kg dose (in diet) group.[19]
Polyaminopropyl Biguanide (in drinking water and in diet)	Groups of 10 male Wistar Han [Crl:WI(Han)] rats	Same test groups, as defined above. Another experiment relating to determination of MOA. Effect on serum and liver TNFα, NFκβ, and IL-1α, (mitogenic cytokines) evaluated	Polyaminopropyl Biguanide (in drinking water) caused a statistically significant decrease ($p < 0.05$) in the serum concen-tration of IL-1α, at a dose of 150 mg/kg. The same was true for Polyaminopropyl Biguanide at a dietary dose of 4000 mg/kg. Polyaminopropyl Biguanide (in drinking water or in diet) had no effect on the serum or liver TNFα and NFκβ levels. Based on results from the short-term oral toxicity study (summarized in Table 9), the metabolism study (in ADME section) and these 2 MOA experiments on Poly-aminopropyl Biguanide (all by same authors), the hypothesized MOA was determined to be: severe dehydration and starvation because of unpalatability, followed by ingestion with rapid absorption and urinary excretion; increased hepatocyte proliferation; and induction of hepatocellular foci and tumors.[19]

Table 15. Dermal Irritation and Sensitization Studies

Ingredient	Number of Animals/Subjects	Protocol	Results
		Irritation Studies	
Animal Studies			
Polyaminopropyl Biguanide	5 male New Zealand White rabbits	Test substance (0.5 g, moistened with distilled water) applied to 3 sites on back (mg/cm^2 not stated); sites covered with cotton gauze patch secured with adhesive tape. Patches removed after 3 minutes, 1 h, or 4 h.	Slight edema at 1 h after patch removal and very slight edema at 24 h and 48 h. After 4 h, very slight to well defined erythema; primary irritation index (PII) = 1. Mean values (at 24 h, 48 h, and 72 h) for erythema, eschar formation or edema formation calculated for each animal tested were ≤ 1. No skin reactions after 7 days. Mild skin irritant.[12]
Polyaminopropyl Biguanide (96%, as powder)	3 male rabbits (strain not specified)	Test substance (0.5 g moistened with 0.5 ml water) applied under occlusive patch to 3 sites on back of 1 rabbit; mg/cm^2 not stated. Patches removed after 3 minutes, 1 h, or 4 h. For remaining 2 rabbits, patch remained in place for 4 h.	No irritation after 3-minute or 1-h application. After 4-h exposure, primary irritation index of 1 reported; very slight (at 1 h, 48 h, and 72 h after patch removal) to well-defined (at 4 h and 24 h) erythema observed. Slight edema (at 1h) and very slight edema (at 24 h and 48 h). No reactions at 7 days after patch removal. Mild skin irritant.[3]
25% aqueous Polyaminopropyl Biguanide	3 female rats (strain not stated)	Test substance applied (dose not specified) under occlusive dressing to intact skin of back for 3 alternating 24-h periods, i.e., each application period followed by 24-h non-treatment period.	Focal ulceration observed after first 24-h application. Reaction increased in severity after 2nd and 3rd applications, by which time there was pronounced edema.[20]
25% aqueous Polyaminopropyl Biguanide	2 groups of 20 (10 males, 10 females/group) healthy SPF albino rats	2 groups received a topical application of test substance to intact skin at dosages of 2.5 ml/kg and 5 ml/kg, respectively. Test substance spread over 1 inch^2 area; site covered with dressing for 24 h.	Severe skin irritation in all animals.[20]
25% aqueous Polyaminopropyl Biguanide	Albino guinea pigs (6 test and 4 control) of Porton strain	Both ears treated (patch application; 0.1 ml per ear) with 25% Polyaminopropyl Biguanide once per day for 3 consecutive days. Next, 0.2 ml of following concentrations (in dimethylformamide) applied to flank (1-cm diameter area): 25% , 12.5%, and 10%	Slight to moderate erythema (irritant effect) on ear at 25%.[12]
20.2% aqueous Polyaminopropyl Biguanide	Groups of 10 rats (5 males, 5 females per group) of the Alpk:APfSD (Wistar-derived) strain	3 groups received applications (occlusive, on the back) of the test substance at doses of 20 mg/kg/day, 60 mg/kg/day, and 200 mg/kg/day, respectively, 6 h per day for 30 days (21 applications total).	Slight irritation at 60 mg/kg/day; in most animals, had regressed by end of study. Moderate irritation in all animals at 200 mg/kg/day; in most animals, persisted until end of study. Skin irritation observed was confirmed microscopically and considered test substance-related.[12]
20% aqueous Polyaminopropyl Biguanide	9 (3 males, 6 females) New Zealand White rabbits	Test substance applied to 6 rabbits (0.5 ml, under occlusive dressing) for 24 h to ~ 6.25 cm^2 area of intact and abraded skin of the flanks. Similar application to 3 male rabbits; animals then killed at 48 h or 72 h post-application for histopathologic examination of test site.	Moderately irritating to intact skin. Severely irritating to abraded skin.[12]
20% aqueous Polyaminopropyl Biguanide	6 New Zealand White rabbits	Skin corrosivity test. Applied to intact and abraded skin (mg/cm^2 and duration of application not stated).	Superficial scabbing and erythema around the abrasions. No signs of necrosis at intact skin sites. Non-corrosive.[12]
20% aqueous Polyaminopropyl Biguanide	6 female albino rabbits	12,000 ppm solution (1 ml) applied to back for 23 h (mg/cm^2 not stated; no occlusion). 21 daily applications.	Non-irritant.[12]
20% aqueous Polyaminopropyl Biguanide	5 female rats of the Alderley Park strain	Test substance (0.04% active ingredient) applied (0.1 ml; mg/cm^2 not stated) to the back on alternate days (6 applications total). Test site remained uncovered or was covered with polyethylene, secured with an adhesive plaster, for 24 h.	Non-irritant.[20]
20% aqueous Polyaminopropyl Biguanide	3 rabbits (strain not specified)	Applied to skin for 24 h (mg/cm^2 not stated).	Moderate erythema at 24 h post-application. Completely reversible within 8 days. No edema.[12]

Table 15. Dermal Irritation and Sensitization Studies

Ingredient	Number of Animals/Subjects	Protocol	Results
Polyaminopropyl Biguanide (0.2% in ethanol, 10% in ethanol and 20% [solvent not specified])	4 groups of SPF Alderley Park mice (50 males, 50 females)	Test substance (0.3 ml) was administered at the following doses 5 days per week for 80 weeks: 0 mg/day (in ethanol), 0.6 mg/day (0.2% Polyaminopropyl Biguanide in ethanol), 6.0 mg/day (20% Polyaminopropyl Biguanide and 30 mg/day [10% Polyaminopropyl Biguanide] in ethanol).	The highest dose (10% concentration; 30 mg/day) caused noticeable skin irritation in males and females immediately after application. Erythema observed during first few weeks. After 4th week, hyperkeratosis became evident, especially in males. Also, occasionally, there was ulceration extending to the deeper layers of the dermis at the application site.[20]
Human Studies			
20% aqueous Polyaminopropyl Biguanide	45 volunteers (17 males, 28 females)	Following concentrations (in purified water) applied topically (Finn chamber) for 24 h to medial surface of upper arm: 0.3%, 0.6%, and 1.5% active ingredient.	Plaster dermatitis observed in all test groups, including vehicle controls. Skin irritation indices of 6.6, 5.5, 5.5 and 8.8 obtained for concentrations of 0 (vehicle control), 0.3, 0.6 and 1.5 % active ingredient. Not a primary skin irritant, given the similarity of skin irritation indices between test and control groups.[12]
Bacterial nanocellulose dressing loaded with 1% w/v sericin and 0.3% w/v Polyaminopropyl Biguanide	105 healthy volunteers	Initially, skin randomly patched with dressings (2 cm x 2 cm area). After 3 days, new dressings patched onto same area. After an additional 3 days, dressings removed; removal followed by 7- to 10- day non-treatment period. Skin then patched (open and closed patch tests) with dressings on same area. After 3 days, dressings removed.	Majority of test sites did not show edema (more than 98 %) or papules (more than 97 %). Neither vesicles nor bullae were observed on the skin. Dressing classified as non-irritating to the skin.[35]
Sensitization Studies			
Animal Studies			
Polyaminopropyl Biguanide		Local lymph node assay (Unilever unpublished data, protocol details not provided). Positive results defined as one or more test concentrations eliciting a 3-fold or greater increase in proliferative activity, compared with concurrent vehicle control	Positive results.[36,37]
20.2% aqueous Polyaminopropyl Biguanide	20 female Alpk:Dunkin Hartley guinea pigs (test group) and 10 female guinea pigs (control group)	Guinea pig maximization test. Induction phase: intradermal induction (0.3 % of test substance as delivered [0.06 % active ingredient], 0.1 ml in shoulder region). One week later, dermal induction performed by occlusively applying neat substance (20.2 % active ingredient) to induction sites for 48 h. Challenge: occlusive epicutaneous application (24 h) of undiluted test substance (20.2% active ingredient) and a 30% solution in deionized water (6 % active ingredient) to previously untreated site	Scattered mild redness or moderate diffuse redness observed in 18/20 test animals at 24 h and 16/20 test animals at 48 hr. Moderate sensitizer (classification scheme not stated).[12]
20% aqueous Polyaminopropyl Biguanide (diluted with saline)	Groups of 10 guinea pigs	Guinea pig maximization test. Intradermal induction with 0.15% Polyaminopropyl Biguanide and topical induction with 20%. Challenge with 20% or 10%	Moderate erythema at 10% and 20% (1 of 10 animals per concentration). Non-sensitizer (classification scheme not stated).[12]
20% aqueous Polyaminopropyl Biguanide	20 Alderley Park female guinea pigs (test animals) and 8 female guinea pigs (controls)	Guinea pig maximization test. Intradermal induction (in scapular region) with 1% of test substance as delivered (0.2% active ingredient). Topical induction and challenge with 20.2 % active ingredient	Mild to moderate erythema in 14 of 20 animals (at 24 h) and in 15 of 20 animals (at 48 h). Moderate to strong sensitizer (classification scheme not stated).[12]
20% aqueous Polyaminopropyl Biguanide	Female Dunkin Hartley guinea pigs (20 test and 8 control animals).	Guinea pig maximization test. Possible cross-reactivity with chlorhexidine also evaluated. Intradermal induction with 0.25%. Topical induction and challenge with 20% Polyaminopropyl Biguanide. Challenge with 0.05 %, 0.5 % and 4 % chlorohexidine gluconate	Challenge reactions to 20% in 8 of 20 animals. Reactions in 3 of 20 at rechallenge. No cross-reactivity with chlorhexidine. Test substance was mild sensitizer (classification scheme not stated).[12]

