Safety Assessment of Polyene Group as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	May 22, 2015
Panel Meeting Date:	June 15-16, 2015

The 2015 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 Director is Lillian J. Gill, DPA. This safety assessment was prepared by Christina Burnett, Senior Scientific Analyst/Writer and Bart Heldreth, Ph.D., Chemist CIR.

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Memorandum

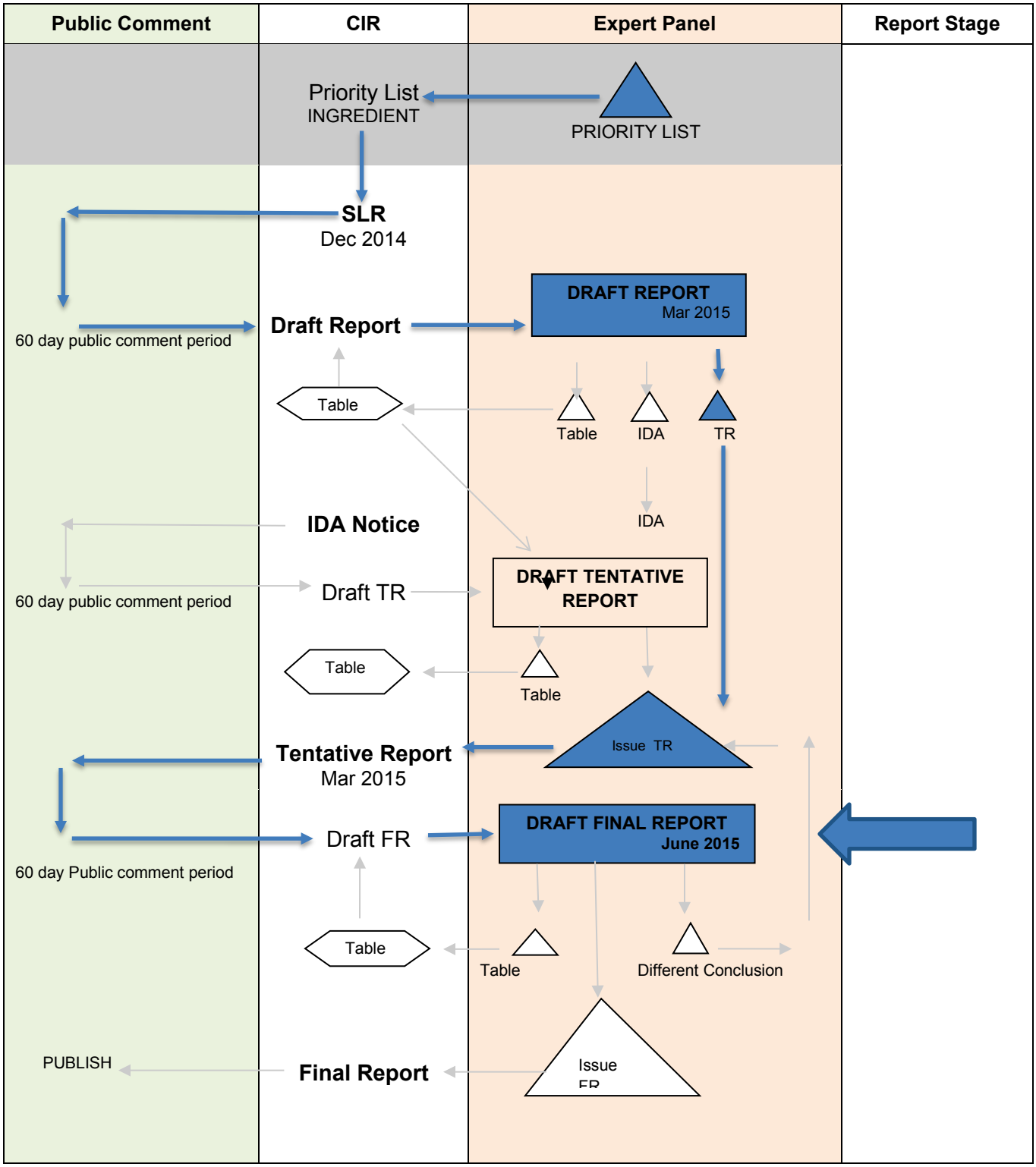
To: CIR Expert Panel Members and Liaisons
From: Christina Burnett, Senior Scientific Writer/Analyst
Date: May 22, 2015
Subject: Draft Final Safety Assessment of Polyenes

Enclosed is the draft Final Report of the Safety Assessment of Polyenes as Used in Cosmetics. (It is identified as *polyen062015rep* in the pdf document.)

At the March 2015 meeting, the Panel issued a tentative safety assessment on polyenes with the conclusion that the 26 ingredients listed in the report are safe in cosmetics in the present practices of use and concentration.

Since March, HRIPT data on polyisoprene were received and incorporated into the report, in addition to the composition data on ethylene/propylene copolymer that was received prior to the March meeting (*polyen062015data1* and *polyene062015data2*). The new data have been highlighted by |margin brackets| in text and by pink shading in tables. Comments that were received from the Council prior to the March meeting, as well as those on the tentative safety assessment, have been considered (*polyen062015pcpc1* to *polyen062015pcpc2*). The comments, along with the previous safety assessments on polybutene, polyethylene, polyisobutene, and hydrogenated polyisobutene (*polyen062015oldrep_1* to *polyene062015oldrep_4*), are available for your review in this report package.

The Panel should carefully review the abstract, discussion, and conclusion of this report and issue a Final Safety Assessment.


Public Comment
CIR
Expert Panel
Report Stage
Priority List
INGREDIENT
PRIORITY LIST
SLR
Dec 2014
60 day public comment period
Draft Report
DRAFT REPORT
Mar 2015
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Issue TR
Tentative Report
Mar 2015
Draft FR
DRAFT FINAL REPORT
June 2015
60 day Public comment period
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Different Conclusion
PUBLISH
Final Report
Issue

Polyenes History

December 2014 – Scientific Literature Review announced.

March 2015 – The Panel issued a tentative report for public comment with the conclusion that the 26 polyene ingredients are safe in cosmetics in the present practices of use and concentration. The Panel noted low systemic toxicity at high doses in single-dose and the repeated-dose animal studies, no teratogenic or carcinogenic effects in animal studies, and no genotoxicity in in vitro and in vivo studies of polyenes. The data indicated use concentrations as high as 95% in lipsticks. However, a human dermal sensitization study of 100% hydrogenated polyisobutene was negative, and no irritation or sensitization was observed in multiple tests when other polyene ingredients were used. The Panel noted that, although molecular weights of some of the ingredients are in a range that could be dermally absorbed, the lack of heteroatomic functional groups substantially limits solubility and would prevent significant absorption. The lack of such functional groups also limits interactions with other biomolecules and probably accounts for the apparent biological inertness of these ingredients in this group.

Although data were not available on the UV absorption of polyenes, because none of the polymer ingredients contain chromophores, the Panel expressed no concern that these ingredients would cause adverse effects from UV exposure.

Polyenes Data Profile – June 2015 – Writers Christina Burnett and Bart Heldreth															
	In-Use	Physical/Chemical Properties	Method of Manufacturing	Composition	Tocikokinetics	Acute Toxicity	Repeated Dose Toxicity	Repro. /Develop. Toxicity	Genotoxicity	Carcinogenicity	Irritation/Sensitization - Animal	Irritation/Sensitization - Clinical	Ocular/Mucosal	Phototoxicity	Case Studies
Butene/Propylene Copolymer															
Butylene/Ethylene Copolymer	X														
Butylene/Ethylene/ Propylene Copolymer	X														
Decene/Butene Copolymer	X														
Ethylene/Octene Copolymer		X		X		X	X		X		X	X	X		
Ethylene/Propylene Copolymer	X														
Hydrogenated Poly(C6-12 Olefin)															
Hydrogenated Poly (C6-14 Olefin)	X														
Hydrogenated Poly(C6-20 Olefin)	X														
Hydrogenated Polybutene															
Hydrogenated Polydecene	X			X	X	X	X	X	X		X	X	X		
Hydrogenated Polydodecene						X	X	X	X						
Hydrogenated Polyisobutene	X		X	X		X	X				X	X	X	X	
Isobutylene/ Isoprene Copolymer															
Isoprene/ Pentadiene Copolymer															
Polybutene	X			X		X	X	X			X	X	X	X	
Poly(C4-12 Olefin)															
Poly(C6-14 Olefin)															
Poly(C20-28 Olefin)															
Poly(C30-45 Olefin)	X														
Polydecene	X														
Polyethylene	X				X	X	X		X	X	X	X	X		X
Polyisobutene	X			X		X	X	X		X	X	X	X		
Polyisoprene	X											X			
Polypentene															
Polypropylene	X									X					

"X" indicates that data were available in the category for that ingredient.
Shaded cells indicate ingredients that have been previously reviewed by CIR.

