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

Status: Draft Final Report for Panel Review
Release Date: November 10, 2017
Panel Date: December 4-5, 2017

The 2017 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 and Ivan Boyer, Ph.D., former CIR Toxicologist.

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Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons

From: Wilbur Johnson, Jr.
Senior Scientific Analyst

Date: November 10, 2017

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

At the September 11-12, 2017 Panel meeting, the Panel issued a Tentative Report with a conclusion stating 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. The Panel also determined that the following data are needed:

- 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.

To date, the data stated above have not been received. Comments on the Tentative Report that were received from the Council (*polyam122017pcpc1, polyam122017pcpc2, polyam122017pcpc3, polyam122017pcpc4, and polyam122017pcpc5*) have been addressed and are attached for the Panel's review. One of the comments (*polyam122017pcpc5,* page 1*)* relates to the inhalation risk assessment, and toxicologists on the Panel are being asked to review this comment and identify the information that needs to be added to the inhalation risk assessment section of the safety assessment.

Also included in this package for your review are the Draft Final Report (*polyam122017rep*), the CIR report history (*polyam122017hist.docx*), Flow chart (*polyam122017flow.docx*), Literature search strategy (*polyam122017strat.docx*), Ingredient data profile (*polyam122017prof.docx*), 2017 FDA VCRP data (*polyam122017FDA.docx*), and minutes from the September 11-12, 2017 Panel meeting and prior Panel meetings (*polyam122017min.docx)*.

Another 2017 case report relating to Polyaminopropyl Biguanide-induced anaphylaxis was identified in the published literature, and a summary (of the publication abstract) is enclosed within horizontal borders in the Case Reports section of the Draft Final Report. An effort to obtain the full publication is underway.

After reviewing these documents, the Panel will determine whether or not a Final Report with the conclusion that is stated above should be issued.

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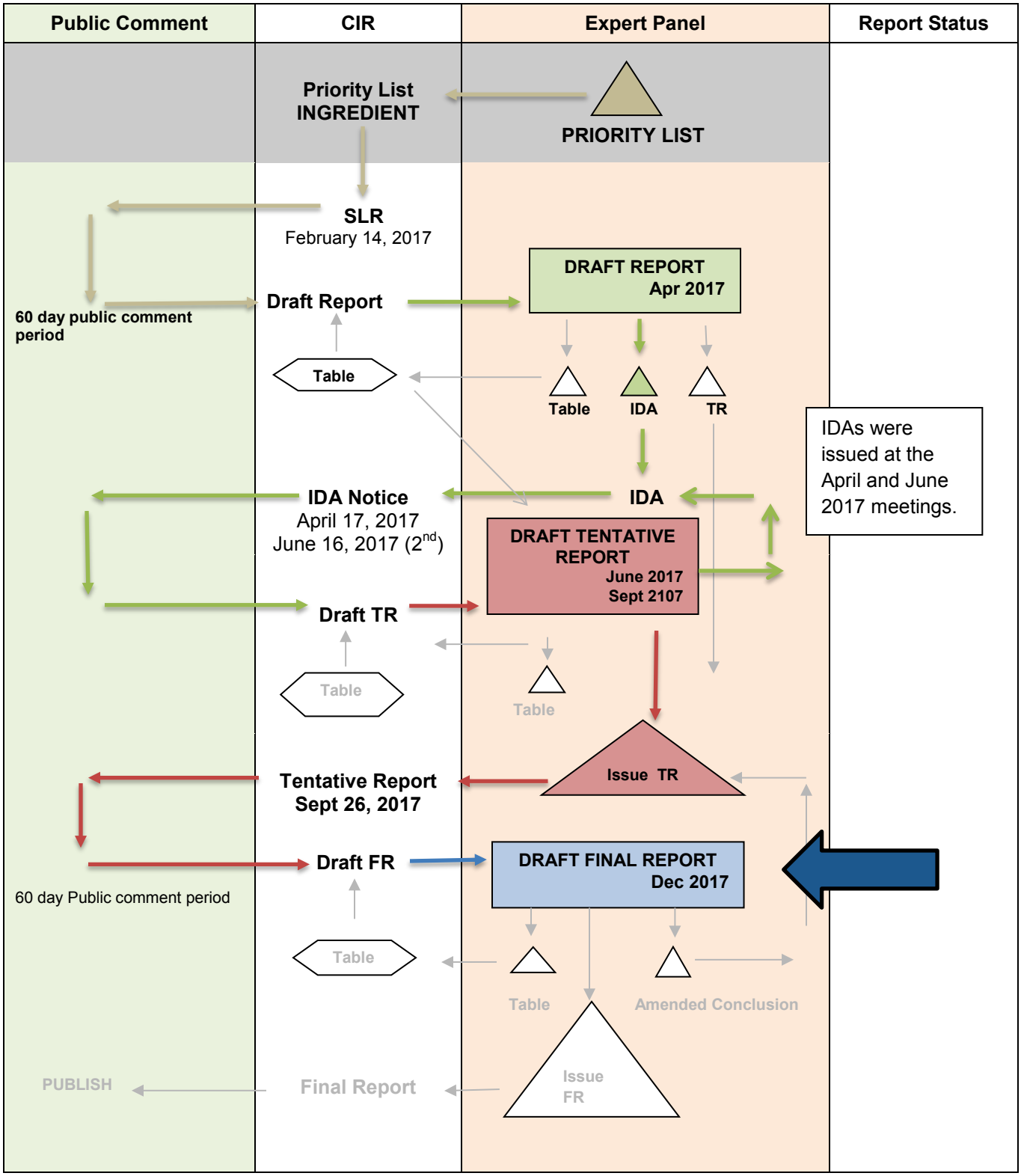
SAFETY ASSESSMENT FLOW CHART

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

MEETING Dec 2017



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 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.

Polyaminopropyl Biguanide Data Profile for December 4th-5th, 2017 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 3/7/2017; Updated on 10/20/2017)

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/

Botanical Websites, if applicable
Dr. Duke's https://phytochem.nal.usda.gov/phytochem/search
Taxonomy database - http://www.ncbi.nlm.nih.gov/taxonomy
GRIN (U.S. National Plant Germplasm System) - https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
Sigma Aldrich plant profiler http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html

Fragrance Websites, if applicable
IFRA (International Fragrance Association) – http://www.ifraorg.org/

RIFM (the Research Institute for Fragrance Materials) should be contacted

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.

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.

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.)

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

Status: Draft Final Report for Panel Review
Release Date: November 10, 2017
Panel Date: December 4-5, 2017

The 2017 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 and Ivan Boyer, Ph.D., former CIR Toxicologist.

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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, as used as a preservative in cosmetics, is reviewed in this assessment.[1] This cosmetic ingredient is the hydrochloride salt of an amino polymer comprising hexyl biguanide repeat units (i.e., polyhexamethylene biguanide hydrochloride (PHMB HCl)); it has a 6-carbon chain in each monomeric repeat unit, and is always supplied as the hydrochloride salt. There is a substance identified by the ***chemical name*** polyaminopropyl biguanide; that substance is not a cosmetic ingredient.

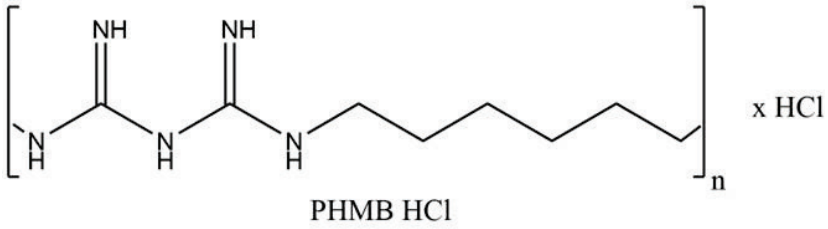
In CIR safety assessments, it is standard procedure to capitalize INCI names, but to use lower case for standard chemical names. Accordingly, throughout this report, when the capitalized INCI name Polyaminopropyl Biguanide is used, it is to be understood that it is referring to the cosmetic ingredient that has the chemical name polyhexamethylene biguanide hydrochloride. It should also be understood that Polyaminopropyl Biguanide 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 (http://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; http://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 is the hydrochloride salt of an amino polymer comprising hexyl biguanide repeat units (PHMB HCl). The definition of this ingredient is also presented in Table 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 (the INCI name, Polyaminopropyl Biguanide, is an artifact of arbitrarily choosing the middle of the C6 alkyl chains to identify the polymer repeating units of the ingredient).[2]

Chemical and Physical Properties

Polyaminopropyl Biguanide is a polymer that, in its neat form, is a solid/powder with purity > 94.2 %, and is often marketed as an approximately 20% aqueous, pre-formulation solution.[3] Chemical and physical properties are summarized in Table 2.