Table 15. Dermal Irritation and Sensitization Studies

Ingredient	Number of Animals/Subjects	Protocol	Results
20% aqueous Polyaminopropyl Biguanide	10 Alderley Park guinea pigs (test animals) and 10 control guinea pigs.	Buehler test. Concentration of 10% (2% active ingredient, 0.4 ml) applied to scapular region (400 mm^2) during topical induction (occlusive dressing) for 6 h. Induction repeated 3 times/week for 3 weeks (10 applications total). Challenge exposures (2 % active ingredient) of 6 h performed 2 weeks after last induction exposure. Rechallenge with concentrations of 20%, 10% and 1% (4%, 2%, and 0.2% active ingredient, respectively).	Faint erythema in 6 of 10 test animals. Rechallenge yielded faint erythema at concentrations of 4% (8 of 9 animals) and 2% (3 of 10 animals) active ingredient. No reaction to 0.2% active ingredient. 2% active ingredient considered moderate sensitizer (classification scheme not stated).[12]
20% aqueous Polyaminopropyl Biguanide	Groups of 20 (10 males and 10 females per group) guinea pigs	Buehler test. Induction and challenge concentrations: induction (0.3%) and challenge (0.3%, 0.15%, 0.075%, and 0.03%); induction (0.8%) and challenge (0.8%, 0.4%, 0.2%, and 0.08%); induction (1.3%) and challenge (1.3%, 0.65%, 0.325%, and 0.13%); induction (1.8%) and challenge (1.8%, 0.9%, 0.45%, and 0.18%); induction (2%), challenge (2%), and rechallenge (2%); 1.2% induction, challenge (1.2%), and rechallenge (1.2% and 15%); and induction (5%), challenge (15%), and rechallenge (2% and 1.2%).	Threshold for eliciting sensitization in guinea pigs was approximately 1%.[12]
Human Studies			
20% aqueous Polyaminopropyl Biguanide	191 subjects (49 on Panel 1, 114 on Panel 2, and 28 on Panel 3)	During induction, test substance applied (2 cm x 2 cm patches moistened with 0.5 ml aliquots) for 24 h to dorsal surface of upper arm at concentrations of 2% active ingredient (effective concentration= 0.4%) and 4% (effective concentration = 0.8%) . Repeated 3 times per week for 10 applications total. Applied at following concentrations during challenge phase: 0.05% (effective concentration = 0.01%), 0.1% (effective concentration = 0.02%), 0.2% (effective concentration =0.04%), 0.5% (effective concentration = 0.1%), 1% (effective concentration = 0.2%), and 2% (effective concentration = 0.4%).	Panel 1: At challenge, 8 of 49 subjects (16%) had skin reactions to 0.4%, 7 of 49 (14%) with reactions to 0.2% and 0.1%, and 2 of 49 (4%) with weak reactions at 0.02%. Panel 2: 18 of 114 subjects (16%) with skin reactions to 0.1 % and 7 of 114 (6%) with reactions to 0.04 %. 2 other subjects with reactions during non-treatment period following 0.4% induction, characterized as likely allergic to 0.4%. Same true for 10 other subjects regarding reactions (described as weak) at late 0.4% induction. Panel 3: 1 of 28 subjects (3.6%) with reaction to 0.1 %. Conclusion: 0.4% concentration not capable of causing primary skin irritation, but capable of causing skin sensitization humans.[3]
Leave-on product containing 20% Polyaminopropyl Biguanide (tested at 0.5% ; effective test concentration = 0.1% Polyaminopropyl Biguanide)	207 subjects	In HRIPT, product (0.1 g on a 2 cm x 2 cm occlusive patch) applied to skin (48-h to 72-h application) at dose density of 25 mg/cm^2. Dose density of Polyaminopropyl Biguanide applied to skin calculated to be 0.025 mg/cm^2 (25 $\mu g/cm^2$). 3-week induction period followed by 2-week non-treatment period. Challenge patch applied to a new test site. Reactions scored at 24 h, 48 h, 72 h, and 96 h.	Product did not induce dermal sensitization.[38]
Neck cream containing 0.2% Polyaminopropyl Biguanide	115 male and female subjects (58 African Americans, 43 Caucasians, and 13 Hispanics). Subjects were free of any systemic or dermatological disorder that might have interfered with the study. Also, subjects were of any skin type or ethnicity, provided that their degree of skin pigmentation did not significantly interfere with evaluations.	During induction, product applied (2 cm x 2 cm occlusive patches containing 0.2 ml of product) for 24 h to upper back (dose = 100 $\mu g/cm^2$). Repeated 3 times per week for 3 weeks. Challenge patch applied for 24 h to new site on opposite side of upper back	Transient, barely perceptible to mild erythema in 43 of 115 subjects (37% of subjects tested) during induction and/or challenge phases: 34 Caucasians, 6 Hispanics, and 3 African Americans. No evidence of clinically meaningful irritation, and no reactions allergic in nature.[39]

Table 15. Dermal Irritation and Sensitization Studies

Ingredient	Number of Animals/Subjects	Protocol	Results
20% Polyaminopropyl Biguanide solution, diluted with distilled water to 1% v/v prior to testing (effective concentration = 0.2%)	108 subjects Asian (~ 2%), Bi-racial (~ 3%), Black (~ 23%), Caucasian (~ 33%), and Hispanic (~ 39%). Data on Fitzpatrick skin types are not included.	HRIPT. During induction, ~ 2 cm x 2 cm semi-occlusive patches containing 0.3 ml of the test material were applied for ~ 24 h to left side of back, 3x/week for 3 weeks, for a total of 9 applications. Test sites were score 24-h (weekdays) or ~ 48-h (weekends) after patch removals. Challenge phase initiated after ~ 2-week non-treatment period. ~ 2 cm x 2 cm semi-occlusive patch containing 0.3 ml the test material applied for ~ 24 h to new site on opposite side of back. Using modified scoring scale of International Contact Dermatitis Research Group, reactions were scored at ~ 24 h, ~ 48 h, ~ 72 h, and ~ 96 h after patch application. Patch testing with vehicle (distilled water) and saline controls according to same procedure.	During induction, low-level (±) reactions observed in 2 subjects. Reactions not observed during challenge phase. Authors noted that no adverse reactions or adverse events reported or observed in any of the subjects tested, and concluded that Polyaminopropyl Biguanide did not induce dermal sensitization in the subjects tested. When the 108 subjects were patch-tested with the vehicle control (distilled water) according to the same procedure, low-level (±) reactions were observed in 2 subjects during induction, and in 4 subjects during the challenge phase. Additionally, when the 108 subjects were patch-tested with saline (control), low-level (±) reactions were observed in 2 subjects during induction, and in 1 subject during the challenge phase. The authors concluded that neither control induced dermal sensitization in the subjects tested.[40]
Patients			
20% aqueous Polyaminopropyl Biguanide	1554 male and female patients	Multicenter study. Patch tests (performed in accordance with recommendations of the International Contact Dermatitis Research Group [ICDRG] and the German Contact Dermatitis Research Group [DKG]) on 2.5% aqueous test substance (effective concentration = 2.5% x 20% = 0.5%). Applied to 389 patients for 1 day and to 1165 patients for 2 days.	6 patients (0.4%) with positive (+) reaction. One of the reactions in patient with atopic dermatitis may have been a false positive. Polyaminopropyl Biguanide sensitization considered extremely rare.[49]
20% aqueous Polyaminopropyl Biguanide	1975 patients	Multicenter study. Patch testing with 2.5% aqueous (effective concentration = 2.5% x 20% = 0.5%) and 5% aqueous (effective concentration = 5% x 20% = 1%). Frequencies of sensitization (as % of patients tested) calculated as crude proportions and additionally standardized for sex and age.	10 patients (0.5 %) with positive reaction and 16 patients (0.8%) with positive reaction to1%. Assumed that, probably, at least 4 reactions at to 0.5% may have been doubtful or irritant, i.e. false positive, because were not confirmed by simultaneous reactions to higher concentrations. Probable cause of sensitization was occupational exposure. Other risk factors included leg dermatitis and old age.[48]
2.5% aqueous Polyaminopropyl Biguanide	374 patients (multicenter study in United Kingdom)	Patch test (protocol not described)	2 positive patch test reactions. Data series suggested that baseline frequency of Polyaminopropyl Biguanide sensitization was very low (0.5%) in United Kingdom. Majority of reactions were weak, and data suggested that Polyaminopropyl Biguanide may not be a relevant contact allergen.[47,43]

Table 16. Ocular Irritation Studies

Ingredient	Number of Animals	Test Protocol	Results
Animal Studies			
Polyaminopropyl Biguanide (powder form, 99.6% pure)	1 New Zealand rabbit	Test substance (0.1 g) instilled into 1 eye.	Moderate redness, chemosis, moderate corneal opacity, iridial congestion, and ulceration of the nictitating membrane and cornea. Severe ocular irritant.[3]
Polyaminopropyl Biguanide (undiluted)	1 male New Zealand White rabbit	Test substance (0.1 ml) instilled into conjunctival sac of right eye; untreated eye served as control. Eye not rinsed after instillation.	Opalescent corneal opacity, iridial inflammation, and severe conjunctival irritation observed initially. Translucent corneal opacity, minimal conjunctival irritation and vascularization were noted at day 21 post-instillation and considered irreversible reactions. Test substance was corrosive to rabbit eye.[3]
25% aqueous Polyaminopropyl Biguanide	3 rabbits (strain not specified).	Single instillation (volume not specified). Procedure repeated with saline rinse after instillation	Severe inflammation and corneal damage in all rabbits (unrinsed eyes). Condition partly resolved in 2 rabbits. 3rd rabbit blinded in treated eye. In rinsed eyes, only slight inflammation observed; eyes normal by day 3.[20]
20% aqueous Polyaminopropyl Biguanide	9 female New Zealand White rabbits	Test substance (0.1 ml) instilled into conjunctival sac of 1 eye; contralateral eye served as untreated control. Eyes of 6 animals not rinsed after instillation. Eyes of remaining 3 animals were rinsed.	Iritis and conjunctivitis in unrinsed eyes and 4/6 rabbits with transient corneal opacity. Conjunctivitis, but no corneal reaction, in rinsed eyes and slight iritis in 1 rabbit. Test substance was moderate eye irritant in unrinsed eyes and a mild irritant in rinsed eyes.[3]
20% Polyaminopropyl Biguanide	3 rabbits (strain not stated)	Test substance (0.12 ml) instilled into 1 eye, followed by rinsing with saline	Slight inflammation, but no corneal ulceration. Changes resolved in 10 days.[20]
20% Polyaminopropyl Biguanide	3 rabbits (strain not stated)	Test substance (diluted to 0.04% active ingredient; 0.1 ml) instilled into eyes	No immediate or delayed irritant effects observed.[20]
In Vitro Study			
20% aqueous Polyaminopropyl Biguanide	Donated human eyes (41) and rabbit eyes	Applied (20 µl for 10 seconds; 100 µl for 1 minute) at superior limbus. Eyes situated in temperature-controlled chamber during application.	1-minute exposure did not cause change in corneal thickness. Normal corneal morphology at histological examination.[45]

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2019 FDA VCRP Data

Polyaminopropyl Biguanide

01C - Other Baby Products	1
03C - Eye Shadow	2
03D - Eye Lotion	3
03E - Eye Makeup Remover	9
03F - Mascara	10
03G - Other Eye Makeup Preparations	3
04E - Other Fragrance Preparation	1
05A - Hair Conditioner	2
05F - Shampoos (non-coloring)	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	6
05H - Wave Sets	1
05I - Other Hair Preparations	2
07C - Foundations	4
07E - Lipstick	1
07H - Makeup Fixatives	1
07I - Other Makeup Preparations	7
08C - Nail Creams and Lotions	1
08G - Other Manicuring Preparations	3
10A - Bath Soaps and Detergents	3
10E - Other Personal Cleanliness Products	7
11A - Aftershave Lotion	1
12A - Cleansing	23
12C - Face and Neck (exc shave)	18
12D - Body and Hand (exc shave)	12
12F - Moisturizing	10
12G - Night	6
12H - Paste Masks (mud packs)	1
12I - Skin Fresheners	4
12J - Other Skin Care Preps	4
Total	**147**

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Polyaminopropyl Biguanide (PHMB) Interested Party Task Force

DATE: March 14, 2019

SUBJECT: Polyaminopropyl Biguanide (PHMB)

SGS Harrison Research Laboratories, Inc. 2019. Repeated insult patch test of Polyaminopropyl Biguanide (750 μg/cm^2) with water and saline controls.