Search Strategy for Polyenes (Performed by Christina Burnett)

April-May 2014: SCIFINDER search for under the answer set for 26 ingredients, including available CAS numbers::

- Initial search for "adverse effect, including toxicity" yielded:
  - 8 references for ethylene/propylene copolymer – none relevant;
  - 24 references for isobutylene/isoprene copolymer – none relevant;
  - 11 references for polybutene – 1 relevant;
  - 2 references for polydecene - 1 relevant;
  - 833 references of polyethylene, further limited to 2001-2014 resulted in 520 references, further limited to cosmetics/dermatitis/dermal – none relevant;
  - 17 references for polyisobutene – none relevant;
  - 14 references for polyisoprene – none relevant;
  - 141 references for polypropylene – 8 relevant;

Search Terms	TOXLINE Hits (excluding PUBMED, English only)	PUBMED Hits	ECHA Hits
April-May 2014			
butene/propylene copolymer	0	10	no
butylene/ethylene copolymer	0	69	no
butylene/ethylene/propylene copolymer	0	0	no
decene/butene copolymer	0	0	no
ethylene/octene copolymer	0	0	no
ethylene/propylene copolymer	0	7	no
hydrogenated poly(C6-12 olefin)	yes under CAS #68037-01-4	0	yes
hydrogenated poly(C6-14 olefin)	yes under CAS #68037-01-4	0	yes
hydrogenated poly(C6-20 olefin)	0	0	no
hydrogenated polybutene	0	1	no
hydrogenated polydecene	yes under CAS #68037-01-4	1	yes
hydrogenated polydodecene	0	0	no
hydrogenated polyisobutene	0	with polyisobutene, restricted to 2006-2014 = 7	no
isobutylene/isoprene copolymer	0	under CAS #9010-85-9 = 22	no
isoprene/pentadiene copolymer	0	0	no
polybutene	0	restricted to 2001-2014 = 34	yes
poly(C4-12 olefin)	0	0	no
poly(C6-14 olefin)	0	0	no
poly(C20-28 olefin)	0	0	no
poly(C30-45 olefin)	0	0	no
polydecene	0	3	no

Search Terms	TOXLINE Hits (excluding PUBMED, English only)	PUBMED Hits	ECHA Hits
polyethylene	0	restricted to 2004-2014 = 35,187 hits, further restricted to "toxicity and NOT glycol, NOT aquatic, NOT polyethyleneimine, NOT PEI" = 164 hits	no
polyisobutene	0	with hydrogenated polyisobutene, restricted to 2006-2014 = 7	no
polyisoprene	0	343 hits, refined with "toxicity" = 7 hits; with CAS # = 36 hits	no
polypentene	0	1	no
polypropylene		8703 hits, refined with "toxicity" = 172 hits, further refined with CAS # = 5 hits	no

Total references ordered or downloaded: 27

Search updated November 2014 and January 2015. No new relevant data discovered.

Search updated April 2015. No new relevant data discovered.

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Polyenes
March 16-17, 2015

Dr. Belsito's Team

DR. BELSITO: Polyenes, so this is the first time we are looking at this report of 26 ingredients, their molecular weight, hydrophobic substances, function mainly as film formers, and the viscosity- increasing agents, non aqueous and cosmetic products.

In Wave 2, we've got really not much. We've got something about the monomer value of ethylene, propylene copolymer. Test material, the extraction vehicle, and there was less than 0.8 parts per million of residual monomer. Is that all pertinent to this one? I hope, I don't know. So, having said that, let's see. I thought they were safe as used, and just was asking why were weren't bringing in some form of summaries from polyethylene, polybutylene, polyisobutene and hydrogenated polyisobutene, especially to support sensitization and safety of high levels in lipstick.

DR. SNYDER: We did bring that in.

MS. BURNETT: We did bring it in.

DR. SNYDER: Yeah. All the italicized ones were brought on, yeah. She brought that on, yeah.

DR. BELSITO: Oh. Sorry. It's safe as used -- Thank you, for bringing in summaries. Okay.

MS. BURNETT: I was going to say, what?

DR. KLAASSEN: I have a little question here. When you bring this in from an older report, which I think is great, but when it's published in a journal, is it also in italics?

MS. BURNETT: It's in italics for your review, so you know it's there, but the journal doesn't like us reprinting stuff, so it will actually be, all that italicized information will be taken out.

DR. KLAASSEN: Oh, it's actually taken out?

MS. BURNETT: Mm-hmm. So it's kind of for us -- it's for you to be able to find easy, but it's also for us to be able to find quickly to delete before it goes --

DR. BELSITO: But is it referenced somehow?

MS. BURNETT: Yes. We refer to it in the intro, and then that way --

DR. BELSITO: Okay. So, I want to be clear on what we are doing here. So, polyethylene, polyisobutene, and hydrogenated polyisobutene are not in the list of ingredients that we are reviewing. Are we adding them? Are they, in fact, being sort of re-reviewed so that in 2030 we don't have to go back to them?

MS. BURNETT: Polybutene, polyethylene and -- Yes, they will -- this will be considered the re-review.

DR. BELSITO: Okay. So they should be in that list as well. Because the ingredients reviewed in the safety assessment are, and when --

MS. BURNETT: They are there -- I'm sorry. They are on the list.

DR. BELSITO: Polyisobutene is not there.

DR. SNYDER: Yeah. It is.

DR. BELSITO: Is it?

DR. SNYDER: Yeah.

MS. BURNETT: After the (inaudible).

DR. SNYDER: In the introduction.

DR. BELSITO: Where? Oh. Oh, yeah.

MS. BURNETT: The C4 -- all of them kind get --

DR. BELSITO: Okay. Sorry. It must have been really late when I was reading this; polyethylene. Okay. Sorry about that.

MS. BURNETT: Not a problem.

DR. SNYDER: When the reports are so good, you struggle to find things.

DR. BELSITO: Sometimes you just struggle.

MS. BURNETT: He was covering for you.

DR. BELSITO: Okay. On the Figure 2, the process flow for the manufacturing of hydrogenated polyisobutene, does this really tell us anything, especially about impurities? I mean, personally I thought it was pretty useless for telling me -- I mean, I guess, general steps of manufacturing, but it didn't really spin off for me, what was coming out in those steps as impurities, which would be the reason why I'd want to know the process flow. No?

DR. SNYDER: I really don't know, I think --

DR. BELSITO: I don't know. I'm just asking.

DR. LIEBLER: I think that this could be summarized in text for all it -- for the -- I mean, I agree basically with Don, for all the information it gives us, it doesn't really tell you much. It's unnecessary.

DR. BELSITO: Otherwise I have a few very minor comment, mainly on a space between two words. It was excellent.

MS. BURNETT: Thank you.

DR. LIEBLER: I agree. And I thought it was excellent too. I think we need to be careful about the argument that these are large, molecular weight compound.

MS. BURNETT: Yes.

DR. LIEBLER: They are actually not that big.

MS. BURNETT: Yeah. We noted the error that we --

DR. LIEBLER: Okay. So they are not that big, they are in the range of several hundred, and they are liquids or, you know, oily, waxy materials. So weight -- molecular size, per se, isn't quite the right argument to make, so we'll need to be careful about that, I had some suggested text for the discussion.

MS. BURNETT: Okay.

DR. LIEBLER: They could be along the lines, and I'll just read it once, and it's in my edits, so you can follow there. But all the molecular weights are in the range of chemicals that could be dermally absorbed. The lack of heteroatom functional groups dramatically limits solubility and would prevent significant absorption. The lack of functional groups also limits interactions with other bio molecules and probably accounts for the apparent biological inertness of these ingredients.

DR. BELSITO: So that would go in the discussion?

DR. LIEBLER: Right.

DR. BELSITO: So you are already starting the right discussion for us. Thank you.

DR. LIEBLER: Yeah. I wrote it.

MS. BURNETT: I appreciate it. I like that.

DR. SNYDER: But we had absorption data and they are poorly absorbed.

DR. LIEBLER: Right.

DR. SNYDER: Okay.

DR. BELSITO: And that's Dan's point but --

DR. LIEBLER: And this is -- it provides the rationale other than, they are big, because they are not that big.

DR. SNYDER: Okay. I got it. Okay. Yeah.

DR. LIEBLER: Because they are not that big.

DR. SNYDER: Because I had it written down, that the -- not the issue where they are poorly absorbed. Okay.

MS. BURNETT: Do you agree with the (inaudible)?

DR. LIEBLER: There is Teflon, as they could be without being fluorinated.

MS. BURNETT: I do want to ask the team how they feel about -- we have isoprene copolymers, and if you have any issue with possible UV absorption.

DR. LIEBLER: I don't think they are going to absorb, right?

MS. BURNETT: I don't know.

DR. LIEBLER: Once they are polymerize, that takes the double bonds out, so they are going to probably not have any absorption above 200 nanometers.

MS. BURNETT: Okay. And then do you feel the irritation and sensitization data are okay for the concentrations at use.

DR. LIEBLER: I'd take that back to Don.

DR. BELSITO: And then again I don't see that as a problem. I mean, these are really not going to get through the stratum corneum.

MS. BURNETT: Okay.

DR. LIEBLER: Right.

DR. BELSITO: So, I guess in terms of photo, I mean, we can put these in the discussion, so sensitization, not permeate the stratum corneum, and for the toxicity lack of double bonds.

DR. LIEBLER: Lack of chromophore.

DR. BELSITO: Anything else? Curt? Okay.

Dr. Marks' Team

DR. MARKS: And now, let's move on to the polyenes.

(Discussion off the record)

DR. MARKS: And this is the first review of this group of 26 ingredients. However, polybutene, polyisobutene and hydrogenated polyisobutene were reviewed previously, and a conclusion of safe was arrived at. So, not all 26 are the first review.

Polyisobutene has 2,763 uses. So, a lot of uses. Concentration, the highest, 95 percent for hydrogenated polyisobutene in a lipstick. So, Tom and Rons, first, are all of these ingredients okay to be in this one group? Are there any outliers that we should not include?

DR. SLAGA: I had that all of them should be included.

DR. SHANK: I believe that was my conclusion, too.

DR. MARKS: Yeah, okay. So, ingredients are okay. And then how about needs? What toxicologic endpoints do we not have in here to say, come to a conclusion of safe?

DR. SLAGA: We have methods of manufacturing and impurities. We have irritation, sensitivity, genotox and some carcinogenicity, plus all of the previous data with the other ones that have been already reviewed. These are extremely large molecules that are probably not absorbed, or probably not -- won't be absorbed.

DR. SHANK: I had a different concern, I guess that wasn't a concern. Three of these compounds are isoprene copolymers. And if I remember correctly, isoprene has a UV absorption.