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 2017 VCRP data, Polyaminopropyl Biguanide is being used in 147 cosmetic products, mostly leave-on products.[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 and concentrations up to 0.1% in rinse-off products (Table 3).[6]

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]

Noncosmetic

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 4.

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 11940 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

The toxicokinetics studies (oral exposure) summarized below are presented in Table 5.

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.[12,19] 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 cyanoguanidino-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]

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Animal

The acute toxicity data summarized below are presented in Table 6 (dermal studies), Table **7** (oral studies), and Table 8 (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.[18] A median lethal dosage of 25.6 mg/kg was reported for rats dosed orally with a 0.4% Polyaminopropyl Biguanide solution.[20]

Inhalation

An LC_{50} was reported to be > 0.36 mg/l in acute inhalation toxicity studies in which rats were exposed for 4 h to Polyaminopropyl Biguanide solutions (concentrations up to 360 mg/m^3 in air).[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.

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 9.

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] 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.[20]

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 10.

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.[12,18] 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.[12,18]

Chronic Toxicity Studies

Animal

The chronic dermal and oral toxicity studies summarized below are presented in Table 11.

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).[18] 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.[18] 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.[18]

Human

Risk Assessment - Dermal

In this risk assessment, the NOAEL from a chronic oral toxicity study (summarized in Table 11) was used in the MOS calculation. According to the test procedure, Polyaminopropyl Biguanide (20.2% aqueous) was administered in the diet daily for 104 weeks at concentrations of 0, 200, 600, and 2000 ppm (corresponding to 0, ~12.1, ~36.3, and ~126.1 mg/kg/day in male rats and 0, ~14.9, ~45.3, and ~162.3 mg/kg/day in female rats). The NOAELs for male and female rats in this study were 36 mg/kg/day and 45 mg/kg/day, respectively. The following assumptions were used to calculate a MOS: all cosmetics contain 0.3% Polyaminopropyl Biguanide, the NOAEL is 36 mg/kg/day, and dermal penetration is 7.65%. The estimated systemic exposure dose (SED) was 0.0666 mg/kg/day and the MOS was calculated to be 46 for Polyaminopropyl Biguanide (based on cosmetic exposure estimate).[12] In this calculation, the value for dermal penetration was determined based on dermal penetration data on one type of cosmetic formulation (oil/water emulsion; specific cosmetic product categories not mentioned). However, it was noted that the dermal penetration data are being used to support the safety of Polyaminopropyl Biguanide in all types of cosmetic products. Also, in this calculation, 17.4 g/day was considered the amount of cosmetic product that was applied daily; the assumed exposure duration was not stated. In more recent MOS calculations (assuming that all cosmetics contain 0.1% Polyaminopropyl Biguanide; from most recent SCCS opinion), an SED of 0.012 mg/kg/day was based on the assumption that the residual stratum corneum + epidermis fractions do not contribute to the SED.

The results of a dermal penetration study (summarized earlier in the report) indicated that absorption through the skin equaled 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%) was added to the absorbed amount, yielding a calculated dermal absorption value of 4.09% (1.56% + 0.03% + 2.5% = 4.09%) that is being used in the SCCS MOS calculation.[3,12] The new 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 SCCS performed the margin of safety calculations.[3]

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 Agency'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 U.S. population and all population subgroups.[14] These estimates were below EPA's level of concern for the general U.S. 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]

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 to be above the EPA's level of concern (ARI of 1).[14]

Risk Assessment - Inhalation

The most recent Council survey of maximum reported use concentrations by product category (updated on July 18, 2017) indicates that Polyaminopropyl Biguanide is no longer being used in pump or propellant hair sprays.[22] 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, 2017 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)[23,24,25,26,27] 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.

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 (Table 12).[25] 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.[27] 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.[25,27] 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 (Table 12).

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 (Table 12).

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 (Table 12).

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 13.

NOAECs of 1,000 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)[12,28] 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] A 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.[12,28] A 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). [21]

GENOTOXICITY STUDIES

The genotoxicity studies (in vitro and in vivo) summarized below are presented in Table 14.

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 15.

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 involving RAW 264.7 mouse macrophages (a macrophage-like, Abelson leukemia virus transformed cell line derived from BALB/c mice), 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]

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.[18] 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.[12,18] 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 Polyaminmopropyl 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.[18] 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.[29]

OTHER RELEVANT STUDIES

Effect on Lung Cells

A study was performed to characterize the inflammatory responses, include the mechanism of action, induced in lung cells exposed to Polyaminopropyl Biguanide.[30] 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 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.[31] 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 *Echerichia 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 ($P \leq 0.0006$).[31]

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.[32] These effects have been assessed in vitro using 3 cell types: Caco-2 cells (from a human colon adenocarcinoma) with non-functional p53 genes (Δp53: mut p53), N2-A (Neuro-2A cells, mouse neural cells), because the brain is a possible target organ in rodents, and HepG2 cells (human hepatocellular carcinoma) with functional p53 genes. 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. 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.[32]

DERMAL IRRITATION AND SENSITZATION STUDIES

The skin irritation, sensitization, and phototoxicity/photosensitization studies summarized below are presented in Table 16.

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.[18] 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.[33] 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.[18] 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.[12]

Sensitization

Results were positive for Polyaminopropyl Biguanide in the local lymph node assay (LLNA).[34,37] 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 Polyaminopropyl Biguanide (2% active ingredient) was not capable of causing primary skin irritation, but was capable of causing sensitization.[3] When a leave-on product containing 0.1 % Polyaminopropyl Biguanide (0.5% of a trade name material containing 20% Polyaminopropyl Biguanide) was evaluated in an HRIPT involving 207 subjects, it was concluded that the product did not induce dermal sensitization.[36] In another HRIPT (115 subjects) on a neck cream containing 0.2% Polyaminopropyl Biguanide, the product did not cause clinically meaningful irritation or sensitization (the racial makeup of the study population is presented in Table 16; Fitzpatrick skin types not stated).[35]

Risk Assessment

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.[38] 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 16) 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 16) involving 1974 patients, 9 (0.5%) had positive reactions to 2.5% aqueous Polyaminopropyl Biguanide. 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.

A quantitative risk assessment (QRA) was performed by industry in response to the Panel's concerns about sensitization potential.[39] The QRA for contact dermatitis with Polyaminopropyl Biguanide in cosmetics yielded a no expected sensitization induction level (NESIL) of 1,000 $\mu g/cm^2$, which supports the use of this ingredient at concentrations of $\leq 0.1\%$. 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 $\mu g/cm^2$, the highest non-sensitizing dose in relation to all of the HRIPT data that were considered. The NESIL of 1,000 $\mu g/cm^2$ was used to determine whether estimated exposure, using maximum use concentrations from a Council survey, could be considered safe. MOEs were all >1, except for the product that contained 0.2% Polyaminopropyl Biguanide.

Photosensitization/Phototoxicity

Animal

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%.[18]

Human

When tested at a concentration of 1% (dose = 1 mg/cm^2) in 26 subjects, Polyaminopropyl Biguanide was essentially non-irritating and did not induce sensitization, phototoxicity, or photoallergenicity.[3] The dose (1 mg/cm^2) used in this study was specified by the Cosmetics Europe Consortium in response to a CIR request for additional information.[40]

OCULAR IRRITATION STUDIES

The ocular irritation studies summarized below are presented in Table 17.