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Personal Care Products Council
HRL Panel #19-103
Test Material #1: Polyaminopropyl Biguanide (PHMB), Batch #8302

PURPOSE:	To evaluate the potential of the Test Material, as a result of repeated applications, to induce dermal sensitization in human subjects.
IRB APPROVAL:	Both the SGS HRL Standard Protocol #100 and the Informed Consent were approved by the Clarus Institutional Review Board (CIRB) on January 29, 2018. A Sponsor-signed Protocol is retained in HRL files.
SPONSOR:	Personal Care Products Council 1620 L Street NW Suite 1200 Washington, DC 20036 Per: Linda Loretz, Ph.D, DABT
SPONSOR AUTHORIZATION:	January 15, 2019
SAFETY ASSURANCE:	January 15, 2019
PRINCIPAL INVESTIGATOR:	Karen Rauen, PhD
CO-INVESTIGATORS:	Deborah R Spey, MD, Board-Certified Dermatologist Kimberly K Ruhl, MD, PhD, Board-Certified Dermatologist Adriana Ros, DO, Board-Certified Dermatologist
TEST FACILITY:	SGS Harrison Research Laboratories, Inc. (HRL) 2497 Vauxhall Road Union, New Jersey 07083
TEST MATERIAL:	Test Material Polyaminopropyl Biguanide (PHMB), Batch #8302, received as a 20% dilution, a clear liquid, was received on January 10, 2019. The following instructions were received: Dilute Test Material to 1% v/v by mixing 5 mls of Test Material with 95 mls of distilled water prior to application to patches; prepare fresh daily. Patch semi-occlusively.
SUBJECTS:	A total of 120 subjects were enrolled; 108 subjects completed the test. One subject, #120 (HRL #45989), was discontinued due to a protocol deviation. One subject, #088 (HRL #45196), was discontinued prior to being patched due

- continued -

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SUBJECTS: (continued)	to screen failure. Ten subjects discontinued due to personal reasons / Investigator termination. No subject discontinued due to test material reaction. Of the subjects who completed this test, approximately 39% are Hispanic, approximately 33% are Caucasian, approximately 23% are Black, approximately 3% are Bi-Racial and approximately 2% are Asian.
METHOD:	This test was conducted according to HRL Standard Protocol #100 and HRL Standard Operating Procedures (including any Sponsor alterations).
TEST DATES:	January 21, 2019 through March 1, 2019.
SCORING SYSTEM:	See Tables I-II.
RESULTS:	See Tables I-II. No adverse reactions or adverse events were reported / observed in any of the subjects. During the Induction Phase, two subjects exhibited low-level (±) reactions. During the Challenge, no reactions were exhibited.
CONCLUSION:	In this Repeated Insult Patch Test, Test Material Polyaminopropyl Biguanide (PHMB), Batch #8302, did not induce dermal sensitization in human subjects.
QUALITY ASSURANCE (QA):	The QA Unit performed an in-phase audit of this study.

Deborah R Spey, MD
Co-Investigator
Board-Certified Dermatologist

Michelle Camacho, BS
Project Manager

Karen Rauen, PhD
Principal Investigator

Date: 3/12/19

Personal Care Products Council
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Test Material #1: Polyaminopropyl Biguanide (PHMB), Batch #8302

SUBJECTS: Each potential subject completed an HRL Subject History Form (HRL Form: SHF), including relevant medical history (an updated History Form is secured approximately every 18 months). At each subject's first visit to HRL, the subject completed a Permission To Release Personal Health Information Form in conformity with the Health Insurance Portability and Accountability Act (HIPAA) and provided proof of age. Each accepted subject was assigned a permanent HRL Identification Number. No subject was used if he or she exhibited any dermatological or other medical or physical condition that would preclude topical application of the Test Material. Upon enrollment, no subject reported using any medication that would interfere with the sensitization results. No known pregnant nor nursing women were used on this RIPT. No minor subjects were used on this RIPT.

An appropriate clearance period had elapsed since a subject was patched on a Repeated Insult Patch Test (RIPT) or a Photoallergy Test (PA) before being used in this RIPT.

Legally valid written IRB-approved Informed Consent, in conformity with: 21 CFR 50.25, Subtitle A, Protection of Human Subjects, was secured from each subject.

METHOD: Induction Phase: An approximately 2 cm X 2 cm webril/adhesive patch was used semi-occlusively. Using a precise, repeating syringe, 0.3 ml of the Test Material was applied to each designated patch. As per HRL Standard Operating Procedures (SOP) (HRL Form:SOP/RIPT), the left side of the back was usually the test area for the Induction Phase. The subject's skin was marked with gentian violet surgical marker at the left side of the test site. The test site was recorded on the anatomical diagram of each subject's individual Data Form. In addition, at that time, the prospective placement of the Challenge test site was also recorded on the anatomical diagram.

Each subject was instructed that the patch was to remain in place and kept dry for approximately 24 hours, at which time the patch was to be removed by the subject. An approximately 24-hour period, during which no test material was applied, followed the weekday patch removals; an approximately 48-hour period followed the weekend patch removals.

Each subject returned to HRL on the appropriate day. The test site was observed by the HRL technician, and the reaction scored and recorded (see **SCORING SYSTEM**, below). The identical test site was then repatched until nine (9) Induction patchings were completed.

In accordance with HRL SOP, if a subject was unable to make up a missed patching during the same week, the subject was either patched four days the following week or was patched at the end of the Induction Phase. Any absences and make-up days are noted by the dates on the individual Data Form.

A series of nine (9) Induction patchings was completed over a period of approximately three weeks.

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Test Material #1: Polyaminopropyl Biguanide (PHMB), Batch #8302

METHOD: (continued)

Rest Period: A Rest Period of approximately two weeks followed the last Induction patching; no test material was applied during the Rest Period. Subjects were instructed to notify HRL if they experienced any reaction during the Rest Period.

Challenge Phase: At the Challenge Phase, the original Induction test site was observed and each subject queried as to whether any reaction was experienced during the Rest Period. Any reactions were recorded on the Data Form. An approximately 2 cm X 2 cm webril/adhesive patch was used semi-occlusively. Using a precise, repeating syringe, 0.3 ml of the Test Material was applied to each designated patch. As per HRL RIPT SOP, the opposite side of the back was usually the virgin test site for the Challenge Phase.

As per HRL RIPT SOP, the Challenge patch was applied to the virgin site only. Each subject was again instructed to keep the patch on and dry.

Each subject reported to HRL approximately 24 hours later (Challenge Reading 1), at which time the patch was removed and the Challenge site scored and recorded by the HRL technician. The original test site was also observed. (See **RESULTS**, below.)

Each subject reported to HRL at approximately 48 hours (Challenge Reading 2), approximately 72 hours (Challenge Reading 3) and approximately 96 hours (Challenge Reading 4) post-patching for additional observations; reactions were scored and recorded.

SCORING SYSTEM: See Tables I-II. The test sites were scored using the modified scoring scale of the International Contact Dermatitis Research Group System: Fisher, Alexander A., *Contact Dermatitis*, Lea & Febiger, Philadelphia, 2008: p 27.

RESULTS: See Tables I-II. No adverse reactions or adverse events related to the Test Material were exhibited / reported by any subject during this test. Erythema, edema, dryness, staining, peeling and hyperpigmentation / hypopigmentation are possible, expected endpoints and not considered Adverse Reactions. This test was conducted under the supervision of a Board-Certified Dermatologist, a Co-Investigator. At Challenge Reading 3, the Dermatologist participated in the scoring of the subjects. A total of 108 subjects completed the test; 32 male and 76 female. The subjects range in age from 18 to 77.

RETENTION: All original Data Forms will be retained at HRL for a period of three years, or such other time as may be required by law. A laboratory retainer bottle of the Test Material shall be retained, in ambient conditions, for at least two years, or as required by law. Return or disposal of unused Test Material shall be as per the Sponsor's instructions—to be communicated within 30 days of receipt of this Final Report. HRL shall appropriately dispose of any remaining Test Material after six months if no Sponsor instructions have been communicated.