DR. MARKS: Has what?

DR. SHANK: UV absorption. I think it's around 300. I'm not quite sure. So, I would like to have on those three, the isoprene copolymers UV absorption data.

DR. MARKS: And which ones were those? Does it actually have isoprene as part of the name? Here, I see isoprene/pentadiene.

DR. SHANK: Okay, yeah.

DR. MARKS: So that's one of them. Okay. Three --

DR. SHANK: There are three of them.

DR. MARKS: -- isoprene --

(Discussion off the record)

MS. BURNETT: Polyisoprene, isoprene/pentadiene and isobutylene/isoprene.

DR. MARKS: So, those three isoprene polymers you would like I -- ultraviolet light absorption.

DR. SHANK: Yes, please.

DR. MARKS: Okay. Ron Hill? Do you have anything?

DR. HILL: Yeah. I mean, there are compounds here, both with molecular weights under a thousand. In some cases, I think substantially below a thousand. So, you know, I know I picked on language near the beginning, suggest otherwise, because there are some fairly smallish polymers in this group. I think there are -- I don't know if they're all calculated, because the trouble with calculating a molecular weight for polymers, it's always going to be an average. But there are some of these that are, evidently, small.

So what I put in my note here, and I've got to go back to PDF page 10 -- let's see. Molecular weight less than a thousand. So, if an ingredient is used in a leave-on formulation at 50 percent or greater, this might represent a means for significant dermal exposure. If we have alkynes, humans can potentially make epoxides, which can potentially generate a hapten.

I'm not sure how this might occur in the skin, because I don't know that we make many epoxides. Are P450 complements modest in skin? But you know, we don't have any sensitization data on some of these low molecular weight puppies. That bugs me a lot. The ones that are larger, it's kind of like, put plastic there. Nothing is going to happen. But there are some low molecular weight ones, and we don't have the sketchy details about low molecular weight impurities in some of these guys. And that, as usual, bugs me.

So, I was looking -- I actually was looking -- the first thing I had in my notes was this person who's responding with the European directive. We hereby confirm that the above-mentioned product -- this is way down on page 218, but nobody really needs to go there.

But they confirm that it doesn't contain residual solvents. You know, I guess there must be a legal definition of when we say it doesn't contain, that there's a certain percentage below which we don't have to worry, because it's sort of like there is no such thing as zero.

DR. SHANK: I think you mean non-detectable.

DR. HILL: Non-detectable, but then in this confirmation, we don't have detection limits. So that's -- I'm always asking -- and actually, our U.S. vendors seem to be better when they do supply, to tell us about detection limits, which is actually useful data. So, I just wondered if there is legal definition for when we make a statement -- it doesn't confirm -- or it does not contain --

(Pause)

DR. HILL: Yeah, okay, at least pesticides, they say in the limit of detectability. But they don't have that on residual solvents or residual monomer. So, I wondered if there is no legal backing yet on those.

Something I'm raising, really, on that one for the future. My big issue with this class was, there are some low molecular weight molecules we don't have data about. Potential for low molecular weight impurities on many of these -- again, because we have some double bonds accessible for making epoxides with the possibility of generating haptens for sensitization. It would be nice to know a little bit more.

DR. MARKS: Okay. The only concern I had was the irritation and the sensitization of the ingredients we had were fine, but they weren't at the levels being used at this point, like polyisobutene is being used at 95 percent concentration, and we have sensitization data that's okay up to 51 percent. So, almost now being used double what (Inaudible) was being -- results. And the same with polybutene. It's 82 percent.

We have data that say it's safe for sensitization at 50 percent. And then, polyisobutane, that's being used at -- we have no data on 52 percent use concentration. So, I think if we're going to ask for the

ultraviolet light absorption of isoprenes, I'd like to also see if we have sensitization data of these three at that higher concentration.

DR. BERGFIELD: Just sensitization or irritation, as well as --

DR. MARKS: I think when we do sensitization, we'll get irritation out of that.

(Simultaneous discussion)

DR. MARKS: So then with that in mind, if there's nothing else, I would move tomorrow, that we have an insufficient data notice, and that those would be the two data points we would liked to have seen. Team, does that sound reasonable to you?

DR. SHANK: Yes.

DR. SADRIEH: I have a question.

DR. MARKS: Yes?

DR. SADRIEH: So, 95 percent -- I mean, I don't understand what is meant when you say that it's used at --

DR. MARKS: That's what --

DR. SADRIEH: -- 95 percent. That means that the product is 95 percent this ingredient?

DR. MARKS: Christina, did I read the table correctly in the use and concentration, that it was being used at 95 percent in lipstick?

DR. SADRIEH: Oh, in lipstick, 95 percent of it would be this.

DR. MARKS: Yes. Yeah, that's in the use and concentration tables. So, that's where I --

DR. EISENMANN: I won't go back, and sometimes, I make mistakes.

SPEAKER: It's okay.

(Simultaneous discussion)

DR. SADRIEH: It's all right. It just cannot be.

DR. EISENMANN: Right, I know. You know, sometimes they sell things in mixtures, and they tell me, and I don't always catch everything. But when I go back to ask for the irritation --

(Simultaneous discussion)

DR. SADRIEH: But even 82 percent on everything -- these are huge amounts. You know? That is just not possible.

DR. EISENMANN: I will go back and ask. Sometimes, they make a mistake, and you know, they're actually using a mixture, and they tell me the concentration of the mixture that has multiple things in it, rather than the concentration of the ingredient. I will go back and check. When I ask for data, frequently, they'll say, oops, that was wrong. Why did we send you that? So, I will go back.

MS. BURNETT: Yeah, looking at the other concentrations, maybe the 95 got transposed. It's supposed to be 59. Because the maximums on some of the others are like 47, 57.

DR. MARKS: I took it at face value, so either way --

(Simultaneous discussion)

DR. MARKS: -- either the concentration is wrong at use, which will be fine. Then, we don't need an HRIPT or if it is at that --

(Simultaneous discussion)

MS. BURNETT: Yeah, we do have sensitization or not sensitization -- irritation data on, I think it's polyisobutene, a hundred percent, if that helps anything. Yeah.

DR. MARKS: A hundred percent. I had 52 percent. But maybe I wrote that incorrectly.

MS. BURNETT: PDF page 19, polyisobutene was -- at a hundred percent was non-irritating to rabbit skin.

DR. MARKS: Yeah, non-irritating. But is that a sensitization study?

MS. BURNETT: No.

DR. MARKS: Yeah. Speak to me --

(Simultaneous discussion)

MS. BURNETT: So you want sensitization?

DR. MARKS: Oh yeah.

MS. BURNETT: Okay.

DR. MARKS: That's the endpoint in this case. I'm (Inaudible) it in.

MS. BURNETT: And then on --

DR. MARKS: Just because it's non-irritating doesn't mean it's non-sensitizing.

MS. BURNETT: Right. And then, on your insufficient data non submit --

If it does absorb in the UV, do you want phototox data?

DR. MARKS: Sure.

MS. BURNETT: Okay.

DR. SADRIEH: I had also another comment that I just wanted to ask about. And that's -- does the 26 ingredients that are listed in this category -- and when we looked, there are quite a few that have zero frequency of use in VCRP. You know, assuming VCRP is representative of anything.

And so, why would we want to look at ingredients that are not being used at all in cosmetics? And there are several products that we're looking at today. Other ingredients, I mean, where they are not in cosmetics. There is no indication that they are in cosmetics, but we are somehow lumping them into a safety review for you know -- it's kind of unclear.

The basis for selection general speaking -- and I'm relatively new to the CIR here -- a number of ingredients are lumped together, and it's unclear what the basis is for why these ingredients are lumped. There's no evaluation of characteristics, physical or chemical properties or anything that might indicate that they need to be somehow, classified together. You know?

And especially here, in the case that they're not even in products. Why would we want to say something is safe, when it's not even in the product?

DR. MARKS: So, is Bart here?

DR. GILL: He's in the other room.

(Simultaneous discussion)

DR. MARKS: So, at least my -- and please, correct me, Lillian. My take on this is that when the groups are decided, it's generally based on their chemical structural -- the chemistry and the structure of the ingredient, and whether they're used or not used is irrelevant in putting that group together.

And then, if you notice at the end of the conclusions, if they're not used, we acknowledge that and say if they were to be used. So, I view it as being futuristic, so it gives the cosmetic formulator the ability in the future, if they want to use an ingredient, which at present time is not being used, they can use it, as long as it's used in the same use and concentration as the ingredients that have already been reviewed.

DR. SADRIEH: But they can use it anywhere. There's nothing to preclude them from using it. So, why do they need previous permission? (Laughter)

(Simultaneous discussion)

DR. MARKS: I don't look at it as permission. I look at it as guidance.

DR. SHANK: These are all listed in the international cosmetic dictionary. All right?

DR. SADRIEH: Yeah, right. The drug ingredients are listed in there, as well. Pharmaceutically active drug ingredients --

(Simultaneous discussion)

DR. SHANK: Okay, but these ingredients --

DR. SADRIEH: -- doesn't mean they're (Inaudible).

DR. SHANK: -- are listed in the cosmetic dictionary. So, that's the source of the source of ingredients, whether used or not.

DR. GILL: I just want to second what they're saying. They are listed, and they are available for use. They've -- manufacturer have applied to have them included. And what we've looked at it is, do we have ingredients that are similar? And in the future, could they be -- have they been used? We're not sure. We don't know when they may be used.

But there is a possibility that they could be used. So, what we're saying in our conclusion is that if these argues (sic) this is the recommended, this is the panel review level at which we're safe or unsafe, or whatever the panel concludes, that they could be used, if they are used. We never know when they would be used.