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.[18] 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 (20% aqueous) into the eyes induced slight inflammation, but no corneal ulceration.[18] Ocular irritation was not observed when Polyaminopropyl Biguanide (0.04% active ingredient) was instilled into the eyes of rabbits.[18] 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.[41]

CLINICAL STUDIES

The patient multicenter studies summarized below are presented in the Human Sensitization Studies section of Table 16.

Retrospective and Multicenter Studies

In a multicenter study involving 374 patients patch tested with 2.5% aqueous Polyaminopropyl Biguanide, 2 sensitization reactions were reported.[38,42] 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.[44] In a multicenter study involving 1554 patients, sensitization reactions were observed in 6 patients patch tested with 0.5% Polyaminopropyl Biguanide.[43]

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.[45] 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.[46] 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.[47] 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.

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.[48]

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.[17,49] 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.[46] 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.[50]

Two cases of severe anaphylaxis were reported following contact of a surgical wound with a hospital disinfectant containing 0.2 % Polyaminopropyl Biguanide.[51] 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.[52] 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.[53] Four of 28 patients were excluded from a cohort study because of adverse effects related to a Polyaminopropyl Biguanide dressing.[54]

Reportedly, the application of very high doses (doses not stated) of Polyaminopropyl Biguanide can trigger fever and a generalized exanthema.[21]

Polyhexamethylene Guanidine Phosphate (PHMG)

Beginning in 2006, epidemics of a fatal lung injury were observed in Korea every spring.[55] 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.

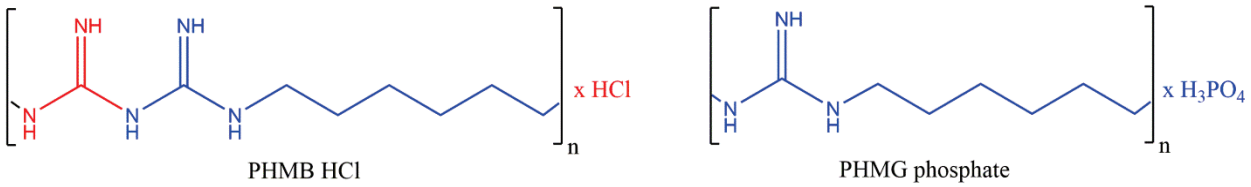


Figure 2. Polyaminopropyl Biguanide (PHMB HCl) vs PHMG phosphate.

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.[56] 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 [CMIT/MIT]) or a guanidinium derivative (oligo(2-(2-ethoxy)ethoxyethyl guanidinium chloride [PHG]).[56]

An analysis of patients and fatalities attributed to inhalation exposure to PHMG indicates that this chemical mainly causes lung diseases, such as pulmonary fibrosis.[57] 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,[58] the time-weighted average (TWA) PHMG concentration in the bedroom air was 0.06 mg/m^3 (calculated value) 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 27 times greater than the 0.0022 mg/m^3 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 12 in the safety assessment reportFurther, 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 (polyhexamethylene biguanide hydrochloride (PHMB HCl)). (It is not synonymous with the substance that has 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 2017 VCRP data, Polyaminopropyl Biguanide is being used in 147 cosmetic products, mostly leave-on product. 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 and concentrations up to 0.1% in rinse-off products.

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% (absorbed dose = 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 rat studies. 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. 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.

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 involving RAW 264.7 mouse macrophages, 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 Polyaminmopropyl 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 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.

Polyhexamethylene biguanide exhibited high antimicrobial activity against *Staphylococcus aureus* and *Echerichia coli*, whereas, though chemically closely related, Polyaminopropyl Biguanide proved to be ineffective in bacterial eradication. When compared to 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.

Case reports with sensitization reactions to Polyaminopropyl Biguanide (reported as an ingredient of wet wipes, contact lens cleansing solutions, wound irrigation solutions, and pre-operative antiseptics) 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 no expected sensitization induction level (NESIL) of 1000 $\mu g/cm^2$, which supports the use of this ingredient at concentrations of $\leq 0.1\%$. 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 $\mu g/cm^2$, 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 $\geq$100 subjects is usually preferred). Furthermore, in an HRIPT on a neck cream containing 0.2% Polyaminopropyl Biguanide (dose = 100 $\mu g/cm^2$) 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 $\mu g/cm^2$ 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 $\mu g/cm^2$ is needed.

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, 2017 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 has 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.

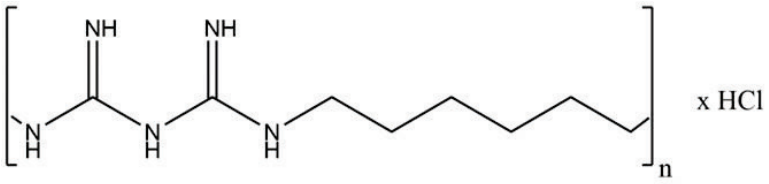
CONCLUSION

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. Definition, idealized structure, and function of the ingredient in this safety assessment.[1; [CIR Staff]]

Ingredient CAS No.	Definition & Idealized Structure	Function
Polyaminopropyl Biguanide 32289-58-0 [PHMB HCl] [27083-27-8 (PHMB HCl)] [28757-47-3 (PHMB)]	Polyaminopropyl Biguanide is the organic compound that conforms to the formula. [Polyaminopropyl Biguanide is the hydrochloride salt of an amino polymer comprising hexyl biguanide repeat units (polyhexamethylene biguanide (PHMB HCl).]	Preservatives



PHMB HCl

Table 2. 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 3. Frequency and concentration 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	*102*	*0.00001-0.2*
Rinse-Off	*45*	*0.00025-0.1*
Diluted for (Bath) Use	*NR*	*NR*
Exposure Type		
Eye Area	28	0.01-0.2
Incidental Ingestion	1	NR
Incidental Inhalation-Spray	1; 29[a]; 31[b]	0.000023-0.1[a]
Incidental Inhalation-Powder	31[b]	NR
Dermal Contact	116	0.00001-0.2
Deodorant (underarm)	NR	0.003
Hair - Non-Coloring	16	0.000023-0.1
Hair-Coloring	NR	0.1
Nail	2	NR
Mucous Membrane	10	NR
Baby Products	NR	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 4. 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 µl/cm^2; ≈ 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]

Table 4. Dermal Penetration Studies

Ingredient	Animals/Protocol	Results
[^{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 µl/cm^2; application rate ≈ 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 radioactivy 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 Biguanideformulation 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]
[^{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 5. 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 (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]
[^{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.[12,19]
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.[12,19]
[^{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.[18]

Table 5. Toxicokinetics Studies

Ingredient	Animals/Protocol	Results
[^{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.[18]
[^{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 6. 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.[18]
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 7. 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.[18]
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.[18]
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.[18]
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.[20]

Table 8. Acute Inhalation Toxicity

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/m^3, respectively, and RD_{50} (concentration causing 50 % depression in respiratory rate) 264 mg/m^3 (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 9. 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.[18]
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).[18]
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.[18]
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]

Table 9. Short-Term Toxicity Studies

Ingredient	Animals	Protocol	Results
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]
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.[20]
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/m^3 (MMAD range: 0.32-1.30 µm), 0.257 mg/m^3 (MMAD range: 0.48-5.06 µm) and 2.47 mg/m^3 (MMAD range: 0.67-1.67 µm)	No treatment-related deaths or clinical signs up to 2.5 mg/m^3. No toxicologically significant changes in hematology or blood clinical chemistry parameters. Lung weights slightly elevated for males and females exposed to 2.5 mg/m^3; thymus weights elevated in males only at 2.5 mg/m^3. 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/m^3, and tracheal inflammation in males and females at 2.5 mg/m^3. Pneumonitis and bronchitis in the lung in males and females exposed to 2.5 mg/m^3, at end of exposure period and recovery period. NOAEC = 0.0239 mg/m^3.[12]