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Test Material #1: Polyaminopropyl Biguanide (PHMB), Batch #8302

TABLE I: SUMMARY OF REACTIONS

TOTAL NUMBER OF SUBJECTS ENROLLED: 120
TOTAL NUMBER OF SUBJECTS COMPLETED: 108

Reaction	Induction Reading									Challenge Reading			
Grade	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**1**	**2**	**3**	**4**
0	115	115	113	112	111	112	111	111	111	108	108	108	108
±				1	2								
1													
1E													
2													
2E													
3E													
4E													
-													
N9R													
Total	115	115	113	113	113	112	111	111	111	108	108	108	108

SCORING SYSTEM:
0 = No visible reaction
± = Faint, minimal erythema
1 = Erythema
2 = Intense erythema, induration
3 = Intense erythema, induration, vesicles
4 = Severe reaction with erythema, induration, vesicles, pustules (may be weeping)
E = Edema
- = No reading
N9R = No 9th reading

Personal Care Products Council

HRL Panel #19-103

Test Material #1: Polyaminopropyl Biguanide (PHMB), Batch #8302

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

						Induction Reading									Challenge Reading			
Sub #	HRL #	Initials	Gender	Age	Race	1	2	3	4	5	6	7	8	9	1	2	3	4
1	47761	FD	M	47	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
2	39333	JM	M	41	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
3	34205	VO	F	54	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
4	42993	MC	F	54	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
5	48013	SR	F	57	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
6	47244	JJ	M	65	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
7	37725	AA	F	52	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
8	33272	BM	F	63	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
9	18875	MH	F	52	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
10	39680	GF	F	56	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
11	30434	LP	F	50	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
12	47532	CS	F	54	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
13	21928	DL	F	55	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
14	31765	PM	M	65	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
15	44323	MT	F	36	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
16	47142	RC	M	63	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
17	47098	JG	F	60	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
18	41212	JM	F	29	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
19	28550	CB	F	42	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
20	48040	YC	F	41	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
21	20617	BB	F	68	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
22	43107	MS	F	57	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
23	42000	DN	M	68	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
24	10420	JC	F	51	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
25	27639	CF	F	46	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0

Personal Care Products Council

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TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

						Induction Reading									Challenge Reading			
Sub #	HRL #	Initials	Gender	Age	Race	1	2	3	4	5	6	7	8	9	1	2	3	4
26	29103	XC	F	52	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
27	33101	VM	F	64	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
28	40251	EC	F	54	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
29	06915	RS	F	68	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
30	48041	DD	F	52	Caucasian	0	0	0	0	0	0	X	X	X	X	X	X	X
31	47277	TS	F	47	Bi-Racial	0	0	0	0	0	0	0	0	0	0	0	0	0
32	27357	SM	M	43	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
33	27367	EM	F	36	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
34	01435	MR	M	63	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
35	37249	MF	F	45	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
36	46871	RB	F	47	Caucasian	0	0	0	±	±	0	0	0	0	0	0	0	0
37	41306	BB	F	49	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
38	29307	YR	F	62	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
39	47876	DF	M	37	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
40	46957	KE	F	37	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
41	11163	LB	F	34	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
42	48042	KK	F	59	Caucasian	0	0	X	X	X	X	X	X	X	X	X	X	X
43	45856	AL	F	55	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
44	41851	SK	F	45	Black	0	0	0	0	0	0	0	0	0	X	X	X	X
45	30799	AP	F	29	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
46	45378	JK	M	39	Caucasian	0	0	0	0	±	0	0	0	0	0	0	0	0
47	47609	PM	F	40	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
48	24505	NM	F	35	Bi-Racial	0	0	0	0	0	0	0	0	0	0	0	0	0
49	43230	MR	M	54	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
50	44591	CO	F	21	Black	0	0	0	0	0	0	0	0	0	0	0	0	0

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TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

						Induction Reading									Challenge Reading			
Sub #	HRL #	Initials	Gender	Age	Race	1	2	3	4	5	6	7	8	9	1	2	3	4
51	48010	CP	F	40	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
52	44992	KH	F	58	Black	0	0	X	X	X	X	X	X	X	X	X	X	X
53	44942	MM	F	44	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
54	44330	DN	F	33	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
55	44331	DR	M	38	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
56	47091	JR	M	45	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
57	05722	TD	F	57	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
58	46788	JF	F	49	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
59	47714	GF	F	18	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
60	34051	KB	F	49	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
61	46638	NA	F	59	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
62	41818	SL	F	47	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
63	38918	CN	F	57	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
64	29288	CC	F	48	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
65	36901	JH	M	51	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
66	45581	AN	F	32	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
67	45839	EG	M	49	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
68	47646	JA	M	53	Asian	0	0	0	0	0	0	0	0	0	0	0	0	0
69	47760	CP	F	33	Hispanic	0	0	0	0	0	0	0	0	0	X	X	X	X
70	38583	GW	M	60	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
71	34457	MG	F	62	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
72	38892	ML	F	57	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
73	42145	MR	F	23	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
74	20113	HA	F	53	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
75	46084	CP	F	40	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0

Personal Care Products Council

HRL Panel #19-103

Test Material #1: Polyaminopropyl Biguanide (PHMB), Batch #8302

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

						Induction Reading									Challenge Reading			
Sub #	HRL #	Initials	Gender	Age	Race	1	2	3	4	5	6	7	8	9	1	2	3	4
76	33516	RC	F	53	Bi-Racial	0	0	0	0	0	0	0	0	0	0	0	0	0
77	08440	FH	F	58	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
78	32673	AH	F	28	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
79	42011	AL	F	69	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
80	46964	KW	M	71	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
81	23295	MC	F	49	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
82	42024	DN	M	36	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
83	28119	HL	F	44	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
84	47873	ZJ	F	42	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
85	25240	CM	M	59	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
86	35008	SW	F	42	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
87	36003	AD	M	58	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
88	45196	SS	F	47	Black	X	X	X	X	X	X	X	X	X	X	X	X	X
89	43707	AC	M	53	Black	X	X	X	X	X	X	X	X	X	X	X	X	X
90	44613	RA	M	43	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
91	42521	NW	F	35	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
92	28196	JF	M	46	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
93	48046	MF	M	43	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
94	40097	DH	F	55	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
95	44216	MB	F	57	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
96	33195	EA	F	73	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
97	45617	DB	M	23	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
98	45157	DB	M	23	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
99	36619	GC	M	77	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
100	46892	SC	F	33	Caucasian	0	0	0	0	0	0	0	0	0	X	X	X	X

Personal Care Products Council

HRL Panel #19-103

Test Material #1: Polyaminopropyl Biguanide (PHMB), Batch #8302

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

						Induction Reading									Challenge Reading			
Sub #	HRL #	Initials	Gender	Age	Race	1	2	3	4	5	6	7	8	9	1	2	3	4
101	33442	MC	F	43	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
102	47211	MR	F	69	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
103	22103	JO	F	36	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
104	48047	RR	M	26	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
105	46317	LP	F	39	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
106	46318	FS	M	49	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
107	46827	MA	F	50	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
108	48048	RB	F	73	Bi-Racial	X	X	X	X	X	X	X	X	X	X	X	X	X
109	47697	GS	M	49	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
110	43506	KR	F	29	Hispanic	X	X	X	X	X	X	X	X	X	X	X	X	X
111	33262	WV	M	50	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
112	06094	BM	F	71	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
113	30519	PV	F	63	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
114	48049	KM	F	40	Asian	0	0	0	0	0	0	0	0	0	0	0	0	0
115	34218	MR	F	74	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
116	46924	KR	M	19	Hispanic	X	X	X	X	X	X	X	X	X	X	X	X	X
117	29587	II	F	55	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
118	47635	CC	M	34	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
119	28879	MR	F	71	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
120	45989	MG	M	47	Caucasian	0	0	0	0	0	X	X	X	X	X	X	X	X

Personal Care Products Council

HRL Panel #19-103

Test Material #1: Polyaminopropyl Biguanide (PHMB), Batch #8302

SCORING SYSTEM*:

0	=	No visible reaction
±	=	Faint, minimal erythema
1	=	Erythema
2	=	Intense erythema
3	=	Intense erythema, induration, vesicles
4	=	Severe reaction with erythema, induration, vesicles, pustules (may be weeping)
E	=	Edema
DR	=	Dryness
P	=	Peeling
S	=	Staining
^	=	Hyperpigmentation / Hypopigmentation
TR	=	Tape Reaction
C	=	Change of test site
N9R	=	No 9th reading
-	=	No patch application and / or reading
X	=	Discontinued

*International Contact Dermatitis Research Group System: Fisher, Alexander A., *Contact Dermatitis*, Lea & Febiger, Philadelphia, 2008: p 27. (Modified)

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Personal Care Products Council
HRL Panel #19-103
Test Material #1: Polyaminopropyl Biguanide (PHMB), Batch #8302

QUALITY ASSURANCE MEMORANDUM

This Final Report was reviewed for accuracy and conformity with both HRL Standard Protocol #100 and HRL Standard Operating Procedures (including any Sponsor alterations) and any written communication from the Sponsor.

Inspections were accomplished by a random sampling approach and reported to the Project Manager and the Principal Investigator immediately following their completion.

Any known protocol deviations have been noted in the Final Report and/or Individual Data Form.

The raw data for this study are retained at SGS Harrison Research Laboratories, Inc.

SGS HARRISON RESEARCH LABORATORIES, INC.

Susan Lauck

SUSAN LAUCK
Quality Assurance Manager

QUALITY ASSURANCE UNIT

Date: 3/12/19

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Personal Care Products Council
HRL Panel #19-103
Test Material #2: Vehicle (distilled water)

PURPOSE:	To evaluate the potential of the Test Material, as a result of repeated applications, to induce dermal sensitization in human subjects.
IRB APPROVAL:	Both the SGS HRL Standard Protocol #100 and the Informed Consent were approved by the Clarus Institutional Review Board (CIRB) on January 29, 2018. A Sponsor-signed Protocol is retained in HRL files.
SPONSOR:	Personal Care Products Council 1620 L Street NW Suite 1200 Washington, DC 20036 Per: Linda Loretz, Ph.D, DABT
SPONSOR AUTHORIZATION:	January 15, 2019
SAFETY ASSURANCE:	January 15, 2019
PRINCIPAL INVESTIGATOR:	Karen Rauen, PhD
CO-INVESTIGATORS:	Deborah R Spey, MD, Board-Certified Dermatologist Kimberly K Ruhl, MD, PhD, Board-Certified Dermatologist Adriana Ros, DO, Board-Certified Dermatologist
TEST FACILITY:	SGS Harrison Research Laboratories, Inc. (HRL) 2497 Vauxhall Road Union, New Jersey 07083
TEST MATERIAL:	Test Material Vehicle (distilled water), a clear liquid, was supplied by SGS HRL. The following instructions were received: Test as received; patch semi-occlusively.
SUBJECTS:	A total of 120 subjects were enrolled; 108 subjects completed the test. One subject, #120 (HRL #45989), was discontinued due to a protocol deviation. One subject, #088 (HRL #45196), was discontinued prior to being patched due to screen failure. Ten subjects discontinued due to personal reasons / Investigator termination. No subject discontinued due to test material reaction.

- continued -

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Personal Care Products Council
HRL Panel #19-103
Test Material #2: Vehicle (distilled water)

SUBJECTS: (continued)	Of the subjects who completed this test, approximately 39% are Hispanic, approximately 33% are Caucasian, approximately 23% are Black, approximately 3% are Bi-Racial and approximately 2% are Asian.
METHOD:	This test was conducted according to HRL Standard Protocol #100 and HRL Standard Operating Procedures (including any Sponsor alterations).
TEST DATES:	January 21, 2019 through March 1, 2019.
SCORING SYSTEM:	See Tables I-II.
RESULTS:	See Tables I-II. No adverse reactions or adverse events were reported / observed in any of the subjects. During the Induction Phase, two subjects exhibited low-level (±) reactions. During the Challenge, four subjects exhibited low-level (±) reactions.
CONCLUSION:	In this Repeated Insult Patch Test, Test Material Vehicle (distilled water), did not induce dermal sensitization in human subjects.
QUALITY ASSURANCE (QA):	The QA Unit performed an in-phase audit of this study.