They could be used 10 years from now, 5 years from now; in 15 years, we would know with a re-review, but we just don't know. So, they are available for use. If they aren't, and we haven't reviewed them, then I think it is -- you might have manufacturers coming back to Carol and saying this hasn't been reviewed. We'd like for it (sic), it's very similar. Can it be included or added to the CIR safety assessment? So, we do this to cover those that may be used that are similar.

DR. HILL: Okay. And I'd like to chime in a little bit, since I'm the chemist on this side of the group. It's that consistency and bio-handling, that's not my word, although Dr. Liebler keeps accusing me that it is, but there are several seminal texts in the early '90s that make use of that word.

The way that a human being handles a particular group of compounds, that there is consistency, although it might not always be evident -- but I made the statement again. I mean, if you asked a hundred medicinal chemists, you know, how do they view this set of substances, they'll get a hundred different answers. But yet, there are certain guidances that come from many years of thinking how chemical structure and chemical composition relates to the biology that goes with that.

And again, my wife would say I do that in the shower and while driving, and she thinks, even while driving. Yeah, I mean, so -- but we're getting much more sophisticated than that. That's the computational effort that -- I mean, Europe is doing some of it, but we've got some people in this country participating in all of that, trying to figure out, okay, this structure looks similar to that. But what do we really mean?

And I'm always saying similar doesn't mean a dad gum (sic) thing, unless we're talking about similarity in bio-handling. But the other side of the coin is that there is value to read across. So, sometimes we see we have toxicology data on a substance that's in the dictionary, and sometimes, we even go outside the dictionary, because it's in the same structural class.

So that -- and I don't remember who it was from -- I think it was Procter & Gamble that came, and they gave a very nice presentation on putting together assemblages of different compounds and the data from groups of compounds, ideally interpolating and not extrapolating to get a more powerful conclusion on a group of substances than you would have from a single substance itself.

And so, I see -- yeah -- and so (Laughter) -- are you a P&G guy? I was thinking so. And you might have been the one that presented.

SPEAKER: No.

DR. HILL: No?

(Simultaneous discussion)

SPEAKER: (Inaudible) Blackburn.

DR. HILL: Okay, Blackburn. Yeah, so -- and I think they published on that subject. And I know they published on that subject. Excuse me.

So, you're right. I mean, we do have -- in fact, we've got four strategies for trying to decide what's in what groups. And we cull out, and we have debates across the table when we get to that segment. You know, which ones do we keep in? Which ones do we toss out? And it always comes down to the biology, really. You know, the bio- handling. How does a human being, given these routes of exposure, deal with those substances in terms of distribution, absorption -- absorption, distribution, metabolism, excretion, and then, anything we can tie together in the toxicology of different compounds.

So, it may not look obvious, and I think those questions should always be asked, and increasingly, we'll be asking them computationally and are asking them computationally, which is a good thing. But then at the end, the way I sell the computation to our graduate students who are earning PhDs in medicinal chemistry is in the end, there are really good hypotheses generators.

When you use them for safety, we have to be pretty careful. And when we talk about things like boundary conditions, and that came up in the PEG cocamine ingredients this time, but we're piloting some of these things through. I think people should just keep asking questions and poking holes, so that we can make it better and better.

DR. SADRIEH: I don't have concerns about lumping things that are similar. My only question was, I don't know that we had the rationale, or at least the data to kind of -- you know, if screening studies were done to indicate that structures were similar, if they were (Inaudible) models that were used to say that these things were similar in structure.

And that's why they were lumped in the same category, that's fine. That at least there's data to support that somehow, something has been looked at. Or, if it's based on physical, chemical properties, on some log P- value or something -- you know, that's fine.

It's just we can at least say that based on these characteristics, we're saying -- you know, and if you were going to look at UV or whatever, you know, one would at least have the information. It's just we don't -- we did not have that information, so it's kind of not clear as to how the determination is made.

And so, to take it at face value, you know, is a little bit difficult sometimes, not having all of the information. So you know, by all means, if the data is there, fine. I'm just saying, you know, show me the data.

MS. BURNETT: Bart helped me write the introduction. And in the beginning paragraph, he has stated what his rationale was for putting these ingredients together. And he actually has four reasons.

There's vinyl type polymers. There are manufacturer -- what's similar starting materials -- each had similar -- simple hydrocarbon structures without functional groups outside the alkanes or alkenes, and they're of sufficient molecular size in the hydrophobicity to decrease the chance of dermal penetration.

DR. SADRIEH: So the word sufficient -- you know, molecular size and hydrophobicities, you know, I don't know what sufficient means. My point is, what are the specifics to indicate -- you know, do you have any criteria or standards or specifications for saying that you know, if you're within this range, then you're going to be considered comparable.

And if you're not -- because then otherwise, you're using adjectives that are very descriptive, that are very, you know, general, and not you know -- don't address the issue. And that's more of a general statement about all the ingredients that we look at, because you know, from we -- not getting any data to look at from sponsors, industry, we have no idea what's available out there or not.

We don't even know the frequency of use base. I mean, VCRP is very limited. We don't know what the amounts in products are, other than what we're told here at CIR. You know? And clearly, 95 percent, that's kind of (Laughter) -- there's just so much that's not known.

DR. HILL: So, I'll speak to a couple of things. One is that the assessment of safety is based on the data that we do have. So, pretty much, if somebody is using it off that map, then it would be found to be insufficient or unsafe. You know?

And then, by our current rules, they have a couple of years, if they want to sign the consumer commitment code to come in line with that, or else, take it out of their product. In terms of -- I disagree with this forced bit of rationale, because we say high molecular weight, but then, here I'm looking on page 11 -- that's what I was just talking about, that we're talking about molecular weight ranges for the hydrogenated polyisobutene of 187 to 486. Those are imminently absorbable, and hydrogenated polydecene, 367 to 596.

So, you know, anything up to about 1,200, we can see -- because I've look at transdermal drug delivery for a long time and a lot. Anything up to about 1,200, we can see, but the higher you get toward a thousand from 500 or 600, the less the absorption rate will be.

That doesn't mean we can't have sensitization in the skin, because you only need to get enough in there to do something. But in terms of systemic toxicity -- so, that factors in. And this is the stage of the draft report, so we're really starting with structural similarity and some parameters.

The usefulness of having these low molecular weights in there, because we've had this debate a lot, in this particular case is, because if we do have toxicology on these, that will speak to the presence of any low molecular weight impurities or residuals that might be present in the larger molecules, because we don't always have information about under the conditions of use -- you know, it's different.

You put it on your hair and then hit it with a hot air dryer, then it's going to be smearing it cold, and like that. So, sometimes, they will contribute to the ability to do read across when we have a diversity of these, and in many cases, we can do a structured activity relationship either formally or informally, and say -- I mean, in this weight range, we were worried, because we have the potential based on their physical chemical characteristics, which would be -- you know, for transdermals, drugs, log P, log P of 4, 5, 6 -- those are actually optimal for transdermal delivery, because when you get above that, they start to at least hang up in the skin, or not penetrate at all.

But then again, Dr. Bronaugh came in, and he had things with log P of 30 that would actually make it into the layers of the skin far enough to potentially be metabolized by enzymes. So, I think we always had to be careful of that, which I've said in here repeatedly, though. But molecular weights are pretty -- because that affects diffusion coefficients, so molecular size, effective molecular size, which is a combination of sphericity versus extended molecule.

You know, again, when you get above 1,200 molecular weight, even penetration into the upper layers of the skin becomes very small, but then lipophilicity is a little shakier, and when it gets sufficiently hydrophilic, we have an ingredient in here that's a sulfonate salt, then absorption in the GI is very low. That's demonstrated by the data.

We would expect it to be very low in skin. Could we ever have sensitization from such a thing, then we need data. You know, and we do have data.

DR. SADRIEH: And any absorption from the skin is also dependent on other components in the formulation, and so I think that you're looking at the skin by itself.

DR. HILL: We talk about the --

DR. SADRIEH: I'm just saying that you know, just because you know, drugs are formulated to penetrate through the skin by making the formulation adequate.

SPEAKER: Is there a question?

DR. SADRIEH: But that's beside the point.

DR. HILL: Well yes. And so if you look at things that we think are (Inaudible) and have toxicology, there will always be a statement in the discussion, and sometimes in the conclusion that should not be

formulated with penetration enhancers. You know? So, then it's incumbent on the people that are putting these formulations together to satisfy that condition or face the potential consequences. And I don't think anybody wants to get sued for facing such consequences, if they can avoid it.

DR. GILL: Yeah, I think the discussion is an important one, and we hear your perspective. I think that is a discussion that is both CIR with the council, because the parameters and the additional data and information that you are considering necessary and vital for us to make a safety conclusion, we'll need to talk about what's critical and how we collect that, and how do we establish those parameters. And I think that is a joint industry with so to speak, on data we get in.

DR. HILL: And in this particular case, to reiterate, it is a draft report, so we're actually still at the stage where we could kick out ingredients, if we decided that we had a broad agreement to do that. I think this panel doesn't think that anything needs to be kicked out, and I personally don't in this case, but that's been happening all the time in my what, five and a half years on the panel. I've lost count. Five years, I guess. Five years this meeting, I believe.

DR. MARKS: Okay. Any other discussion? Otherwise, tomorrow, I'll move for an insufficient data notice. Get the HRIPT or the correct use concentrations for the hydrogenated polyisobutene, polybutene and polyisobutene, which interestingly, were found safe before. And then the UV absorption of the three isoprene polymers, and if they do absorb light, then phototox test. Any other comments?

DR. BERGFIELD: I'm just wondering if you want to add some kind of summary of what's just been stated to be a further direction of the CIR and the scientific commission that supports us.