Table 9. 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 10. 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.[18]
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]

Table 10. Subchronic Toxicity Studies

Ingredient	Animals	Protocol	Results
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.[12,18]
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 11. 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).[3,18]
		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.[18]

Table 11. Chronic Toxicity Studies

Ingredient	Animals	Protocol	Results
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]
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.[18]
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.[18]
Polyaminopropyl Biguanide	Strain not specified	Chronic toxicity study (protocol not described).	NOEL = 200 mg/kg/day.[21]

Table 11. Chronic Toxicity Studies

Ingredient	Animals	Protocol	Results
Polyaminopropyl Biguanide	Strain not specified	2-year chronic toxicity study (protocol not detailed). Dosage weight: 100 mg/kg/day	No adverse effects.[21]

Table 12. Exposure Concentrations and Margins of Safety (MOSs) for Hair Spray Products Calculated using the ConsExpo Web Model (ver. 1.0.1).[24]

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.[25,27]

[b]default room ventilation rate specified in REACH guidance (Chapter R.15 Consumer exposure estimation, ECHA 2012), as noted in RIVM report.[27]

[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.[26]

[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 13. 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.[12,18]
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]

Table 13. Developmental and Reproductive Toxicity Studies

Ingredient	Animals	Protocol	Results
20% aqueous Polyaminopropyl Biguanide (in 0.5% aqueous polyoxyethylene(20)sorbitan monooleate)	Groups of 47 to 49 specific pathogen-free 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.[12,28]
0.04% Polyaminopropyl Biguanide	Animal strain not specified.	Oral dosing (test protocol not included)	Embryotoxic at 32 mg/kg/day.[21]
Polyaminopropyl Biguanide	Rats (number and strain not specified)	Rats dosed orally with 100 mg/kg/day	Embryotoxic.[21]
Polyaminopropyl Biguanide	Rats (number and strain not specified)	Rats dosed intraperitoneally with 10 mg/kg/day	Teratogenic.[21]
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 14. 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 15. 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.[18]

Table 15. Carcinogenicity Studies

Ingredient	Animals/Cells	Protocol	Results
		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]
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.[18] According to the SCCS, these data were considered to be of low reliability due to high mortality.[12]

Table 15. Carcinogenicity Studies

Ingredient	Animals/Cells	Protocol	Results
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.[18]
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.[18]
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.[29]

Table 16. 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.[18]
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.[18]
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]

Table 16. Dermal Irritation and Sensitization Studies

Ingredient	Number of Animals/Subjects	Protocol	Results
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.[18]
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]
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.[18]
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]

Table 16. Dermal Irritation and Sensitization Studies

Ingredient	Number of Animals/Subjects	Protocol	Results
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.[33]
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.[34,37]
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 16. 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 volunteers (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% and 4% active ingredient. Repeated 3 times per week for 10 applications total. Applied at following concentrations during challenge phase: 0.05%, 0.1%, 0.2%, 0.5%, 1% and 2% active ingredient.	Panel 1: At challenge, 8 of 49 subjects (16%) had skin reactions to 2%, 7 of 49 (14%) with reactions to 1% and 0.5 %, and 2 of 49 (4%) with weak reactions at 0.1%. Panel 2: 18 of 114 subjects (16%) with skin reactions to 0.5% and 7 of 114 (6%) with reactions to 0.2%. 2 other subjects with reactions during non-treatment period following 2% induction, characterized as likely allergic to 2%. Same true for 10 other subjects regarding reactions (described as weak) at late 2% induction. Panel 3: 1 of 28 subjects (3.6%) with reaction to 0.5%. Conclusion: 2% concentration not capable of causing primary skin irritation, but capable of causing skin sensitization humans.[3]

Table 16. Dermal Irritation and Sensitization Studies

Ingredient	Number of Animals/Subjects	Protocol	Results
Leave-on product containing 0.1 % Polyaminopropyl Biguanide (0.5% of a trade name material containing 20% 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 µg/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.[36]
Neck cream containing 0.2% Polyaminopropyl Biguanide	115 male and female subjects (58African Americans, 43 Caucasians, and 13 Hispanics)	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 µg/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.[35]
		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.[43]
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.[44]
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.[42,38]

Table 16. Dermal Irritation and Sensitization Studies

Ingredient	Number of Animals/Subjects	Protocol	Results
Phototoxicity/Photosensitization Studies			
Animal Study			
20% aqueous Polyaminopropyl Biguanide	10 male rats	2 concentrations of test substance (in distilled water) evaluated: 10% (effective concentration = 10% x 20% = 2%) and 25% (25% x 20% = 5%). Each test concentration (0.1 ml) applied to dorsal skin once daily for 4 days. Site irradiated with UVC (black lamp) for 3 h daily.	Very strong irritant potential, but no significant photoirritancy.[18]
Human Study			
20% aqueous Polyaminopropyl Biguanide	26 male and female subjects	Diluted test substance (1:20 in water; effective concentration = 1%; dose = 1 mg/cm^2) evaluated. Patches (20 mm x 20 mm square of Webril affixed to 40 mm x 40 mm adhesive square) moistened with 0.4 ml of the test substance. Patches applied to upper arm for 24 h, 3 times per week for 4 successive weeks. Immediately after patch removal, sites exposed to direct rays of mid-day sun for 1 h. Challenge application at week 6.	Test substance (at 1%) essentially non-irritating and did not induce sensitization, phototoxicity, or photoallergenicity.[18,40]

Table 17. 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.[18]
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.[18]
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.[18]
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.[41]

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2017 FDA VCRP Data

Polyaminopropyl Biguanide

03C - Eye Shadow	2
03D - Eye Lotion	3
03E - Eye Makeup Remover	8
03F - Mascara	12
03G - Other Eye Makeup Preparations	3
04E - Other Fragrance Preparations	1
05A - Hair Conditioner	5
05F - Shampoos (non-coloring)	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	7
05H - Wave Sets	1
05I - Other Hair Preparations	2
07C - Foundations	4
07E - Lipstick	1
07H - Makeup Fixatives	1
07I - Other Makeup Preparations	6
08C - Nail Creams and Lotions	1
08G - Other Manicuring Preparations	1
10A - Bath Soaps and Detergents	2
10E - Other Personal Cleanliness Products	7
11A - Aftershave Lotion	1
12A - Cleansing	20
12C - Face and Neck (exc shave)	18
12D - Body and Hand (exc shave)	13
12F - Moisturizing	12
12G - Night	6
12H - Paste Masks (mud packs)	1
12I - Skin Fresheners	4
12J - Other Skin Care Preps	4
Total	**147**

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Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: February 21, 2017

SUBJECT: Comments on the Scientific Literature Review: Safety Assessment of Polyaminopropyl Biguanide as Used in Cosmetics (release date: February 14, 2017)

Key Issue

The summary of the new dermal penetration study in the 2016 preliminary SCCS opinion does not accurately reflect the study. The description of this study begins on p.35 of the SCCS opinion. In this study, two test preparations were used, aqueous micellar solution and oil/water emulsion. In one part of the study, the skin was exposed for 24 hours and penetration determined directly after exposure. In the second part of the study, the skin was exposed for 24 hours and then there was an additional 72 hour period to determine if the material in the skin moved to the receptor fluid. The results indicated that most of the radioactivity in the skin stayed in the skin during the additional 72 hour period. The SCCS said (p.39): "Therefore the SCCS agrees that the amount found in the epidermis may be excluded from the total absorbed dose." Although this is suggested in CIR report Table 11, it is not made clear in the text (Dermal Penetration section) or in Table 4.

Additional Considerations

Cosmetic Use - Please state the specific FDA product categories (hair grooming products and skin cleansers) in which Polyaminopropyl Biguanide is being used at the maximum reported concentrations.