Deborah R Spey, MD	Michelle Camacho, BS	Karen Rauen, PhD
Co-Investigator	Project Manager	Principal Investigator
Board-Certified Dermatologist		

Date: 3/12/19

Personal Care Products Council
HRL Panel #19-103
Test Material #2: Vehicle (distilled water)

SUBJECTS: Each potential subject completed an HRL Subject History Form (HRL Form: SHF), including relevant medical history (an updated History Form is secured approximately every 18 months). At each subject's first visit to HRL, the subject completed a Permission To Release Personal Health Information Form in conformity with the Health Insurance Portability and Accountability Act (HIPAA) and provided proof of age. Each accepted subject was assigned a permanent HRL Identification Number. No subject was used if he or she exhibited any dermatological or other medical or physical condition that would preclude topical application of the Test Material. Upon enrollment, no subject reported using any medication that would interfere with the sensitization results. No known pregnant nor nursing women were used on this RIPT. No minor subjects were used on this RIPT.

An appropriate clearance period had elapsed since a subject was patched on a Repeated Insult Patch Test (RIPT) or a Photoallergy Test (PA) before being used in this RIPT.

Legally valid written IRB-approved Informed Consent, in conformity with: 21 CFR 50.25, Subtitle A, Protection of Human Subjects, was secured from each subject.

METHOD: Induction Phase: An approximately 2 cm X 2 cm webril/adhesive patch was used semi-occlusively. Using a precise, repeating syringe, 0.3 ml of the Test Material was applied to each designated patch. As per HRL Standard Operating Procedures (SOP) (HRL Form:SOP/RIPT), the left side of the back was usually the test area for the Induction Phase. The subject's skin was marked with gentian violet surgical marker at the left side of the test site. The test site was recorded on the anatomical diagram of each subject's individual Data Form. In addition, at that time, the prospective placement of the Challenge test site was also recorded on the anatomical diagram.

Each subject was instructed that the patch was to remain in place and kept dry for approximately 24 hours, at which time the patch was to be removed by the subject. An approximately 24-hour period, during which no test material was applied, followed the weekday patch removals; an approximately 48-hour period followed the weekend patch removals.

Each subject returned to HRL on the appropriate day. The test site was observed by the HRL technician, and the reaction scored and recorded (see **SCORING SYSTEM**, below). The identical test site was then repatched until nine (9) Induction patchings were completed.

In accordance with HRL SOP, if a subject was unable to make up a missed patching during the same week, the subject was either patched four days the following week or was patched at the end of the Induction Phase. Any absences and make-up days are noted by the dates on the individual Data Form.

A series of nine (9) Induction patchings was completed over a period of approximately three weeks.

Personal Care Products Council
HRL Panel #19-103
Test Material #2: Vehicle (distilled water)

METHOD: (continued)

Rest Period: A Rest Period of approximately two weeks followed the last Induction patching; no test material was applied during the Rest Period. Subjects were instructed to notify HRL if they experienced any reaction during the Rest Period.

Challenge Phase: At the Challenge Phase, the original Induction test site was observed and each subject queried as to whether any reaction was experienced during the Rest Period. Any reactions were recorded on the Data Form. An approximately 2 cm X 2 cm webril/adhesive patch was used semi-occlusively. Using a precise, repeating syringe, 0.3 ml of the Test Material was applied to each designated patch. As per HRL RIPT SOP, the opposite side of the back was usually the virgin test site for the Challenge Phase.

As per HRL RIPT SOP, the Challenge patch was applied to the virgin site only. Each subject was again instructed to keep the patch on and dry.

Each subject reported to HRL approximately 24 hours later (Challenge Reading 1), at which time the patch was removed and the Challenge site scored and recorded by the HRL technician. The original test site was also observed. (See **RESULTS**, below.)

Each subject reported to HRL at approximately 48 hours (Challenge Reading 2), approximately 72 hours (Challenge Reading 3) and approximately 96 hours (Challenge Reading 4) post-patching for additional observations; reactions were scored and recorded.

SCORING SYSTEM: See Tables I-II. The test sites were scored using the modified scoring scale of the International Contact Dermatitis Research Group System: Fisher, Alexander A., *Contact Dermatitis*, Lea & Febiger, Philadelphia, 2008: p 27.

RESULTS: See Tables I-II. No adverse reactions or adverse events related to the Test Material were exhibited / reported by any subject during this test. Erythema, edema, dryness, staining, peeling and hyperpigmentation / hypopigmentation are possible, expected endpoints and not considered Adverse Reactions. This test was conducted under the supervision of a Board-Certified Dermatologist, a Co-Investigator. At Challenge Reading 3, the Dermatologist participated in the scoring of the subjects. A total of 108 subjects completed the test; 32 male and 76 female. The subjects range in age from 18 to 77.

RETENTION: All original Data Forms will be retained at HRL for a period of three years, or such other time as may be required by law. A laboratory retainer bottle of the Test Material shall be retained, in ambient conditions, for at least two years, or as required by law. Return or disposal of unused Test Material shall be as per the Sponsor's instructions—to be communicated within 30 days of receipt of this Final Report. HRL shall appropriately dispose of any remaining Test Material after six months if no Sponsor instructions have been communicated.

Personal Care Products Council
HRL Panel #19-103
Test Material #2: Vehicle (distilled water)

TABLE I: SUMMARY OF REACTIONS

TOTAL NUMBER OF SUBJECTS ENROLLED: 120
TOTAL NUMBER OF SUBJECTS COMPLETED: 108

Reaction	Induction Reading									Challenge Reading			
Grade	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**1**	**2**	**3**	**4**
0	115	115	113	113	111	112	111	111	111	108	105	107	107
±					2						3	1	1
1													
1E													
2													
2E													
3E													
4E													
-													
N9R													
Total	115	115	113	113	113	112	111	111	111	108	108	108	108

SCORING SYSTEM:
0 = No visible reaction
± = Faint, minimal erythema
1 = Erythema
2 = Intense erythema, induration
3 = Intense erythema, induration, vesicles
4 = Severe reaction with erythema, induration, vesicles, pustules (may be weeping)
E = Edema
- = No reading
N9R = No 9th reading

Personal Care Products Council

HRL Panel #19-103

Test Material #2: Vehicle (distilled water)

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

						Induction Reading									Challenge Reading			
Sub #	HRL #	Initials	Gender	Age	Race	1	2	3	4	5	6	7	8	9	1	2	3	4
1	47761	FD	M	47	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
2	39333	JM	M	41	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
3	34205	VO	F	54	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
4	42993	MC	F	54	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
5	48013	SR	F	57	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
6	47244	JJ	M	65	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
7	37725	AA	F	52	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
8	33272	BM	F	63	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
9	18875	MH	F	52	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
10	39680	GF	F	56	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
11	30434	LP	F	50	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
12	47532	CS	F	54	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
13	21928	DL	F	55	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
14	31765	PM	M	65	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
15	44323	MT	F	36	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
16	47142	RC	M	63	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
17	47098	JG	F	60	Hispanic	0	0	0	0	±	0	0	0	0	0	0	0	0
18	41212	JM	F	29	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
19	28550	CB	F	42	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
20	48040	YC	F	41	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
21	20617	BB	F	68	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
22	43107	MS	F	57	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
23	42000	DN	M	68	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
24	10420	JC	F	51	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
25	27639	CF	F	46	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0

Personal Care Products Council

HRL Panel #19-103

Test Material #2: Vehicle (distilled water)

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

						Induction Reading									Challenge Reading			
Sub #	HRL #	Initials	Gender	Age	Race	1	2	3	4	5	6	7	8	9	1	2	3	4
26	29103	XC	F	52	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
27	33101	VM	F	64	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
28	40251	EC	F	54	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
29	06915	RS	F	68	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
30	48041	DD	F	52	Caucasian	0	0	0	0	0	0	X	X	X	X	X	X	X
31	47277	TS	F	47	Bi-Racial	0	0	0	0	0	0	0	0	0	0	0	0	0
32	27357	SM	M	43	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
33	27367	EM	F	36	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
34	01435	MR	M	63	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
35	37249	MF	F	45	Black	0	0	0	0	0	0	0	0	0	0	0	±	±
36	46871	RB	F	47	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
37	41306	BB	F	49	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
38	29307	YR	F	62	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
39	47876	DF	M	37	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
40	46957	KE	F	37	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
41	11163	LB	F	34	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
42	48042	KK	F	59	Caucasian	0	0	X	X	X	X	X	X	X	X	X	X	X
43	45856	AL	F	55	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
44	41851	SK	F	45	Black	0	0	0	0	0	0	0	0	0	X	X	X	X
45	30799	AP	F	29	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
46	45378	JK	M	39	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
47	47609	PM	F	40	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
48	24505	NM	F	35	Bi-Racial	0	0	0	0	0	0	0	0	0	0	0	0	0
49	43230	MR	M	54	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
50	44591	CO	F	21	Black	0	0	0	0	0	0	0	0	0	0	0	0	0

Personal Care Products Council

HRL Panel #19-103

Test Material #2: Vehicle (distilled water)

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

						Induction Reading									Challenge Reading			
Sub #	HRL #	Initials	Gender	Age	Race	1	2	3	4	5	6	7	8	9	1	2	3	4
51	48010	CP	F	40	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
52	44992	KH	F	58	Black	0	0	X	X	X	X	X	X	X	X	X	X	X
53	44942	MM	F	44	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
54	44330	DN	F	33	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
55	44331	DR	M	38	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
56	47091	JR	M	45	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
57	05722	TD	F	57	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
58	46788	JF	F	49	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
59	47714	GF	F	18	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
60	34051	KB	F	49	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
61	46638	NA	F	59	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
62	41818	SL	F	47	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
63	38918	CN	F	57	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
64	29288	CC	F	48	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
65	36901	JH	M	51	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
66	45581	AN	F	32	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
67	45839	EG	M	49	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
68	47646	JA	M	53	Asian	0	0	0	0	0	0	0	0	0	0	0	0	0
69	47760	CP	F	33	Hispanic	0	0	0	0	0	0	0	0	0	X	X	X	X
70	38583	GW	M	60	Black	0	0	0	0	0	0	0	0	0	0	±	0	0
71	34457	MG	F	62	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
72	38892	ML	F	57	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
73	42145	MR	F	23	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
74	20113	HA	F	53	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
75	46084	CP	F	40	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0

Personal Care Products Council

HRL Panel #19-103

Test Material #2: Vehicle (distilled water)

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

Sub #	HRL #	Initials	Gender	Age	Race	Induction Reading									Challenge Reading			
						1	2	3	4	5	6	7	8	9	1	2	3	4
76	33516	RC	F	53	Bi-Racial	0	0	0	0	0	0	0	0	0	0	0	0	0
77	08440	FH	F	58	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
78	32673	AH	F	28	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
79	42011	AL	F	69	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
80	46964	KW	M	71	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
81	23295	MC	F	49	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
82	42024	DN	M	36	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
83	28119	HL	F	44	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
84	47873	ZJ	F	42	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
85	25240	CM	M	59	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
86	35008	SW	F	42	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
87	36003	AD	M	58	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
88	45196	SS	F	47	Black	X	X	X	X	X	X	X	X	X	X	X	X	X
89	43707	AC	M	53	Black	X	X	X	X	X	X	X	X	X	X	X	X	X
90	44613	RA	M	43	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
91	42521	NW	F	35	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
92	28196	JF	M	46	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
93	48046	MF	M	43	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
94	40097	DH	F	55	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
95	44216	MB	F	57	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
96	33195	EA	F	73	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
97	45617	DB	M	23	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
98	45157	DB	M	23	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
99	36619	GC	M	77	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
100	46892	SC	F	33	Caucasian	0	0	0	0	0	0	0	0	0	X	X	X	X