DR. MARKS: My reaction was, you know, do we need to have a percutaneous absorption discussion again from an expert in the future, just like we had this morning, the quantitative AR discussion and the baby product -- baby skin discussion. So, I don't know. That was what came to my mind.

It's been a while, perhaps, but Ron, Ron and Tom, you can comment, and obviously, Lillian will take that in consideration.

DR. SHANK: Are you asking for a presentation on the difference penetration and absorption?

DR. MARKS: No.

DR. SHANK: (Laughter) Okay, good.

DR. MARKS: But I don't know. I don't know that -- but obviously, the issue came up, so you know, I think that's a consideration. It will be in the minutes, Wilma.

DR. BERGFIELD: Sure.

DR. MARKS: This robust discussion that we had now. I don't know that we need to include that in these set of ingredients, because it's pertinent for all of the ingredients that we review.

DR. BERGFIELD: You might want to add that to the discussion time, though. Just put it out there for panel discussion.

DR. MARKS: My sense is, Ron Shank, you didn't feel (Laughter) we needed to review this again in terms of having an outside expert. And Tom also feels that way.

DR. HILL: You know, it might be something to consider, and Ivan's not in here, either, but -- and Bart's not in here, is to perhaps -- this would be dangerous, but sort of a -- because we do have guidances on our web site pertaining to certain topic areas -- a collection of seminal references that we use to consider dermal penetration. But I'm just tossing that out there for just people to chew in on in their minds for a while.

DR. MARKS: Thank you for your comments. Actually, that raises a lot of issues.

Full Panel Meeting

DR. BERGFELD: Any other comments? Seeing none, we'll move ahead then to the second ingredient polyenes. Dr. Marks.

DR. MARKS: Okay, this is the first review of these 26 ingredients there. Although among the 26 are 3 that had a previous reported safe, that's polybutene, polyisobutene and hydrogenated polyisobutene. A lot of uses. What was reported, 2763 for the polyisobutene and very high concentration, if indeed this is correct. And you're shaking your head Carol. Do you want to comment on that?

DR. EISENMANN: In the old report there was a 97 percent lip product. So this consistent, it's probably, like, a liquid lip gloss type product.

DR. MARKS: So 95 percent for the hydrogenated polyisobutene in lipstick. So lots of uses for one of these ingredients and high concentration for one of these ingredients. After our discussion, we felt that we wanted to issue an insufficient data notice. I wanted to see an HRIPT for the hydrogenated polyisobutene. It's used at 75 percent in the previous report. We had -- in the present data we have data up to 51 percent, that it's safe as far as sensitization is concerned. So I thought it was a bit of a leap to go from 51 percent to 95 percent.

Polybutene use is 82 percent and again, we have data to support safety up to 50 percent, and polyisobutene was being used at 52 percent. And we have no sensitization data. So I'd like to see HRIPT on those three ingredients. And then Ron Shank brought up the issue of three of the isoprene polymers may have UV absorption. And so he would like to see the absorption spectrum of those three isoprene polymers, and if absorbed, a photo tox test on those.

So our team would move an insufficient data notice, asking for HRIPT for those three ingredients and also UBL absorption on these isoprene polymers.

DR. BERGFELD: Second or comment?

DR. BELSITO: Yeah, so we cannot second, at least based upon our discussion yesterday. We thought they were safe as used. We thanked Christina for bringing in the summaries from polyethylene and polybutene, polyisobutene and hydrogenated polyisobutene.

We felt that they were poorly absorbed, not because of their molecular weight, but simply because of their Kow. And Dan did not feel that there was a chromophore in any of these molecules. So I will let him comment, and I'll let my other team mates comment on the absorption issues, since those are areas that are beyond my expertise.

DR. BERGFELD: Dan?

DR. LIEBLER: With respect to the chromophore issue with the isoprene polymers, I think the isoprenes leave you with isolated double bonds in the structures, which would not absorb over about 200 nanometers. So I don't think there's going to be an issue there. Unless there's something else in these that's not shown in these structures. So that's why I think there's not a chromophore issue. That's the first point.

DR. SHANK: Then that should be in the discussion because isoprene itself does absorb around 300.

DR. LIEBLER: Right, and of course the polymerization reaction consumes one of the double bonds, which leaves you with a single isolated double bond, which won't absorb any longer. But that can certainly be incorporated into the discussion.

And then the other issue, when we first talked about these last time, I think somebody said, you know, these are large molecules. And then I started looking at it and they're actually not very big. In fact the relatively small size gives them their desirable properties. But I still agree that these would be very poorly absorbed, if at all, because they basically have no functional groups other than carbon and hydrogen. They don't have any heterotomic groups that would facilitate their absorption, and they are going to be -- their relative biological inertness based on the data we have in front of us, is probably attributed to the fact that they have very limited ways to interact with other biological molecules.

So that's something that could be incorporated into the discussion. I don't mean that as suggesting that I object to the HRIPT question because if you did have some data for that very high use concentration, that would -- and it turned out to be negative, that would actually reinforce the sort of reasoning from the chemical properties.

DR. BERGFELD: Ron Hill?

DR. HILL: Yeah, my thinking on that was, for the smallest molecular weight ones that we have, you can get penetration into skin with KOWs up to 30'ish. That we got from Dr. Bronaugh some years back. So given that there are remaining double bonds potentially in some of these substances, there is at least a reasonable thought that we can make an epoxide that's an electrophile, react with protein substances in the skin and generate a hapten.

So it seems to me it would be prudent for, even if we have just one of these smaller ones that's representative of the structure in terms of sensitization, I think I agree there should be no photosensitization issue at all. But I don't think we can exclude the possibility that it would get far enough into the skin. I'm not worried about systemic toxicology. There really isn't anything that suggests to me that. But sensitization still seems to me a possibility. That's my view on it.

DR. BERGFELD: Any other comments? Jim, you want to comment again about the needs or --

DR. MARKS: Clearly we've addressed the concern that our team have with the UV absorption and that'll go in the discussion. Don, what do you think in terms of HRIPT when we have -- I hear Dan, your comment about they are -- they can be small. Less than 400 molecular weight when we look at it.

DR. LIEBLER: Right, I mean, they're oil liquids in many cases. So I guess, although I don't know any clinical alerts, that caught my eye as to there had been HRIPT. But Carol, you're commenting --

DR. EISENMANN: I think you should look in the old report. I believe there is HRIPT at 100 percent for hydrogenated polyisobutene. There was some supplier data. I looked in the report this morning and I thought there was more HRIPT in the old report.

DR. MARKS: Okay, if that's the case, then I withdraw that. When I went through and I thought I'd looked at the old report, and in fact I --

DR. EISENMANN: We'll look again, but even if it's not there and if it's not there, we'll ask. But I'm pretty sure there was data in the old report.

DR. MARKS: Interesting.

DR. HILL: And that's one of the small molecular weight (inaudible) right? And there's it's actually in the --

DR. BELSITO: So in animals, it doesn't really say. It says, the test substance was injected interdermally in the area skin on the back and flanks, clipped here. And point oh five --

MS. BURNETT: There is an irritation study, a human irritation study at 100 percent for polyisobutene. How many --

DR. MARKS: Well, the problem with that is, an irritation study is not the same as a sensitization study. So I tend to, when I want to see HRIPTs, I'm focused on sensitization not irritation. You only have a couple of hits maybe or one or two within irritation study. So that doesn't, to me, substitute for a sensitization.

MS. BURNETT: And the study didn't give any further detail. So I can't tell you how many patients are --

DR. BELSITO: Yeah, so wait a minute, CTFA submitted a study that investigated whether the following ingredients caused any allergic sensitization in human skin. A hundred percent polysinlane, 100 percent squaline, 207 subjects participated in the study. Seven dropped out. They were patch tested with the

four materials using (inaudible) and self patch test procedure. And the results were negative. So now I don't know what sinlane is. I don't remember polysinlane.

DR. MARKS: That's probably one of the problems I had, is polysinlane a trade -- what is that? A trade name? And what percentage of that contains the polyisobutene or polybutene?

DR. BELSITO: Well, let me see if I can Google it. Oh my, it's St. Patrick's day. The Irish.

MS. FIUME: PDF page 184 has it parenthesis what it is. It's hydrogenated polyisobutene.

DR. HILL: So 100 percent hydrogenated polyisobutene was negative in a Draize test Okay, so I think we can go -- I withdraw my motion, and we [inaudible] I think. So the question that remains in my mind here is, if the only low molecular weight guys are totally hydrogenated, wiped up any terminal double bonds, then -- and particularly because I do see the sensitization study you're talking about on the hydrogenated. But it's hydrogenated, which means we've probably wiped out most or all of the double bonds which would abrogate the concern I raised. But the question is, are there any low molecular weight players here, relatively low molecular weights.

So I'm seeing one that's 900. That's still dermally penetrable. Certainly less so, that could still have double bonds in it, and we don't have data for that. But I have to double check again now. So this isn't the last time we're seeing this report, right. But yet the conclusion, we wouldn't want to go back and change. So I'm still questioning.

DR. MARKS: Well, I think -- I'll withdraw, ask my team to concur. I think now we have the data I was concerned about. Ron, your data has been okay. So I think we can move the issue of tentative report with safe conclusion.

DR. BERGFELD: And you're seconding it Don?

DR. BELSITO: Second.

DR. BERGFELD: Any other questions or comments or discussion? Yeah? Discussion points to these -- so just verify the discussion points for me.

DR. BELSITO: The discussion points are that we're aware that the concentration is increased, but we have the report, hydrogenated polyisobutene from the prior at 100 percent. That we don't have UV absorption or phototoxicity, but the polymerization will result in molecules that would not absorb in the UVA -- in UVB [inaudible] UVA range that you're worried about. And I think that's really it about these molecules.

DR. MARKS: Yes.

DR. BELSITO: Does anyone have any other issues with them? And I had no other safety issues.