In the following sentence "in cosmetic products" needs to be deleted as use in cosmetics does not impact whether or not a substance is classified as CMR. "CMR substances are substances that are classified as carcinogenic, mutagenic, or toxic for reproduction in cosmetic products."

Dermal Penetration - As stated above, the Dermal Penetration section needs to revised to accurately describe the most recent *in vitro* human dermal penetration study summarized in the 2016 preliminary SCCS opinion. An additional 72 hours did not significantly

increase the amount of material in the receptor fluid. Therefore, the amount found in the skin can be considered as not absorbed.

Risk Assessment - What was the value for the acute population adjusted dose (aPAD) used by the EPA?

Acute, Inhalation - Please state the duration of exposures in the text.

Short-term, Inhalation - Please state the hours/day, days/week the rats were exposed.

Chronic, Dermal, Summary, Table 11 - What was the mortality rate for the other dose groups? Did they really complete microscopic examinations of just the eye and thyroids? It should be stated if other organs were also examined.

Chronic Oral, Summary, Table 11 - The MOS calculations should be presented in the Risk Assessment section. It is not clear what the MOS values represent, e.g.,46 is the value calculated assuming all cosmetics contain 0.3% Polyaminopropyl Biguanide, and the higher values were calculated assuming all cosmetics contain 0.1% Polyaminopropyl Biguanide. The assumptions for dermal penetration used in these MOS calculations should also be stated.

Risk Assessment - What NOAEL did EPA use to calculate the MOEs?

Developmental and Reproductive Toxicity Studies - Please state the media, e.g., food or water, in which the rat NOAECs of 1000 and 1300 ppm were identified. What was the duration of the inhalation study reporting degeneration of the seminiferous tubules?

Carcinogenicity, Dermal - What was the mortality in the other treatment groups?

Sensitization, Summary, Table 15 - In the text, please include the reference for the local lymph node assay (LLNA). Table 15 does not provide any details of the LLNA and states that Polyaminopropyl Biguanide was a weak sensitizer, while the Sensitization section and the summary state the results of the LLNA as "non-sensitizer".

Ocular Irritation - Please state the volume (100 µl) and duration of exposure (1 minute) used in the *in vitro* study of human and rabbit eyes.

Retrospective Multicenter Studies - As the original SCCS opinion (reference 4) is a secondary source, it is not clear why it is presented as a reference for patient multicenter studies.

Summary - The Summary should give some indication on how much Polyaminopropyl Biguanide penetrates the skin (about 0.02% in 24 hours).

Please state the route of exposure for the 60-day study in rats.

The HRIPTs should also be mentioned in the Summary.

Table 2 - It is not clear why this table states "liquid" under heading physical form and "solid" under the heading color. The most useful molecular weight distribution information from the recent preliminary SCCS opinion should be added to this table. The preliminary opinion states 6% is <500; 14.1% is between 500 and 1000; and 75.8% is greater than 1000 dalton.

Table 4 - As the composition of the receptor fluid impacts how much penetrates the skin, the identity of the receptor fluid should be stated for all *in vitro* dermal penetration studies.

As stated above, the summary of the new dermal penetration study needs to be significantly revised. For example, in the Ingredient column, it incorrectly states that the

exposure concentration was "0.1% w/w in oil-in-water emulsion" for the study with the extended 72 hour collection period. For this study, the concentration was 0.3% in both an aqueous micellar solution and an oil/water emulsion. It is not clear what is meant by "absorbed dose". Is this the amount found in the receptor fluid? Two values are given for mass balance and it states "respectively", but it is not clear what these values represent.

Table 5 - In the Results column for the last study, please correct: "At a of 200 g..". It is not clear that g is the correct units as the Protocol column says 200 $\mu l/cm^2$. Please state who concluded that it "was not possible to derive a realistic dermal absorption rate from this study." The last two studies cited to the original SCCS opinion (reference 4) are cited to the same reference in the opinion (opinion reference 10). The reference title "Characterisation of the Urinary Polymer-related Material from Rats given Poly[biguanide-1,5-diylhexamethylene hydrochloride" suggests that all the studies reported in this paper were completed in rats (Table 5 says "Animal species not stated"). The following link is found when Google is used to search for this reference title: http://onlinelibrary.wiley.com/doi/10.1002/macp.1976.021770902/full. As this is a published study, it would be helpful if the studies were cited to the primary reference rather than the SCCS opinion.

In the second last study of Table 5, it says that 3 male rats were used. The results column gives values for 3 weeks, 5 weeks, and after a 3 week recovery group. Did they look at just one rat at each time point, or were there 3 rats/group?

In the last study, when after dosing was the whole body autoradiography completed?

Table 6, Table 9, Table 11, Table 12, Table 14, Table 15 - In a number of tables the term "SPF strain" is used. Specific-pathogen-free is not a "strain". It is "a term used for laboratory animals that are guaranteed free of particular pathogens."

Table 7 - Please provide the mg/kg dose or the dose volume used in the study of 25% aqueous Polyhexamethylene Biguanide Hydrochloride in 3 female rats (reference 17).

Table 9, oral, last study - What were the "few deleterious effects in internal organs"?

Table 11 - Please look at the reference section of reference 19 (a review) to see if the last two studies in Table 11 are reported elsewhere in this table.

Table 12 - The two studies in Alderley Park mice appear to be the same study (one is cited to the original SCCS opinion and one is cited to the new SCCS opinion). The results in the description of the first study Alderley Park mouse study appear to be the results for the rat (Alderley Park) rather than the mouse study.

Table 14, Dermal Studies - Please check the reference sections of the SCCS opinions. Were there really two 80 week dermal studies in Alderley Park mice at doses of 0, 0.6, 6 and 30 mg/mouse? The first presentation of this study does not include a reference.

Regarding the oral study in female Swiss mice, please state who concluded: "Data considered to be of low reliability due to high mortality."

Table 15, Sensitization - As a local lymph node assay (LLNA) is completed in mice, it is not clear why it needs to be placed under a In Vivo Assay subheading. If available, please

provide more details about the LLNA. It is cited to reference 25 which seems to be a secondary reference. If the primary reference was published, it should be retrieved. It should be stated if the primary reference was an unpublished study cited in this secondary reference.

Please correct: "fait erythema"

Is the abstract (reference 26) really the correct reference for two multicenter studies (one in the United Kingdom, one in Germany)?

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Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: April 4, 2017

SUBJECT: Draft Report: Safety Assessment of Polyaminopropyl Biguanide as Used In Cosmetics (draft prepared for the April 10-11, 2017 CIR Expert Panel Meeting)

Key Issues

Please review the Dossier from Cosmetics Europe. Some of the details presented in the CIR report are not correct. For example, the presentation of the new dermal penetration studies (Dermal Penetration section, Summary, Table 4) is not correct. The study with the 72-hour washout period was completed at one concentration, 0.3% in two formulations, aqueous micellar solution and in an oil/water emulsion. They also completed a 24-hour dermal penetration study at 0.1% in two formulations, aqueous micellar solution and in an oil/water emulsion. It is not correct to state that: "Study results indicated that the value for the absorption of Polyaminopropyl Biguanide through the skin was 4.09%." Although 4.09% was the absorption value used by the SCCS in their margin of safety calculations, it is not the absorbed dose from the study. As explained on p.12-13 of the Dossier, the study with 72-hour washout period indicated that it was not necessary to include the residual in the stratum corneum plus epidermis fraction in the absorbed fraction. The 0.1% dermal penetration study resulted in 1.56% in the dermis + 0.03% absorbed. Based on SCCS Notes of Guidance, one standard deviation (2.5%) is then added to the absorbed amount to get the 4.09% value used in the margin of safety calculations.

The summary of the 80-week mouse painting study in the CIR report is also misleading. The Dossier indicates that the hepatic changes observed at the high dose (30 mg/mouse) may have been due to infection with *Helicobacter hepaticus*, which may have been the cause for increased mortality and the higher incidence of liver tumors in the high dose. It should also be stated that the high dose was considered to exceed the maximum tolerated dose (MTD) due to excessive mortality and reduced body weight gain (up to 50% in both sexes).