Personal Care Products Council
HRL Panel #19-103
Test Material #2: Vehicle (distilled water)

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

						Induction Reading									Challenge Reading			
Sub #	HRL #	Initials	Gender	Age	Race	1	2	3	4	5	6	7	8	9	1	2	3	4
101	33442	MC	F	43	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
102	47211	MR	F	69	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
103	22103	JO	F	36	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
104	48047	RR	M	26	Hispanic	0	0	0	0	0	0	0	0	0	0	±	0	0
105	46317	LP	F	39	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
106	46318	FS	M	49	Hispanic	0	0	0	0	±	0	0	0	0	0	±	0	0
107	46827	MA	F	50	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
108	48048	RB	F	73	Bi-Racial	X	X	X	X	X	X	X	X	X	X	X	X	X
109	47697	GS	M	49	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
110	43506	KR	F	29	Hispanic	X	X	X	X	X	X	X	X	X	X	X	X	X
111	33262	WV	M	50	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
112	06094	BM	F	71	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
113	30519	PV	F	63	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
114	48049	KM	F	40	Asian	0	0	0	0	0	0	0	0	0	0	0	0	0
115	34218	MR	F	74	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
116	46924	KR	M	19	Hispanic	X	X	X	X	X	X	X	X	X	X	X	X	X
117	29587	II	F	55	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
118	47635	CC	M	34	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
119	28879	MR	F	71	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
120	45989	MG	M	47	Caucasian	0	0	0	0	0	X	X	X	X	X	X	X	X

Personal Care Products Council
HRL Panel #19-103
Test Material #2: Vehicle (distilled water)

SCORING SYSTEM*:

0	=	No visible reaction
±	=	Faint, minimal erythema
1	=	Erythema
2	=	Intense erythema
3	=	Intense erythema, induration, vesicles
4	=	Severe reaction with erythema, induration, vesicles, pustules (may be weeping)
E	=	Edema
DR	=	Dryness
P	=	Peeling
S	=	Staining
^	=	Hyperpigmentation / Hypopigmentation
TR	=	Tape Reaction
C	=	Change of test site
N9R	=	No 9th reading
-	=	No patch application and / or reading
X	=	Discontinued

*International Contact Dermatitis Research Group System: Fisher, Alexander A., *Contact Dermatitis*, Lea & Febiger, Philadelphia, 2008: p 27. **(Modified)**

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Personal Care Products Council
HRL Panel #19-103
Test Material #2: Vehicle (distilled water)

QUALITY ASSURANCE MEMORANDUM

This Final Report was reviewed for accuracy and conformity with both HRL Standard Protocol #100 and HRL Standard Operating Procedures (including any Sponsor alterations) and any written communication from the Sponsor.

Inspections were accomplished by a random sampling approach and reported to the Project Manager and the Principal Investigator immediately following their completion.

Any known protocol deviations have been noted in the Final Report and/or Individual Data Form.

The raw data for this study are retained at SGS Harrison Research Laboratories, Inc.

SGS HARRISON RESEARCH LABORATORIES, INC.

Susan Lauck

SUSAN LAUCK
Quality Assurance Manager

QUALITY ASSURANCE UNIT

Date: 3/12/19

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Personal Care Products Council
HRL Panel #19-103
Test Material #3: Saline (control)

PURPOSE:	To evaluate the potential of the Test Material, as a result of repeated applications, to induce dermal sensitization in human subjects.
IRB APPROVAL:	Both the SGS HRL Standard Protocol #100 and the Informed Consent were approved by the Clarus Institutional Review Board (CIRB) on January 29, 2018. A Sponsor-signed Protocol is retained in HRL files.
SPONSOR:	Personal Care Products Council 1620 L Street NW Suite 1200 Washington, DC 20036 Per: Linda Loretz, Ph.D, DABT
SPONSOR AUTHORIZATION:	January 15, 2019
SAFETY ASSURANCE:	January 15, 2019
PRINCIPAL INVESTIGATOR:	Karen Rauen, PhD
CO-INVESTIGATORS:	Deborah R Spey, MD, Board-Certified Dermatologist Kimberly K Ruhl, MD, PhD, Board-Certified Dermatologist Adriana Ros, DO, Board-Certified Dermatologist
TEST FACILITY:	SGS Harrison Research Laboratories, Inc. (HRL) 2497 Vauxhall Road Union, New Jersey 07083
TEST MATERIAL:	Test Material Saline (control), a clear liquid, was supplied by SGS HRL (RICCA Chemical Company, Lot 2803C86, Exp. 03/20). The following instructions were received: Test as received; patch semi-occlusively.
SUBJECTS:	A total of 120 subjects were enrolled; 108 subjects completed the test. One subject, #120 (HRL #45989), was discontinued due to a protocol deviation. One subject, #088 (HRL #45196), was discontinued prior to being patched due to screen failure. Ten subjects discontinued due to personal reasons / Investigator termination. No subject discontinued due to test material reaction.

- continued -

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Personal Care Products Council
HRL Panel #19-103
Test Material #3: Saline (control)

SUBJECTS: (continued)	Of the subjects who completed this test, approximately 39% are Hispanic, approximately 33% are Caucasian, approximately 23% are Black, approximately 3% are Bi-Racial and approximately 2% are Asian.
METHOD:	This test was conducted according to HRL Standard Protocol #100 and HRL Standard Operating Procedures (including any Sponsor alterations).
TEST DATES:	January 21, 2019 through March 1, 2019.
SCORING SYSTEM:	See Tables I-II.
RESULTS:	See Tables I-II. No adverse reactions or adverse events were reported / observed in any of the subjects. During the Induction Phase, two subjects exhibited low-level (±) reactions. During the Challenge, one other subject exhibited a low-level (±) reaction.
CONCLUSION:	In this Repeated Insult Patch Test, Test Material Saline (control), did not induce dermal sensitization in human subjects.
QUALITY ASSURANCE (QA):	The QA Unit performed an in-phase audit of this study.

Deborah R Spey, MD
Co-Investigator
Board-Certified Dermatologist

Michelle Camacho, BS
Project Manager

Karen Rauen, PhD
Principal Investigator

Date: 3/13/19

Personal Care Products Council
HRL Panel #19-103
Test Material #3: Saline (control)

SUBJECTS: Each potential subject completed an HRL Subject History Form (HRL Form: SHF), including relevant medical history (an updated History Form is secured approximately every 18 months). At each subject's first visit to HRL, the subject completed a Permission To Release Personal Health Information Form in conformity with the Health Insurance Portability and Accountability Act (HIPAA) and provided proof of age. Each accepted subject was assigned a permanent HRL Identification Number. No subject was used if he or she exhibited any dermatological or other medical or physical condition that would preclude topical application of the Test Material. Upon enrollment, no subject reported using any medication that would interfere with the sensitization results. No known pregnant nor nursing women were used on this RIPT. No minor subjects were used on this RIPT.

An appropriate clearance period had elapsed since a subject was patched on a Repeated Insult Patch Test (RIPT) or a Photoallergy Test (PA) before being used in this RIPT.

Legally valid written IRB-approved Informed Consent, in conformity with: 21 CFR 50.25, Subtitle A, Protection of Human Subjects, was secured from each subject.

METHOD: Induction Phase: An approximately 2 cm X 2 cm webril/adhesive patch was used semi-occlusively. Using a precise, repeating syringe, 0.3 ml of the Test Material was applied to each designated patch. As per HRL Standard Operating Procedures (SOP) (HRL Form:SOP/RIPT), the left side of the back was usually the test area for the Induction Phase. The subject's skin was marked with gentian violet surgical marker at the left side of the test site. The test site was recorded on the anatomical diagram of each subject's individual Data Form. In addition, at that time, the prospective placement of the Challenge test site was also recorded on the anatomical diagram.

Each subject was instructed that the patch was to remain in place and kept dry for approximately 24 hours, at which time the patch was to be removed by the subject. An approximately 24-hour period, during which no test material was applied, followed the weekday patch removals; an approximately 48-hour period followed the weekend patch removals.

Each subject returned to HRL on the appropriate day. The test site was observed by the HRL technician, and the reaction scored and recorded (see **SCORING SYSTEM**, below). The identical test site was then repatched until nine (9) Induction patchings were completed.

In accordance with HRL SOP, if a subject was unable to make up a missed patching during the same week, the subject was either patched four days the following week or was patched at the end of the Induction Phase. Any absences and make-up days are noted by the dates on the individual Data Form.

A series of nine (9) Induction patchings was completed over a period of approximately three weeks.

Personal Care Products Council
HRL Panel #19-103
Test Material #3: Saline (control)

METHOD: (continued)

Rest Period: A Rest Period of approximately two weeks followed the last Induction patching; no test material was applied during the Rest Period. Subjects were instructed to notify HRL if they experienced any reaction during the Rest Period.

Challenge Phase: At the Challenge Phase, the original Induction test site was observed and each subject queried as to whether any reaction was experienced during the Rest Period. Any reactions were recorded on the Data Form. An approximately 2 cm X 2 cm webril/adhesive patch was used semi-occlusively. Using a precise, repeating syringe, 0.3 ml of the Test Material was applied to each designated patch. As per HRL RIPT SOP, the opposite side of the back was usually the virgin test site for the Challenge Phase.

As per HRL RIPT SOP, the Challenge patch was applied to the virgin site only. Each subject was again instructed to keep the patch on and dry.

Each subject reported to HRL approximately 24 hours later (Challenge Reading 1), at which time the patch was removed and the Challenge site scored and recorded by the HRL technician. The original test site was also observed. (See **RESULTS**, below.)

Each subject reported to HRL at approximately 48 hours (Challenge Reading 2), approximately 72 hours (Challenge Reading 3) and approximately 96 hours (Challenge Reading 4) post-patching for additional observations; reactions were scored and recorded.

SCORING SYSTEM: See Tables I-II. The test sites were scored using the modified scoring scale of the International Contact Dermatitis Research Group System: Fisher, Alexander A., *Contact Dermatitis*, Lea & Febiger, Philadelphia, 2008: p 27.

RESULTS: See Tables I-II. No adverse reactions or adverse events related to the Test Material were exhibited / reported by any subject during this test. Erythema, edema, dryness, staining, peeling and hyperpigmentation / hypopigmentation are possible, expected endpoints and not considered Adverse Reactions. This test was conducted under the supervision of a Board-Certified Dermatologist, a Co-Investigator. At Challenge Reading 3, the Dermatologist participated in the scoring of the subjects. A total of 108 subjects completed the test; 32 male and 76 female. The subjects range in age from 18 to 77.