DR. MARKS: No, those were the only --

DR. BELSITO: Lack of any other safety issues.

MS. BURNETT: Dr. Liebler you still want me to use your language that you had, okay.

DR. LIEBLER: Yes.

DR. BERGFELD: All right, any other discussion points that need to be added to this list? Seeing none, I'll call the question. All those in favor of a safe conclusion, unanimous. Thank you.

DR. LIEBLER: I'm going to abstain (inaudible).

DR. BERGFELD: Okay, one abstaining. Thank you.

Safety Assessment of Polyene Group as Used in Cosmetics

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The 2015 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 Director is Lillian J. Gill, DPA. This safety assessment was prepared by Christina Burnett, Senior Scientific Analyst/Writer and Bart Heldreth, Ph.D., Chemist CIR.

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ABSTRACT

The Cosmetic Ingredient Review Expert Panel (Panel) reviewed the safety of polyenes, which function in cosmetics primarily as film formers and viscosity increasing agents. The Panel reviewed relevant data related to these ingredients, noting gaps in the available safety data for some of the polyenes in this safety assessment. The data available for many of the ingredients are sufficient, and can be extrapolated to support the safety of the entire group because of the similarities in the chemical structures, physicochemical properties, use concentrations, and reported functions across the group. The Panel concluded that polyenes were safe in cosmetics in the present practices of use and concentration described in this safety assessment:

INTRODUCTION

The 26 ingredients in this report are simple polyolefins that are the polymerization products of vinyl-type monomers. The polyenes reviewed in this report cover a wide range of molecular weights, but have very similar structures and reaction starting materials (monomers). These similarities include: 1) each being the product of the same vinyl-type polymerization methodologies; 2) each being manufactured from very similar starting materials (i.e., olefin/alkene monomers); 3) each having similar, simple hydrocarbon structures without any functional groups outside of alkanes or alkenes; and 4) many being of sufficient molecular size to significantly decrease the chance for dermal penetration. The following polyenes function mainly as film formers and/or viscosity increasing agents-nonaqueous in cosmetic products.

butene/propylene copolymer
butylene/ethylene copolymer
butylene/ethylene/propylene copolymer
decene/butene copolymer
ethylene/octene copolymer
ethylene/propylene copolymer
hydrogenated poly(C6-12 olefin)
hydrogenated poly(C6-14 olefin)
hydrogenated poly(C6-20 olefin)
hydrogenated polybutene
hydrogenated polydecene
hydrogenated polydodecene
hydrogenated polyisobutene
isobutylene/isoprene copolymer
isoprene/pentadiene copolymer
polybutene
poly(C4-12 olefin)
poly(C6-14 olefin)
poly(C20-28 olefin)
poly(C30-45 olefin)
polydecene
polyethylene
polyisobutene
polyisoprene
polypentene
polypropylene

Polybutene (published in 1982), polyethylene (published in 2007), polyisobutene (published in 2008), and hydrogenated polyisobutene (published in 2008) have previously been reviewed by the CIR Expert Panel, which concluded that these ingredients are safe as cosmetic ingredients in the practices of use and concentration as described in each safety assessment.[1-4] Information from these safety assessments are summarized in *italics* in each appropriate section of this report.

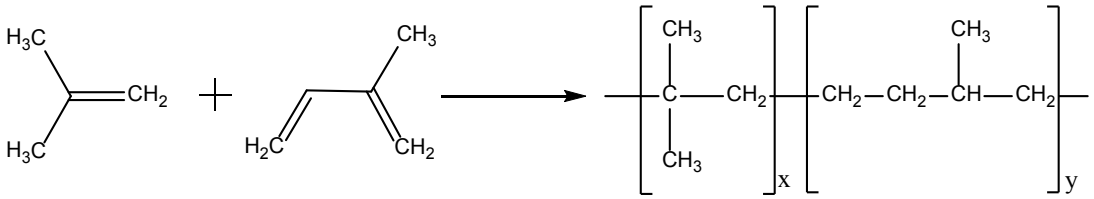
Some chemical and toxicological data on hydrogenated polydecene and polybutene included in this safety assessment were obtained from robust summaries of data submitted to the European Chemical Agency (ECHA) by companies as part of the REACH chemical registration process. These data summaries are available on the ECHA website.[5,6] The ECHA data summaries include information on analogs (e.g. diisobutylene, di-n-butene, tributene, triisobutylene, and tetrabutene for polybutene; hydrogenated decene dimer and trimer for hydrogenated polydecene; and hydrogenated dodecene trimer for hydrogenated polydodecene) for read-across purpose. Where deemed appropriate, those data summaries have been included in this report.

CHEMISTRY

The definitions and CAS registry numbers, where available, of the polyene ingredients are presented in Table 1.

Polyenes are the polymerization products of vinyl-type monomers (a.k.a. alkenes or olefins). These polyolefins are either homopolymers (e.g., polybutene) or vinyl-type copolymers of two or more monomers (e.g., butene/propene copolymers). The term “vinyl-type copolymers” means that all of the monomers utilized to make these polymer ingredients have in common an ethylene unit whose pi electrons are directly involved in the polymerization process. Typically, a catalyst is utilized to initiate the polymerization.[7] There are a large multitude of relevant initiating catalysts, ranging from ultraviolet (UV) light to Ziegler-Natta-type catalysts, which can result

in a range of varied characteristics, such as crystallinity (and resultant hardness). The synthesis of these ingredients is typically carried out in one or more organic solvents in the presence of one or more of these catalysts.



Isobutylene Isoprene Isobutylene/Isoprene Copolymer

Figure 1. An example of polyene synthesis (Isobutylene/Isoprene Copolymer)

For example, formation of polyisoprene occurs by reacting the isoprene monomer in the presence of catalyst in a hydrocarbon solution, usually hexane.[8] The process is stopped with the addition of a terminating reagent. The in situ stabilization of the polymer is often enhanced with the addition of an antioxidant. Subsequent steps in the process include stripping of the solvent, water washing of the polymer to remove catalyst and reagent residues, and finally pressing and formation of a granular product.

Chemical and Physical Properties

Table 2 summarizes available data on chemical properties, including some information from the original CIR safety assessments of polybutene, polyethylene, polyisobutene, and hydrogenated polyisobutene. Further chemical data on these previously reviewed ingredients can be found in these reports.[1-3] Table 3 summarizes available data on molecular weights.

Many of these polyene ingredients are high molecular weight, large, inert polymers. However, even the smaller, liquid ingredients in this group each comprise simple hydrocarbon structure without any functional groups outside of alkanes or alkenes. Thereby, dermal penetration is limited. These ingredients are completely insoluble in aqueous solutions or organic solvents, but may be swellable in certain organic solvents.

While some of these ingredients may be somewhat smaller polymers, molecular weights such as those reported for CAS No. 68037-01-4 (as recited on ChemIDplus and associated with the ingredient hydrogenated poly(C6-12 olefin)) are obvious mischaracterizations. Indeed, the 140.268 Da molecular weight associated with this registry number more closely represents the median formula weight of the *monomer* of hydrogenated poly(C6-12 olefin), specifically C6-12 olefin. While it is unknown what number of monomers make up the polymer, a hypothetical average of eight monomeric repeat units in a resulting polymer would yield a molecular weight of hydrogenated poly(C6-12 olefin) over 1000 Da.

Method of Manufacturing

Hydrogenated Polyisobutene

According to a supplier, hydrogenated polyisobutene is produced from the polymerization of isobutene, which is then hydrogenated, purified, and then super refined before yielding the final product.[9]

Composition and Impurities

Ethylene/Octene Copolymer

A supplier has reported that a trade name mixture comprised in part of ethylene/octene copolymer contains 14-16% ethylene/octene copolymer and 84-86% C14-22 alkane.[10] Residual monomer levels are 2 ppm octene and 0 ppm ethylene. Ethylene oxide, 1,4-dioxane, and heavy metals were reported to be below the detection limit of 0.1 ppm.[11]

A second trade name mixture was reported to contain 30-50% ethylene/octene copolymer and ethylene/sodium acrylate copolymer and 50-70% water.[10] The residual monomer levels were reported to be less than 165 ppm acrylic acid, less than 5 ppm ethylene, and less than 52 ppm octene. A heavy metals analysis reported arsenic was not detected (limited of detection, 27 ppb), however lead and mercury levels were 22 ppb and 52 ppb, respectively (limits of detection for each are 5 ppb).[12]

Ethylene/Propylene Copolymer

A redox titration of ethylene/propylene copolymer measured 0.8 ppm of the starting material residue in the final product.[13]

Polybutene

Impurities of polybutene include isoparaffins, vinylidene and terminal vinyl structures, chloride, and sulfur-containing compounds.[3]

Polyisobutene

A supplier reported that polyisobutene does not contain detectable levels of residual solvents or monomers, and has heavy metal specifications of lead < 10 ppm, arsenic < 2 ppm, and mercury < 1 ppm.[14,15]

Hydrogenated Polyisobutene

A supplier reported that hydrogenated polyisobutene does not contain detectable levels of residual solvents or monomers, and has heavy metal specifications of lead < 10 ppm, arsenic < 2 ppm, and mercury < 1 ppm.[16-19]

An anonymous source reported that hydrogenated polyisobutene may contain a maximum of 10 ppm n-hexane as residual solvent.[9]

Hydrogenated Polydecene

A supplier reported that hydrogenated polydecene does not contain residual solvents, has a residual monomer specification (decene 1) of < 10 ppm, and has heavy metal specifications of lead < 10 ppm, arsenic < 2 ppm, and mercury < 1 ppm.[20-23]

USE

Cosmetic

The safety of the cosmetic ingredients included in this safety assessment is evaluated on the basis of the expected use in cosmetics. The Panel utilizes data received from the Food and Drug Administration (FDA) and the cosmetics industry in determining the expected cosmetic use. The data received from the FDA are those it collects from manufacturers on the use of individual ingredients in cosmetics by cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP), and those from the cosmetic industry are submitted in response to a survey of the maximum reported use concentrations by category conducted by the Personal Care Products Council (Council).