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Additional Considerations

Chemistry - If the structures are presented in Table 1, is Figure 1 needed? Is the structure of PABA still needed? Please define "wINCI" or delete this acronym from the text as it is presented in the reference. As the structure in the INCI monograph has been corrected, if the description of the old structure is left in the report, it should be made clear that the structure has been corrected.

Noncosmetic Use - It would be helpful to include the International Nonproprietary Name (INN) (polihexanide) in this section.

Risk Assessment, Summary - The description of the calculation of the MOS values is not complete. It should also be stated that the first exposure dose was calculated assuming all cosmetics contain 0.3% Polyaminopropyl Biguanide and that the second exposure dose was calculated assuming all cosmetics contain 0.1% Polyaminopropyl Biguanide.

Developmental and Reproductive Toxicity Studies, Table 12 - The Dossier from Cosmetic Europe indicates that there is only one prenatal developmental toxicity study in mice. Table 12 appears to present this study three times, and the text suggests that there is more than one study.

Summary - As LLNAs are animal studies, it is misleading to present the LLNA and then say that results were mixed in animal studies. All of the other animal sensitization studies were guinea pig studies (the Dossier says there were 4 maximization tests and 2 Buehler tests).

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Memorandum

TO: COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: June 6, 2017

SUBJECT: Draft Tentative Report: Safety Assessment of Polyaminopropyl Biguanide (polyhexamethylene biguanide hydrochloride) as Used in Cosmetics (draft prepared for the June 12-13, 2017 CIR Expert Panel Meeting)

Key Issues

Although the new summary of sensitization studies from Cosmetics Europe did not include any new studies, they did state that in the negative human photosensitization study, the dose used was 1 mg/cm^2. This dose should be added to the CIR report as it helps to address the CIR Expert Panel's request for data to help determine a no-effect level for dermal sensitization.

The maximum reported use concentration is incorrectly reported as 0.1% in the CIR report. It was 0.2% (eye lotion), and based on the most recent concentration of use table (wave 2) it is 0.5% (non-spray suntan product).

The SCCS opinion was finalized by written procedure on April 7, 2017. This needs to be corrected in several places in the report. Now that the SCCS opinion on Polyaminopropyl Biguanide (PHMB) has been finalized, the last paragraph of the cosmetic use section should be deleted. CMR materials with an SCCS opinion can be used in cosmetics. At a minium, reference 13 (article from Kemi Taenk) should be deleted from the CIR report. This organization is a Danish consumer chemistry watchdog. If the reference is left in the report, the text should explain the source.

Sensitization - It should be made clear that the following sentence of the Sensitization section was a conclusion of the SCCS, and that the 0.2% concentration was in water not a formulation: "It was also determined that skin sensitization in humans can be elicited at concentrations beginning at 0.2% active ingredient." Among the references listed for this sentence only reference 5 is correct.

Information from reference 28 (Jowsey 2007) is not in the Sensitization paragraph and it is not included in Table 15. This is a surveillance study in which sensitization to Polyaminopropyl Biguanide (PHMB) was not increased even after use in underarm

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deodorants at <0.2%. The CIR Expert Panel may find this paper useful as it also discusses surveillance in relationship to QRA.

References 29 (abstract), 30, 31 and 33 are about positive patch test reactions to Polyaminopropyl Biguanide (PHMB) and are not actually discussed in the sensitization paragraph.

Reference 32 should be associated with the LLNA.

Reference 34 is the HRIPT on the product containing 0.2% Polyaminopropyl Biguanide (PHMB).

Additional Considerations

Impurities - It should be made clear that the metal concentrations reported were for 5 batches of technical grade (solid) PHMB.

Dermal Penetration, In Vitro, Summary - The following sentence in the Dermal Penetration section, and a similar sentence in the Summary needs to be revised as the dermal penetration studies at 0.1% and 0.3% both used the aqueous micellar solution and the oil-in-water emulsion as vehicles. "Polyaminopropyl Biguanide solutions (polyhexamethylene biguanide hydrochloride as a 0.1% aqueous micellar solution and as a 0.3% oil-in-water emulsion) were applied to human split-thickness skin in a 2-part dermal penetration study."

It should be made clear that the margin of safety calculation was done by the SCCS.

Short-Term, Oral - There was only one 28-day drinking water study in rats and one 28-day drinking water study in mice. Therefore, it is not clear why the text implies that were multiple 28-day oral rat studies. Where does the dose of "~0.0002 mg/kg bw/day" come from? The LOAEL was 0.1 mg/ml in drinking water (which is not clearly stated in the text); if a 200 g rat drinks 25 ml of water/day, a more appropriate estimated dose is 0.1 mg/ml x 25 ml x 1/0.2 kg = 12.5 mg/kg bw/day.

Short-Term, Inhalation - In the text, please state that the exposures were 6 hours/day, 5 days/week, nose-only.

Chronic, Dermal - It is not clear why more details of the 80 week dermal study are not stated in this section. The SCCS opinion indicated that this study had a NOAEL of 0.6 mg/mouse (15 mg/kg/day).

Chronic, Oral - Please include the species used in the 104-week oral study. The high dose of the 1-year dog dietary study is not stated correctly. They started at a dietary concentration of 4500 ppm then at weeks 11/12 because of toxicity they reduced the dietary concentration to 3000 ppm. It should state that the SCCS completed the MOS calculations.

Carcinogenicity, Dermal - It should be made clear that the 80 week dermal study in mice is the same study that was described in the Chronic section. The doses used in this study (0, 0.6, 6 and 30 mg/mouse/day in ethanol or 0, 25, 150 or 750 mg/kg/day) should be clearly stated. It should also be stated that the NOAEL was 0.6 mg/mouse (or 15 mg/kg/day).

Cytotoxicity and Antimicrobial Activity - Perhaps when using the name polyaminopropyl biguanide for the actual compound, the first letters of this name should not be capitalized (capitalization should only be used when it is an INCI name for PHMB).

Epigenetic Effects - Please state the source of the classification scheme for which Polyaminopropyl Biguanide (PHMB) is considered a "category 3 carcinogen."

Photosensitization - Please add the dose (1 mg/cm^2 - provided in the most recent submission from Cosmetics Europe) used in the human photosensitization study of aqueous 1% Polyaminopropyl Biguanide (PHMB).

Ocular Irritation, Summary - Please make it clear that the human eyes into which Polyaminopropyl Biguanide was instilled were from cadavers.

Other Clinical Reports - Please add the subheading polyhexamethylene guanidine for the studies of the humidifier disinfectant. Adding the structure of this material would also be helpful.

Summary - It is not correct to state that the study results showed that dermal penetration was 4.09%. This was the value that was used by the SCCS - it includes one standard deviation added to the study results.

It should be made clear that the LOAEL of 0.1 mg/ml from the 28-day study is a concentration in drinking water. There was only one 28-day drinking water study in rats. There was also a 28-day drinking water study in mice.

The descriptions of the MOS calculations are not complete as they do not indicate that the lower value was calculated assuming products contained 0.3% Polyaminopropyl Biguanide (PHMB) and the higher value was calculated assuming products contained 0.1% Polyaminopropyl Biguanide (PHMB).

It should be made clear that the following sentence was a conclusion of the SCCS: "It was also determined that skin sensitization in humans can be elicited at concentrations beginning at 0.2% active ingredient." It should also be stated that it was an aqueous solution that was tested.

Discussion - It needs to be made clear that the maximum use concentration reported is now 0.5%.

The Discussion should mention that the photosensitization study was completed at a dose of 1 mg/cm^2.

Table 1 - Is this table needed for a single ingredient report?

Table 3 - The use table needs to be updated as there is a 0.2% eye lotion product and a 0.5% suntan (not spray) that are not yet included in this table.

Table 4 - The last 2 sentences in the results column for the 0.3% 72 hour post exposure study needs to be moved to the 0.1% study as it concerns the results of the 0.1% study not the 0.3% study.