RETENTION: All original Data Forms will be retained at HRL for a period of three years, or such other time as may be required by law. A laboratory retainer bottle of the Test Material shall be retained, in ambient conditions, for at least two years, or as required by law. Return or disposal of unused Test Material shall be as per the Sponsor's instructions—to be communicated within 30 days of receipt of this Final Report. HRL shall appropriately dispose of any remaining Test Material after six months if no Sponsor instructions have been communicated.

Personal Care Products Council
HRL Panel #19-103
Test Material #3: Saline (control)

TABLE I: SUMMARY OF REACTIONS

TOTAL NUMBER OF SUBJECTS ENROLLED: 120
TOTAL NUMBER OF SUBJECTS COMPLETED: 108

Reaction	Induction Reading									Challenge Reading			
Grade	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**1**	**2**	**3**	**4**
0	114	115	113	113	112	112	111	111	111	108	107	108	108
±	1				1						1		
1													
1E													
2													
2E													
3E													
4E													
-													
N9R													
Total	115	115	113	113	113	112	111	111	111	108	108	108	108

SCORING SYSTEM:

0 = No visible reaction
± = Faint, minimal erythema
1 = Erythema
2 = Intense erythema, induration
3 = Intense erythema, induration, vesicles
4 = Severe reaction with erythema, induration, vesicles, pustules (may be weeping)
E = Edema
- = No reading
N9R = No 9th reading

Personal Care Products Council
HRL Panel #19-103
Test Material #3: Saline (control)

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

						Induction Reading									Challenge Reading			
Sub #	HRL #	Initials	Gender	Age	Race	1	2	3	4	5	6	7	8	9	1	2	3	4
1	47761	FD	M	47	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
2	39333	JM	M	41	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
3	34205	VO	F	54	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
4	42993	MC	F	54	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
5	48013	SR	F	57	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
6	47244	JJ	M	65	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
7	37725	AA	F	52	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
8	33272	BM	F	63	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
9	18875	MH	F	52	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
10	39680	GF	F	56	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
11	30434	LP	F	50	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
12	47532	CS	F	54	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
13	21928	DL	F	55	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
14	31765	PM	M	65	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
15	44323	MT	F	36	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
16	47142	RC	M	63	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
17	47098	JG	F	60	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
18	41212	JM	F	29	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
19	28550	CB	F	42	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
20	48040	YC	F	41	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
21	20617	BB	F	68	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
22	43107	MS	F	57	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
23	42000	DN	M	68	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
24	10420	JC	F	51	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
25	27639	CF	F	46	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0

Personal Care Products Council

HRL Panel #19-103

Test Material #3: Saline (control)

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

						Induction Reading									Challenge Reading			
Sub #	HRL #	Initials	Gender	Age	Race	1	2	3	4	5	6	7	8	9	1	2	3	4
26	29103	XC	F	52	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
27	33101	VM	F	64	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
28	40251	EC	F	54	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
29	06915	RS	F	68	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
30	48041	DD	F	52	Caucasian	0	0	0	0	0	0	X	X	X	X	X	X	X
31	47277	TS	F	47	Bi-Racial	0	0	0	0	0	0	0	0	0	0	0	0	0
32	27357	SM	M	43	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
33	27367	EM	F	36	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
34	01435	MR	M	63	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
35	37249	MF	F	45	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
36	46871	RB	F	47	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
37	41306	BB	F	49	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
38	29307	YR	F	62	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
39	47876	DF	M	37	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
40	46957	KE	F	37	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
41	11163	LB	F	34	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
42	48042	KK	F	59	Caucasian	0	0	X	X	X	X	X	X	X	X	X	X	X
43	45856	AL	F	55	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
44	41851	SK	F	45	Black	0	0	0	0	0	0	0	0	0	X	X	X	X
45	30799	AP	F	29	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
46	45378	JK	M	39	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
47	47609	PM	F	40	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
48	24505	NM	F	35	Bi-Racial	0	0	0	0	0	0	0	0	0	0	0	0	0
49	43230	MR	M	54	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
50	44591	CO	F	21	Black	0	0	0	0	0	0	0	0	0	0	0	0	0

Personal Care Products Council

HRL Panel #19-103

Test Material #3: Saline (control)

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

						Induction Reading									Challenge Reading			
Sub #	HRL #	Initials	Gender	Age	Race	1	2	3	4	5	6	7	8	9	1	2	3	4
51	48010	CP	F	40	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
52	44992	KH	F	58	Black	0	0	X	X	X	X	X	X	X	X	X	X	X
53	44942	MM	F	44	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
54	44330	DN	F	33	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
55	44331	DR	M	38	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
56	47091	JR	M	45	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
57	05722	TD	F	57	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
58	46788	JF	F	49	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
59	47714	GF	F	18	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
60	34051	KB	F	49	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
61	46638	NA	F	59	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
62	41818	SL	F	47	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
63	38918	CN	F	57	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
64	29288	CC	F	48	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
65	36901	JH	M	51	Caucasian	0	0	0	0	±	0	0	0	0	0	0	0	0
66	45581	AN	F	32	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
67	45839	EG	M	49	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
68	47646	JA	M	53	Asian	0	0	0	0	0	0	0	0	0	0	0	0	0
69	47760	CP	F	33	Hispanic	0	0	0	0	0	0	0	0	0	X	X	X	X
70	38583	GW	M	60	Black	0	0	0	0	0	0	0	0	0	0	±	0	0
71	34457	MG	F	62	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
72	38892	ML	F	57	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
73	42145	MR	F	23	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
74	20113	HA	F	53	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
75	46084	CP	F	40	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0

Personal Care Products Council

HRL Panel #19-103

Test Material #3: Saline (control)

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

						Induction Reading									Challenge Reading			
Sub #	HRL #	Initials	Gender	Age	Race	1	2	3	4	5	6	7	8	9	1	2	3	4
76	33516	RC	F	53	Bi-Racial	0	0	0	0	0	0	0	0	0	0	0	0	0
77	08440	FH	F	58	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
78	32673	AH	F	28	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
79	42011	AL	F	69	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
80	46964	KW	M	71	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
81	23295	MC	F	49	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
82	42024	DN	M	36	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
83	28119	HL	F	44	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
84	47873	ZJ	F	42	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
85	25240	CM	M	59	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
86	35008	SW	F	42	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
87	36003	AD	M	58	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
88	45196	SS	F	47	Black	X	X	X	X	X	X	X	X	X	X	X	X	X
89	43707	AC	M	53	Black	X	X	X	X	X	X	X	X	X	X	X	X	X
90	44613	RA	M	43	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
91	42521	NW	F	35	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
92	28196	JF	M	46	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
93	48046	MF	M	43	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
94	40097	DH	F	55	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
95	44216	MB	F	57	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
96	33195	EA	F	73	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
97	45617	DB	M	23	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
98	45157	DB	M	23	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
99	36619	GC	M	77	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
100	46892	SC	F	33	Caucasian	0	0	0	0	0	0	0	0	0	X	X	X	X

Personal Care Products Council
HRL Panel #19-103
Test Material #3: Saline (control)

TABLE II: INDIVIDUAL SUBJECT DATA

(see Scoring System, page 11)

						Induction Reading									Challenge Reading			
Sub #	HRL #	Initials	Gender	Age	Race	1	2	3	4	5	6	7	8	9	1	2	3	4
101	33442	MC	F	43	Hispanic	±	0	0	0	0	0	0	0	0	0	0	0	0
102	47211	MR	F	69	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
103	22103	JO	F	36	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
104	48047	RR	M	26	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
105	46317	LP	F	39	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
106	46318	FS	M	49	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
107	46827	MA	F	50	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
108	48048	RB	F	73	Bi-Racial	X	X	X	X	X	X	X	X	X	X	X	X	X
109	47697	GS	M	49	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
110	43506	KR	F	29	Hispanic	X	X	X	X	X	X	X	X	X	X	X	X	X
111	33262	WV	M	50	Black	0	0	0	0	0	0	0	0	0	0	0	0	0
112	06094	BM	F	71	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
113	30519	PV	F	63	Caucasian	0	0	0	0	0	0	0	0	0	0	0	0	0
114	48049	KM	F	40	Asian	0	0	0	0	0	0	0	0	0	0	0	0	0
115	34218	MR	F	74	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
116	46924	KR	M	19	Hispanic	X	X	X	X	X	X	X	X	X	X	X	X	X
117	29587	II	F	55	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
118	47635	CC	M	34	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
119	28879	MR	F	71	Hispanic	0	0	0	0	0	0	0	0	0	0	0	0	0
120	45989	MG	M	47	Caucasian	0	0	0	0	0	X	X	X	X	X	X	X	X

Personal Care Products Council
HRL Panel #19-103
Test Material #3: Saline (control)

SCORING SYSTEM*:

0	=	No visible reaction
±	=	Faint, minimal erythema
1	=	Erythema
2	=	Intense erythema
3	=	Intense erythema, induration, vesicles
4	=	Severe reaction with erythema, induration, vesicles, pustules (may be weeping)
E	=	Edema
DR	=	Dryness
P	=	Peeling
S	=	Staining
^	=	Hyperpigmentation / Hypopigmentation
TR	=	Tape Reaction
C	=	Change of test site
N9R	=	No 9th reading
-	=	No patch application and / or reading
X	=	Discontinued

*International Contact Dermatitis Research Group System: Fisher, Alexander A., *Contact Dermatitis*, Lea & Febiger, Philadelphia, 2008: p 27. (Modified)

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Personal Care Products Council
HRL Panel #19-103
Test Material #3: Saline (control)

QUALITY ASSURANCE MEMORANDUM

This Final Report was reviewed for accuracy and conformity with both HRL Standard Protocol #100 and HRL Standard Operating Procedures (including any Sponsor alterations) and any written communication from the Sponsor.

Inspections were accomplished by a random sampling approach and reported to the Project Manager and the Principal Investigator immediately following their completion.

Any known protocol deviations have been noted in the Final Report and/or Individual Data Form.

The raw data for this study are retained at SGS Harrison Research Laboratories, Inc.

SGS HARRISON RESEARCH LABORATORIES, INC.

Susan Lauck

SUSAN LAUCK
Quality Assurance Manager

QUALITY ASSURANCE UNIT

Date: 3/12/19

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: April 16, 2019

SUBJECT: Polyaminopropyl Biguanide (PHMB): QRA Worksheet

Attached is the QRA worksheet updated to use a NESIL of 750 μg/cm^2.