According to the 2015 VCRP survey data, polyethylene is reported to be used in 2773 formulations; the single category with the most reported uses was lipstick with 885 (Table 4, Table5).[24] Hydrogenated polyisobutene is reported to be used in 1963 formulations; the single category with the most reported uses was lipstick with 865. Most of the other in-use ingredients are mainly used in leave-on products and lipsticks. The results of the concentration of use survey conducted in 2013 and 2014 by the Council indicate hydrogenated polyisobutene has the highest reported maximum concentration of use; it is used at up to 95% in lipsticks.[25,26]

Both historical and current use data for polybutene, polyethylene, polyisobutene, and hydrogenated polyisobutene are provided in Table 5. Concentrations of use for polybutene and hydrogenated polyisobutene have remained about the same, with the highest maximum use concentration in hydrogenated polyisobutene at 95% in lip products. The highest maximum use concentration for polyethylene has increased from 24% (eye shadow) to 67.6% (skin cleansing agents), while the highest maximum use concentration for polyisobutene has decreased from 76% to 40% (both concentrations in lip products. Uses for all four ingredients have increased by several fold since their original reviews.

The ingredients not in use according to the VCRP and industry survey are listed in Table 6.

In some cases, reports of uses were received from the VCRP, but concentration of use data were not provided. For example, hydrogenated polybutene is reported to be used in 51 formulations, but no use concentration data were reported. In other cases, no uses were reported in the VCRP, but concentration of use data were received from industry. Hydrogenated poly(C6-20 olefin) had no reported uses in the VCRP, but a use concentration in a lipstick was provided in the industry survey. Therefore, it should be presumed there is at least one use in every category for which a concentration is reported.

Some of these ingredients were reported to be used in pump and aerosol hair sprays, underarm deodorant sprays, face and neck sprays, body and hand sprays, and aerosol suntan products and could possibly be inhaled. For example, hydrogenated polyisobutene was reported to be used in face and neck sprays at a maximum concentration

of 8.5% and polyethylene was reported to be used in aerosol deodorants at a maximum concentration of 1.6%. 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.[27-30] 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.[28,29] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[29] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

The polyene ingredients in this safety assessment currently are not restricted from use in any way under the rules governing cosmetic products in the European Union (EU).[31]

Noncosmetic

Many of the polyene ingredients have been approved by the FDA for use as indirect food additives and in medical devices. Additionally, isobutylene/isoprene copolymer, polyethylene, and polyisobutene are approved direct food additives for chewing gum bases.

Polyethylene and polypropylene are used as negative control materials for International Organization for Standardization (ISO) 10993-6 international standard biological evaluation of medical devices.[32] Ultra high molecular weight polyethylene is the most used biomaterial for the articulating surface of total joint replacements.[33] Polyisobutene is used in transdermal drug delivery patches and patch adhesives.[34,35] Polyisoprene (*trans*-1,4) is widely used in root canal filling material.[36]

Table 7 lists of many of the regulated uses in foods and medical devices.

TOXICOKINETICS

Absorption

Hydrogenated Polydecene

A study assessed the absorption potential of undiluted hydrogenated polydecene in male Fischer rats.[5] Groups of 3 rats/time-point received a single or daily (for 15 days) oral gavage dose of 30, 210, or 1500 mg ^{3}H-hydrogenated polydecene. Tissues and body fluids were sampled at 0.08, 0.25, 0.5, 1, 2, 4, 8, 24, 48, 72, 120, and/or 168 h post-dosing. With all 3 dose levels, very little of the administered dose was absorbed. What was absorbed was found in the liver, fat, lymph nodes, kidney and spleen. The majority of the test compound was excreted into the feces (> 92%). Urinary excretion was low (< 1%), and very little of the dose was recovered in the bile (0.01%).

Biocompatibility

Polyethylene

Cellular and tissue responses to polyethylene, determined as part of implant biocompatibility testing, include fibrous connective tissue build-up around the implant material that varies as a function of the physical form of the implant material.[1] Specific assays for osteoblast proliferation and collagen synthesis demonstrated a reduction as a function of exposure to polyethylene particles that is inversely related to particle size. However, polyethylene particles had a stimulatory effect on monocyte-derived macrophages, prolonging the survival of these cells in culture.

TOXICOLOGICAL STUDIES

Single Dose (Acute) Toxicity

Animal acute dose toxicity studies are presented in Table 8.[5,6,37-43] In acute oral toxicity studies in rats, the LD_{50}s of diisobutylene, and triisobutylene were > 2000 mg/kg/body weight each. The oral LD_{50}s of di-n-butene, tributene, and tetrabutene (containing 30% pentabutene) in rats were > 10,000 mg/kg each. The oral LD_{50} values for ethylene/octene copolymer, undiluted hydrogenated polydecene and undiluted hydrogenated polydodecene were > 5000 mg/kg in rat studies. The LD_{50} of undiluted polyisobutene was > 15,400 mg/kg in an oral rat study.

Acute dermal studies of diisobutylene and hydrogenated polydodecene found the LD_{50} values > 2000 mg/kg in rats. In rabbit studies, the dermal LD_{50} values for ethylene/octene copolymer, hydrogenated decene dimer, hydrogenated polyisobutene, and polyisobutene were > 5000 mg/kg, > 3000 mg/kg, >2000 mg/kg, and >25,000mg/kg, respectively.

In acute inhalation studies, the LC_{50} of diisobutylene vapor in albino rats was > 4185 ppm (19,171 mg/m^3) after a 4- hour, single, whole-body exposure. The LC_{50} for an aerosol of hydrogenated polydecene was > 5.2 mg/L

in rats. The LC_{50} for the dimer of hydrogenated decene was 1.17 mg/L in rats. In another acute inhalation study of the dimer of hydrogenated decene, the LC_{50} could not be determined in rats tested at 5 mg/L because 9/10 animals died within 3 days of administration of the test material. The LC_{50} for hydrogenated polydodecene was > 5.06 mg/L. The LC_{50} for 100% hydrogenated polyisobutene was > 5 mg/l.

The oral, inhalation and dermal acute dose toxicity data that were presented in the original reviews of polybutene, polyethylene, and hydrogenated polyisobutene are summarized below and not in the tables. All previously reviewed data will be removed from this safety assessment prior to report publication.

Oral

Polybutene

When tested for acute oral toxicity in albino rats, concentrations of polybutene ranging from 15% to 75% were relatively harmless (average molecular weight not specified).[3]

Polyethylene

The LD_{50} for polyethylene (average molecular weight of 450) in rats (201 to 223 g) was found to be > 2000 mg/kg, and in polyethylene with an average molecular weight of 655, the LD_{50} was determined as >5.0 g/kg.[1]

Hydrogenated Polyisobutene

No deaths in mice were observed in an acute oral toxicity test at a maximum dose of 89.608 g/kg of a hydrogenated polyisobutene mixture.[2] *No deaths were observed in several oral toxicity rat studies of 5 g/kg hydrogenated polyisobutene; however, lethargy and wetness in the anogenital area after dosing was observed. The authors of these studies also concluded that the LD_{50} is greater than 5.0 g/kg body weight. The average molecular weight was reported to be 900 in one of the studies.*

Inhalation

Polybutene

Polybutene produced no abnormalities in rats during a 4-h inhalation exposure up to concentrations of 18.5 mg/L.[3]

Dermal

Polybutene

In acute dermal toxicity tests, polybutene in formulations produced no abnormalities or irritation in rabbits. The LD_{50} of polybutene in formulation was greater than 10.25 g/kg (average molecular weight not specified).[3]

Repeated Dose Toxicity Studies

Repeated dose toxicity studies in animals are presented in Table 9.[5,37-43] No treatment-related gross of microscopic changes were observed following exposure to 100% polyisobutene in a 90-day dietary study ofrats and 2-year dietary studies in rats or dogs. No adverse effects were observed in oral repeated dose studies of hydrogenated polydecene, with the no observed adverse effect levels (NOAELs) determined to be 1000 mg/kg/day in one 90-day rat study and over 4000 mg/kg/day in another. In a 4-week oral repeated dose study, the NOAEL for hydrogenated polydecene was 6245 mg/kg/day in males and 6771 mg/kg/day in females. Gross necropsy, histopathology, and microscopic findings did not reveal any significant treatment-related findings. The NOAEL for the oral administration of the trimer of hydrogenated dodecene in two respective oral repeated dose toxicity studies in rats was 1000 mg/kg/day. Treatment-related effects in mortality, clinical signs, body weight, food consumption, hematology, clinical chemistry, organ weights, or gross and histologic pathology were not observed in either study. In a 4-week dermal study in rats, 100% hydrogenated polyisobutene produced minimal to mild dermal irritation in the majority of treated animals. Histopathologic examinations of the high-dose group found effects limited to the application site and included minimal to mild epidermal hyperplasia and hyper-keratosis with reactive hyperplasia of the underlying inguinal lymph nodes.

The oral and dermal repeated dose toxicity data that were presented in the original reviews of polybutene and polyethylene are summarized below and not in the tables. All previously reviewed data will be removed from this safety assessment prior to report publication.