Table 5, first study - It is not clear what the values (0.22 and 0.28%) in the carcasses represent.

Table 5, male rat, reference 19 - To be consistent with the other studies in this table, the Ingredient column should indicate that a radiolabeled compound was studied.

Table 7, third study - The dose (2 g/kg) for this study from reference 19 needs to be added to this table.

Table 10, last study - It does not make sense that they changed the drinking water concentration to 0.3 mg/ml during the 2nd week and it was also at 0.3 mg/ml from the 3rd week until study termination. Because of palatability issues, it is likely that they used a concentration between 0.1 and 0.3 mg/ml, e.g., 0.2 mg/ml, during week 2.

Table 11, first study (dermal) - It should be stated that the SCCS indicated that the high dose exceeded the maximum tolerated dose and that the NOAEL was 0.6 mg/day (15 mg/kg/day).

Table 11, 1 year dog study - Please review the doses, as it currently states: "at dietary concentrations of 0 ppm, 300 ppm, 1500 ppm and 4500 ppm (corresponding to 0 ppm, ~11 ppm, ~54 ppm, and ~169 or ~108 mg/kg/day)". This does not make sense. Should all of the units of the "corresponding" values be mg/kg/day?

Table 11, 26-week dog study - This study should not be included in the Chronic table.

Table 12 - There was only one Alderly Park mouse developmental toxicity study completed. It is not clear why two studies with the same protocol are included in Table 12.

Table 13, last study - The strain of rats used does not belong in the Dose/Concentration column as it is already stated in the Strain/cell type column.

Table 14, dermal - There was only one 80-week study in Alderly Park mice. Please look at the references in CIR report reference 19 and CIR report reference 5. Reference 19 cites the 80-week study to Report No. CTL/P/331. Reference 5 cites this study to Central Toxicology Laboratory....Report No: CTL/P/331 - the same report as cited in reference 19. Therefore, it is the same study cited in two secondary references.

Table 14, oral - Please check the two studies in 60 male and 60 female rats (terminated at 124 weeks) cited to references 5 and 19, as these are likely the same study cited in two sources.

Table 15 - It is not necessary to present the 80-week study in mice in this table.

Table 15, Sensitization - The LLNA is not an *in vitro* assay and should not be presented under an *in vitro* subheading.

Table 15, Sensitization, last guinea pig study - It would be helpful to provide more details of the results of this study (see table 3 of reference 2). For example no sensitization was observed in guinea pigs at induction concentrations of 1.8% and lower.

Table 15, Phototoxicity/Photosensitization, human - The dose of 1 mg/cm^2 from the new Cosmetics Europe summary of sensitization data needs to be added to the 26 subject study.

Table 16 - It needs to be made clear that the last study is an *in vitro* study.

Reference 19 - Please correct "recreartional"

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Interim Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: September 6, 2017

SUBJECT: Draft Tentative Report: Safety Assessment of Polyaminpropyl Biguanide (polyhexamethylene biguanide hydrochloride) as Used in Cosmetics (draft prepared for the September 11-12, 2017 CIR Expert Panel Meeting)

Key Issues

Cosmetic Use - The last paragraph of this section should be deleted as it is repetitive of the previous statement and it is not correct. PHMB has an SCCS review and can be used in cosmetics in Europe.

Sensitization, Summary, Table 16 - Please revise the text describing the guinea pig sensitization studies to focus on the results, e.g., the number of guinea pigs responding, rather than the classification, e.g., weak, moderate, strong. If the classification is stated, the CIR report needs to clearly state which classification scheme was used. The SCCS used the CLP scheme which considers the injection concentrations in a guinea pig maximization test rather than the topical concentrations. In contrast, the ECETOC scheme (described in Technical Report No. 87; http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-087.pdf) was used by Procter & Gamble in the proposed QRA.

Industry is not supporting use in spray products. The risk assessment using the ConsExpo web model should be deleted from the report. If it is left in the report, doses (how much the rat inhaled estimated using breathing rates and duration, and estimate of how much humans inhale when using a hair spray) should be compared in addition to exposure concentrations.

Additional Considerations

Definition and General Characterization - Without providing the original structure included in the Dictionary, it is not necessary to indicate that the structure and definition have been updated.

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Carcinogenicity, Oral - Please correct: "increased cell proliferation was noted in mice? fed 1200 ppm"

Sensitization, Summary - For the HRIPTs, please add the dose/unit area (25 $\mu g/cm^2$ for the 0.1% product; 100 $\mu g/cm^2$ for the 0.2% product).

Other Clinical Reports - What is meant by "very high doses"?

Summary, Discussion - Please revise the first sentence of these sections to be consistent with the Abstract: The safety of Polyaminopropyl Biguanide, which is used as a preservative, was reviewed. It is possible that this ingredient may be in a product without functioning as a preservative in the product.

Summary - The use paragraph needs to be corrected. The 0.2% product was a leave-on product and 0.1% was the highest concentration reported in a rinse-off product.

The Summary needs to be revised to indicate that the SCCS opinion is final.

It should be made clear that there was only one mouse developmental toxicity study completed.

Table 9, reference 21 - In the Results column of the 60-day rat study it states: "50% of the rats dosed with 32 mg/kg had either mild hepatocyte cytolysis with or without lymphocyte infiltration and feathery degeneration." The word "either" needs to be deleted, or another effect needs to be added.

Table 11 - Please check the references in the review (reference 22) to determine if the chronic studies with no details are the studies already described in Table 11. Without any details, these studies (last two studies in Table 11 that do not state the species or protocol) do not add anything to the report and should be deleted.

Table 13 - It should be made clear that there was only one mouse developmental toxicity study. One of the problems with this study was the poor fertility rate. It took mating of more than 40 mice per group to get at least 21 pregnant mice per group. The description that says groups of 47 to 49 mice includes the non-pregnant mice.

Table 16 - What is the difference between the "In Vivo Assay" and "Animal Studies" headings? LLNAs are animal studies, and guinea pig sensitization tests are *in vivo* studies.

Personal Care Products Council
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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: October 23, 2017

SUBJECT: Tentative Report: Safety Assessment of Polyaminpropyl Biguanide (polyhexamethylene biguanide hydrochloride) as Used in Cosmetics

Key Issues

Cosmetic Use - The last paragraph of this section should be deleted as it is repetitive of the previous statement and it is not correct. PHMB has an SCCS review and can be used in cosmetics in Europe.

Sensitization, Summary, Table 16 - Please revise the text describing the guinea pig sensitization studies to focus on the results, e.g., the number of guinea pigs responding, rather than the classification, e.g., weak, moderate, strong. If the classification is stated, the CIR report needs to clearly state which classification scheme was used. The SCCS used the CLP scheme which considers the injection concentrations in a guinea pig maximization test rather than the topical concentrations. In contrast, the ECETOC scheme (described in Technical Report No. 87; http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-087.pdf) was used by Procter & Gamble in the proposed QRA.

Rather than include all references at the end of a paragraph, please include the reference with the information that came from that reference.

If an inhalation risk assessment is included in the report, doses should be compared to calculate a margin of safety (MOS). The 28-day rat NOAEC concentration for the 28-day study (6 hours/day; 5 days/week) was about 0.000024 mg/L. Assuming a rat breaths 0.14 L/min, the rats were exposed to about:
0.000024 mg/L x 0.14 L/min x 360 min x 1/0.187 kg = 0.0064 mg/kg/day

To achieve an MOS of 100 or greater, the human exposure dose from incidental inhalation exposure should 0.000064 mg/kg/day or less. Exposure from spray products is highly variable and dependent on the packaging, composition, distance of spray from the breathing zone, and the room in which the product is sprayed. Spray product exposure

should be determined by each product manufacturer using tiered as described in Steiling et al. (2014)[1].