Product Category	Max Use (%)	Product Exposure (µg/cm^2)	PHMB CEL (µg/cm^2)	PHMB NESIL (µg/cm^2)	SAF	PHMB AEL	AEL/CEL	Reference for Exposure
Baby lotions, oils, powders, creams	0.1	2200	2.20	750	300	**2.50**	1.14	IFRA RIFM QRA Information Booklet version 7.1 July 2015 (Category 3)
Eye shadow	0.03	2170	0.65	750	300	**2.50**	3.84	Api et al., 2008 Eye products.
Eye lotion	0.2	2170	4.34	750	300	**2.50**	0.58	Api et al., 2008 Eye products.
Eye makeup remover	0.056	900	0.50	750	100	**7.50**	14.88	Api et al., 2008 Make-up remover.
Mascara	0.1	2170	2.17	750	300	**2.50**	1.15	Api et al., 2008 Eye products.
Other eye makeup	0.01	2170	0.22	750	300	**2.50**	11.52	Api et al., 2008 Eye products.
Hair conditioners	0.06	200	0.12	750	100	**7.50**	62.50	Api et al., 2008 Conditioners, rinse-off.
Hair straighteners	0.01	4200	0.42	750	100	**7.50**	17.86	IFRA RIFM QRA Information Booklet version 7.1 July 2015 (Category 5, relaxers)
Shampoos (noncoloring)	0.008	170	0.01	750	100	**7.50**	551.47	Api et al., 2008 Shampoos.
Tonics, dressings and other hair grooming aids	0.1	990	0.99	750	100	**7.50**	7.58	Api et al., 2008 Hair styling aids
Other noncolring hair products	0.002	1000	0.02	750	100	**7.50**	375.00	IFRA RIFM QRA Information Booklet version 7.1 July 2015 (Category 8).
*Hair dyes and colors	0.1	1000	1.00	750	100	**7.50**	7.50	IFRA/RIFM QRA Information Booklet version 7.1 July 2015, (Category 8).
Foundations	0.01	3170	0.32	750	100	**7.50**	23.66	Api et al., 2008 Women's facial liquid makeup.
Deodorants (underarm)	0.003	8500	0.26	750	300	**2.50**	9.80	Api et al., 2008 Solid AP.
Other personal cleanliness products	0.006	4400	0.26	750	300	**2.50**	9.47	Api et al., 2008 Intimate wipes.
Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.1	900	0.90	750	100	**7.50**	8.33	Api et al., 2008 Make-up remover.
Face and neck creams, lotions, powders and sprays	0.02	2700	0.54	750	100	**7.50**	13.89	Api et al., 2008 Women's facial cream
Body and hand creams, lotions and powders	0.009	1120	0.10	750	300	**2.50**	24.80	Api et al., 2008 Body creams and lotions
Moisturizers	0.00075	2700	0.02	750	100	**7.50**	370.37	Api et al., 2008 Women's facial cream
Skin fresheners	0.0085	150	0.01	750	100	**7.50**	588.24	Api et al., 2008 Face washes, gels, scrubs.
Suntan gels, creams, liquids	0.1	2200	2.20	750	100	**7.50**	3.41	IFRA RIFM QRA Information Booklet version 7.1 July 2015 (Category 4)
Eye lotiion with maximum supportable PI	0.11	2170	2.39	750.00	300	**2.50**	1.05	Api et al., 2008 Eye products.

Product Category	Max Use (%)	Product Exposure ($\mu g/cm^2$)	PHMB CEL ($\mu g/cm^2$)	PHMB NESIL ($\mu g/cm^2$)	SAF	PHMB AEL	AEL/CEL	Reference for Exposure
Baby lotions, oils, powders, creams	0.1	2200	2.20	1000	300	**3.33**	1.52	IFRA RIFM QRA Information Booklet version 7.1 July 2015 (Category 3)
Eye shadow	0.03	2170	0.65	1000	300	**3.33**	5.12	Api et al., 2008 Eye products.
Eye lotion	0.2	2170	4.34	1000	300	**3.33**	0.77	Api et al., 2008 Eye products.
Eye makeup remover	0.056	900	0.50	1000	100	**10.00**	19.84	Api et al., 2008 Make-up remover.
Mascara	0.1	2170	2.17	1000	300	**3.33**	1.54	Api et al., 2008 Eye products.
Other eye makeup	0.01	2170	0.22	1000	300	**3.33**	15.36	Api et al., 2008 Eye products.
Hair conditioners	0.06	200	0.12	1000	100	**10.00**	83.33	Api et al., 2008 Conditioners, rinse-off.
Hair straighteners	0.01	4200	0.42	1000	100	**10.00**	23.81	IFRA RIFM QRA Information Booklet version 7.1 July 2015 (Category 5, relaxers)
Shampoos (noncoloring)	0.008	170	0.01	1000	100	**10.00**	735.29	Api et al., 2008 Shampoos.
Tonics, dressings and other hair grooming aids	0.1	990	0.99	1000	100	**10.00**	10.10	Api et al., 2008 Hair styling aids
Other noncolring hair products	0.002	1000	0.02	1000	100	**10.00**	500.00	IFRA RIFM QRA Information Booklet version 7.1 July 2015 (Category 8).
*Hair dyes and colors	0.1	1000	1.00	1000	100	**10.00**	10.00	IFRA/RIFM QRA Information Booklet version 7.1 July 2015, (Category 8).
Foundations	0.01	3170	0.32	1000	100	**10.00**	31.55	Api et al., 2008 Women's facial liquid makeup.
Deodorants (underarm)	0.003	8500	0.26	1000	300	**3.33**	13.07	Api et al., 2008 Solid AP.
Other personal cleanliness products	0.006	4400	0.26	1000	300	**3.33**	12.63	Api et al., 2008 Intimate wipes.
Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.1	900	0.90	1000	100	**10.00**	11.11	Api et al., 2008 Make-up remover.
Face and neck creams, lotions, powders and sprays	0.02	2700	0.54	1000	100	**10.00**	18.52	Api et al., 2008 Women's facial cream
Body and hand creams, lotions and powders	0.009	1120	0.10	1000	300	**3.33**	33.07	Api et al., 2008 Body creams and lotions
Moisturizers	0.00075	2700	0.02	1000	100	**10.00**	493.83	Api et al., 2008 Women's facial cream
Skin fresheners	0.0085	150	0.01	1000	100	**10.00**	784.31	Api et al., 2008 Face washes, gels, scrubs.
Suntan gels, creams, liquids	0.1	2200	2.20	1000	100	**10.00**	4.55	IFRA RIFM QRA Information Booklet version 7.1 July 2015 (Category 4)
Eye lotiion with maximum supportable PHMB	0.15	2170	3.26	1000.00	300	**3.33**	1.02	Api et al., 2008 Eye products.

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Memorandum

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

FROM: Alexandra Kowcz
Industry Liaison to the CIR Expert Panel

DATE: May 30, 2018

SUBJECT: Draft Final Report: Safety Assessment of Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride) as Used in Cosmetics (draft prepared for the June 4-5, 2018 CIR Expert Panel meeting)

The Council respectfully submits the following comments on the draft final report, Safety Assessment of Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride) as Used in Cosmetics.

Key Issues

Rather than comparing exposure concentrations, the inhalation risk assessment should compare mg/kg/day doses.

The search strategy does not indicate that the search was updated before the June meeting draft was prepared. A new study[1] (abstract attached) concerning effects on rat liver was published in March 2018.

Sensitization - When discussing the HRIPT of the product containing 0.2% Polyaminopropyl Biguanide, it should be noted that the inclusion criteria stated: "Were of any skin type or ethnicity, provided their degree of skin pigmentation did not significantly interfere with evaluations."

Additional Considerations

Dermal Penetration - The identity of the receptor fluids used should be stated for the *in vitro* dermal penetration studies.

Acute, Inhalation - There is a second acute (4 hour) inhalation exposure study (cited in the SCCS opinion; reference 12) that is presented in Table 8 that is not presented in the text. As this study used more exposure concentrations, they were able to estimate an LC_{50} value. This

[1]Chowdhury A, Arnold LL, Wang Z, et al. 2018. Effect of polyhexamethylene biguanide on rat liver. *Toxicol Lett* 285: 94-103.

study should also be mentioned in the text. Please provide a reference for the mouse acute inhalation study.

Risk Assessment, Dermal - Only the most recent MOS calculation from the SCCS should be presented in the CIR report.

Case Reports - The study in which 29 patients were exposed to a pre-operative antiseptic for cataract surgery is a clinical study and should not be presented in the Case Reports subsection.

Toxicol Lett. 2018 Mar 15;285:94-103. doi: 10.1016/j.toxlet.2017.12.032. Epub 2018 Jan 2.

Effect of polyhexamethylene biguanide on rat liver.

Chowdhury A[1], Arnold LL[1], Wang Z[2], Pennington KL[1], Dodmane P[1], Farragut-Cardoso AP[1], Klaunig JE[2], Cros D[3], Creppy EE[4], Cohen SM[5].

Author information

Abstract

Polyhexamethylene **biguanide** (PHMB), an amphiphilic polymeric biocide, increased liver tumor incidence in male and female rats at 1000 and 1500 mg/L in drinking water, but not at 500 mg/L in previous studies. In another study, PHMB administered in diet at 4000 mg/kg was negative for hepatocellular tumors. The present studies evaluated bioavailability and distribution of PHMB administered in drinking water and diet and possible modes of action (MOA). PHMB in drinking water was unpalatable during the first 3 days, resulting in markedly decreased food consumption and decreased body weight. Ki-67 labeling index was increased in hepatocytes and endothelial cells dose responsively with PHMB administered in drinking water but not diet. Vitamin E had no effect on this. There was no cytotoxicity by histopathology or serum enzymes, and no increase in cytokines TNFα, IL-1α or NF-κB. Focal iron deposition in sinusoidal lining cells was detected. Microarray analyses were non-contributory. No effect on CAR or PPARα activation was detected. ^{14}C-PHMB administered at 500, 1000, or 1500 mg/L in the drinking water or 4000 mg/kg in the diet was nearly completely absorbed and excreted in urine, with some fecal excretion. The hypothesized MOA for liver tumors induced by PHMB in drinking water is: 1) severe dehydration and starvation because of unpalatability, followed by ingestion with rapid absorption and urinary excretion; 2) increased hepatocyte proliferation; and 3) induction of hepatocellular foci and tumors. The PHMB-induced rat hepatocellular tumors are unlikely to pose a human cancer risk. However, the actual MOA has not been determined.

KEYWORDS: CAR activation; Dehydration; Hepatocellular proliferation; Iron deposition; Mitogenesis; PPARα activation

PMID: 29305328 DOI: 10.1016/j.toxlet.2017.12.032

[Indexed for MEDLINE]

MeSH terms, Substances

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Memorandum

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

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

DATE: November 28, 2018

SUBJECT: Strategy Memo: Polyaminopropyl Biguanide (prepared for the December 3-4, 2018 CIR Expert Panel Meeting)

The Council respectfully submits the following comment on the strategy memo on Polyaminopropyl Biguanide.

Key Issue

The memo states: "The most recent use data reported in the Council's survey indicated the maximum use concentration of Polyaminopropyl Biguanide in pump and propellant hair sprays is 0.053% and 0.0004%, respectively." This is not correct. An updated table was provided on July 17, 2017. The hair spray products were removed from the table. The Council no longer has any reported uses in spray products.

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