Additional Considerations

Abstract, Conclusion - It is not clear what is meant by "intended conditions of use". Generally, the CIR Expert Panel considers whether the ingredients are safe for use in cosmetics with uses as reported to the VCRP and the Council's concentration of use surveys.

Absorption, Distribution, Metabolism and Excretion, Oral - Table 5 does not include any studies in which the species was not specified. Therefore, it is not clear why there is a study in this section for which it states "species not specified". As dosing method influences kinetics, how each study was completed (gavage, dietary, drinking water) should be stated. Table 5 includes a mouse gavage study that is not mentioned in the text.

Acute, Dermal - Reference 2 is not included in Table 6.

Acute, Oral - Table 7 only includes information from references 12, 19 and 21. It is not clear why references 2, 18 and 22 are also included in the text.

Acute, Inhalation - Rather than describing the exposure durations as "most for 4 h", it would be more accurate to stated that exposures were for 4 h, unless the rat died before the end of the exposure period.

Short-term, Oral, Summary - What effects were observed at the LOAEL of 0.1 mg/ml? It should be made clear that these were a drinking water studies. The text includes reference 21 as a citation for 28-day rat and mouse drinking water studies. This reference is not included in Table 9. It should be made clear that the 60-day oral study in rats was a gavage study.

Short-term Inhalation - The adverse effects observed in the 21 and 28-day rat inhalation studies should be stated.

Subchronic, Oral - What was the drinking water concentration used in the 90-day drinking water study in mice? In Table 10, the mouse drinking water study is cited to reference 2 which is not listed as a reference in the text.

Chronic, Oral - In the description of the "97-week study", it is not clear that the parents were treated and then the offspring were treated for 97 weeks after they were selected for the study. It would be helpful if the 26-week dog study were presented before the 1-year dog study.

Chronic, Human, Risk Assessment, Oral - Although human dermal exposure is compared to an oral NOAEL, this risk assessment also uses an estimate of dermal absorption and it should be considered a dermal risk assessment not an oral risk assessment. It should be made clear that the MOS calculation with the 0.1% cosmetic use concentration is from the most recent SCCS opinion.

Developmental and Reproductive Toxicity(DART) Studies, Summary - For all studies in the DART section, the method of dosing (gavage, drinking water, diet) and the timing of dosing relative to gestation needs to be stated. Without knowing anything about the protocol, the statement that Polyaminopropyl Biguanide is embryotoxic at an oral dose of

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[1]Steiling W, Bascompte M, Carthew P, et al. 2014. Principle considerations for the risk assessment of sprayed consumer products. *Toxicol Lett* 227(1): 41-49.

32 mg/kg/day should be deleted from the report.

Carcinogenicity, Dermal - The meaning of the following sentence is not clear "The source of these results is the chronic oral toxicity study that is summarized above." As this is the dermal subsection, this sentence is probably referring to the 80-week dermal study that was also summarized in the chronic, dermal section.

Chronic, Oral - It should be made clear that the 97-week period was after the offspring were selected for inclusion in the study.

Other Cellular Effects and Antimicrobial Activity - The following sentence is not clear: "In fibroblast or keratinocyte cultures, concentrations for both test substances ranged from 0.005% to 1% v/v and, for polyaminopropyl biguanide (C3) only, also at concentrations ranging from 0.25% to 3% v/v."

It states that Polyaminopropyl Biguanide "has been evaluated" for effects on gene expression for genes involved in apoptosis, but it does not say whether or not any effects were observed.

Irritation - What concentration of Polyaminopropyl Biguanide was classified as a mild skin irritant in rabbits?

Sensitization, Risk Assessment - The description of the QRA is not complete as it does not state that the 1000 $\mu g/cm^2$ NESIL was used to determine if estimated exposure using maximum use concentrations from the Council survey could be considered safe. Margins of exposure (MOE) were all greater than one with the exception of the product containing 0.2% Polyaminopropyl Biguanide.

Retrospective and Multicenter Studies - It should be made clear what is meant by a "low incidence of skin sensitization reactions."

Case Reports - The report of two cases of severe anaphylaxis should be moved to the Contact Urticaria section, and perhaps this section should be re-titled "Type I Allergy".

Polyhexamethylene Guanidine Phosphate (PHMG) - Please state how they determined the TWA of 0.06 mg/m^3. It should be noted that Lee et al. (2013) used the 28-day inhalation study on Polyaminopropyl Biguanide as a comparison for the PHMG humidifier exposures.

Summary - What concentrations were used in the *in vitro* studies on epigenetic properties?

It is not clear why the human HRIPTs are presented in the paragraph concerning irritation.

Discussion - In the second paragraph of the Discussion it is not clear what is meant by "Dermal toxicity". Generally, this means effects on the skin, but in this paragraph is it supposed to imply that there were no systemic effects following dermal exposure at 0.4%? The maximum use concentration reported was 0.2% rather than 0.1% as stated in this paragraph.

Rather than being "near the MTD", the SCCS stated that the tumors occurred in rats at doses above the MTD.

There were no protocol details reported for the LLNA. It is not clear why this study was

even mentioned in the Discussion.

Table 2 - It is not clear why both units of g/100 ml and % are needed for solubility values.

Table 4 - The identity of the receptor fluid should be stated for each *in vitro* study.

For the second study in this table (cited to reference 12) to what was DMSO added, the dosing solution or the receptor fluid?

The results of the 0.3% study with the additional 72-hour period are not correct (the values from the 0.1% 24-hour study are stated for the 0.3% study. See the second table in the final SCCS report for the results of the 0.3% study. For example, in the 0.3% study, the dislodgeable amount at 24 hours was 53.3% for the aqueous micellar solution and 58.1% for the oil-in water emulsion (not 48.43% and 52.35% as reported in the results column). The description of absorption value used by SCCS (4.09%) is from the 0.1% study and does not need to be presented with the 0.3% study.

The protocol is missing from the 5th study (cited to reference 12).

Table 5 - Please correct the following in the results column of the first study in this table: "single oral dose of low, medium or high MW fraction: 94.9%, 101.4%, and 96% of radioactivity from low, mid and high MW fractions, respectively"

In the description of the second study, it should be made clear that essentially all of the dose was excreted during the 72 hour collection period.

Table 8 - 0.1, 0.3 and 0.5 mg/l should be 100, 300 and 500 mg/m^3 (not 10, 30 and 50 mg/m^3) as stated in the first study of Table 8 (cited to reference 12).

Table 10 - The first two studies (90-day dog studies) appear to be the same study cited to different secondary references. In the first row the concentrations are of the 25% aqueous Polyaminopropyl Biguanide (0, 5500 and 11000 ppm) and in the row the doses are of the active ingredient (25% of 5500 and 1100 are 1375 and 2750 ppm).

What was the "marked toxicity" observed at 4000 ppm? Did they actually include a 6000 ppm concentration? What were the mg/kg/day doses at 6000 ppm?

What species was used in the last two studies in this table? If no details are provided, perhaps these descriptions should not be included in the report. They are likely descriptions of the studies already in the table.

Table 13 - It is not clear why the 3-generation rat study needs to be presented twice in this table (cited to secondary references 12 and 19). The mouse developmental toxicity study is also presented twice (cited to reference 28 and 12). The number of mice used appear to be different because they had difficulties getting pregnant mice. It took mating of 47-49 to get groups of 21 pregnant mice.

Table 15 - In the description of the mouse study (Swiss-derived) it should be made clear that 97 weeks was the dosing time after selection of the offspring.

Table 16 - In the study described in the second row, the "Number of Animals/Subjects" column

says "rats", while the "Protocol" column says "rabbit". What species was used in this study?

Did the authors of reference 33 provide any statement about sensitization? As the subjects had dressings containing Polyaminopropyl Biguanide on their skin for 6 days followed by a 7-10 day rest period and another dressing application, this study could also be helpful for assessing sensitization potential.

The criteria used to rate sensitization should be stated in this table.

The last two rows under the "Patients" subheading (cited to reference 35, 40 and 36, 40) should be deleted as these studies are presented earlier in the table.