Oral

Polybutene

A 2-year chronic oral toxicity study of polybutene (75% concentrate) in Charles River albino rats given up to 20,000 ppm polybutene blended into their regular diets revealed no gross or microscopic pathological changes that could be correlated with polybutene ingestion.[3] No significant differences were found after 24 months of feeding in the body weights or weight of food consumption, hematological results, urology, or tumor formation between the animals fed polybutene and those that were not. In the 20,000 ppm group, three out of six males that died between weeks 17 and 24 exhibited hematuria. In a 2-year chronic oral toxicity study of polybutene (75% concentrate) in Beagle dogs, daily oral administration of polybutene at doses up to 1000 mg/kg/day caused no abnormalities in body weight, food consumption, survival, behavioral patterns, hematology, blood chemistry, urinalysis, liver function, gross and histopathologic examinations, or organ weights and ratios. Average molecular weights of polybutene were not specified in these studies.

Polyethylene

Toxicity testing in rats showed no adverse effects to polyethylene at doses of 7.95 g/kg or at 1.25%, 2.50%, or 5.00% in feed for 90 days.[1] The average molecular weight of polyethylene was not specified in this study.

Dermal

Polybutene

Polybutenes did not affect hepatic or skin enzymatic activities in rats following once daily treatments for 6 days (average molecular weight not specified).[3]

REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY

Polybutene

No teratogenic effects were found when polybutene was fed to rats at 1% or 10% in the diet for six months.[3] A three-generation reproductive study in Charles River albino rats that ingested polybutene up to 20,000 ppm demonstrated that, except for the test (F_2) male parental animals that were fed 20,000 ppm polybutene, none of the animals in successive generations differed from controls with regard to weight gains. The F_2 male parental animals showed slight weight gain depression, although their growth patterns were still within the normal range. In all three generations, there were no significant differences between test and control animals with regard to litter size, the number of stillborn, and the number of viable pups during lactation. The survival, body weights, and reactions of test animals were comparable to those of controls. Average molecular weights were not specified in these studies.

Hydrogenated Polydecene

The reproductive effects of hydrogenated polydecene were studied in rats that received the test material via gavage (average molecular weight not specified).[5] Groups of 30 male and 30 female Sprague-Dawley rats received 0, 100, 500, or 1000 mg/kg bw/day hydrogenated polydecene in polyethylene glycol daily for 4 weeks prior to mating and through mating. At the end of mating, males were sacrificed. Females were treated through gestation and until lactation day 21. No treatment-related effects were observed on clinical signs, body weight, or gross pathology in the parental generation or in the pups through lactation day 21. There were no treatment related effects on reproduction or pup viability. The NOAEL for parental systemic effects, parental reproductive effects, and offspring effects in this one generation rat study is 1000 mg/kg bw/day.

Polyisobutene

In a 3-generation reproductive toxicity study, an unreported number of Charles River rats received 0, 800, or 20,000 ppm 100% polyisobutene in their feed (molecular weight range 654-2168).[37,38] No further details about dosing were provided. Weight gain was slightly reduced in the second generation high-dose male rats, but the changes were within normal control ranges. No other effects on body weights, clinical signs, organ weights or histopathology were observed. No treatment-related reproductive effects were noted in any of the parameters measured (no furthered details provided). No differences were observed in offspring survival, litter size, number of stillborn, and number of viable pups in any generation of the treated groups when compared to controls. No remarkable post-mortem findings were reported.

Hydrogenated Polydodecene

The reproductive effects of the trimer of hydrogenated polydodecene were studied in one generation of rats that received the test material via gavage.[5] Groups of 24 male and 24 female Sprague-Dawley rats received 0, 50, 250, or 1000 mg/kg/day of the test material in arachis oil daily for 20 weeks (during maturation, mating, gestation, and lactation). No treatment-related effects on offspring growth or development were observed. Litter sizes were comparable to controls in all dose groups. No adverse effects were observed during gross necropsy or histopathological examination. The NOAEL for reproductive and development toxicity in this rat study is 1000 mg/kg/day.

GENOTOXICITY

In Vitro

Ethylene/Octene Copolymer

A trade name mixture containing 30%-50% ethylene/octene copolymer and sodium acrylate copolymer was not mutagenic in an Ames test or in an in vitro chromosomal aberration test (no further details provided).[12]

Polyethylene

Genotoxicity testing of polyethylene was negative in two bacterial studies.[1] Average molecular weights were not specified in these studies.

Polyisobutene

In a study to determine the ability of various insulating fluids to induce transformation in the Syrian hamster embryo (SHE) cell transformation assay and to enhance 3-methylcholanthrene (MCA)-induced transformation of C3H/10T1/2 cells, a low-viscosity polyisobutene-based oil did not induce transformation activity and was slightly cytotoxic.[2] In the two-stage transformation assay of C3H/10T1/2 cells, the polyisobutene oil had promoter activity. Average molecular weights were not specified in these studies.

Hydrogenated Polydecene

Hydrogenated polydecene was not mutagenic in an Ames test at concentrations up to 500 µg/plate (molecular weight range 367-596; no further details provided).[43]

Hydrogenated polydecene was not mutagenic in a reverse gene mutation assay in *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 and *Escherichia coli* strain WP2uvrA (average molecular weight not specified).[5] The test material was incorporated in emulsions with sorbitan stearate and polysorbate 60 at concentrations of 156.25, 312.5, 625, 1250, 2500, or 5000 µg/plate, with and without metabolic activation using the pre-incubation method. The positive controls yielded expected results.

In reverse mutation assays, *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 were treated with hydrogenated polydecene at concentrations up to 10 mg/plate (average molecular weight not specified).[5] The positive controls yielded expected results. Hydrogenated polydecene was not mutagenic with or without S9 metabolic activation at all tested concentrations.

Hydrogenated Polydodecene

The genotoxic potential of the trimer of hydrogenated polydodecene was assayed in 2 chromosome aberration experiments using human lymphocyte cultures.[5] In the first experiment, the test material was cultured at concentrations of 0, 39, 78.1, 156.25, 312.5, 625, 1250, 2500 and 5000 µg/mL. In the second experiment, the test material was cultured at concentrations of 625, 1250, 2500 and 5000 µg/mL for 20 hours or 1250, 2500, and 5000 µg/mL for a 44 hour harvest time. All experiments were conducted in duplicate, with and without S9 metabolic activation. Cytotoxicity was not observed in a range finding test conducted prior to the main assay at concentrations ≤ 5000 µg/ml. The test material did not induce chromosomal aberrations or polyploidy cells, with or without metabolic activation. Positive controls, ethyl methanesulfonate in the absence of S9, and cyclophosphamide in the presence of S9, yielded expected results. The authors concluded that the trimer of hydrogenated polydodecene was not clastogenic to human lymphocytes in vitro when tested at concentrations ≤ 5000 µg/mL.

In a mammalian cell gene mutation assay (HGPRT locus), Chinese hamster ovary (CHO) cells cultured in vitro were exposed to the trimer of hydrogenated polydodecene in ethanol at concentrations of 0, 313, 625, 1250, 2500, or 5000 µg/mL with and without metabolic activation for 4 hours.[5] In the range-finding test, relative cloning frequencies (RCEs) ranged from 97% to 73% for concentrations ranging from 0.5 to 5000 µg/mL without metabolic

activation. RCEs were 122% to 80% for the same concentration range with metabolic activation. RCEs in the first mutation assay were 92% to 77% and 111% to 89% for concentrations ranging 313 to 5000 µg/mL with and without metabolic activation, respectively. The activated portion of the first mutation assay was repeated and RCE was 100% to 71% for the same dose range. In the confirmatory assay, the RCEs among the test material-treated cultures ranged from 50% to 23% and 89% to 52% for the concentrations of 313 to 5000 µg/mL with and without metabolic activation, respectively. A significant response was observed at 625 µg/mL when compared to the solvent control data in the repeat definitive mutation assay with activation; however, the increase was not significant when it was compared to the historical, cumulative solvent control data. The same was true at 2500 µg/mL, with activation, in the confirmatory mutation assay. The increase in the number of mutants was not significant when compared to historical, cumulative solvent control data. The response seen in the definitive mutation assay at 625 µg/mL was not reproduced in the confirmatory assay. Controls were within the historical negative control values. The trimer of hydrogenated polydodecene was not mutagenic in this mammalian cell gene mutation assay.

CARCINOGENICITY

Polyethylene

Numerous investigations on the tumor production of polyethylene implantation have produced mixed results.[1] *Polyethylene causes tumors in rats implanted with squares of the test substance; however, testing involving implanting coverslips and powdered polyethylene suggest that tumors are caused by the physical reaction to imbedded plastic films and not the polyethylene itself. International Agency for Research on Cancer (IARC) lists polyethylene as "not classifiable as to carcinogenicity in humans" based on no adequate human data and inadequate animal data. Average molecular weights were not specified.*

Polyisobutene

In a carcinogenicity study conducted to determine the skin tumorigenicity effects of certain oils used for impregnation of paper-insulated power cables and their synthetic alternatives, including polyisobutene oil, no evidence of a direct tumorigenic or carcinogenic effect was reported and polyisobutene oil (average molecular weight 250) appeared to reduce the number of 7,12-dimethylbenz[a]anthracene-induced tumors in mice.[2]

Polyisobutene (100%) was not carcinogenic in rats (dosed up to 20,000 ppm) or dogs (dosed up to 1000 mg/kg) in oral studies described in Table 9 (molecular weight range 654-2168).[37,38]

Polypropylene

IARC determined that polypropylene is not classifiable as to its carcinogenicity to humans (Group 3) based on no adequate human data and inadequate animal data.[44]

IRRITATION AND SENSITIZATION

Irritation

Non-human and human dermal irritation studies are presented in Table 10 and non-human ocular irritation studies are presented in Table 11.[5,12,37-43,45,46] Ethylene/octene copolymer and sodium acrylate copolymer (30%-50% in a trade name mixture was minimally/slightly irritation to rabbit skin. Polyisobutene and hydrogenated polyisobutene at 100% were not irritating to rabbit skin in respective irritation studies. Hydrogenated polydecene and the trimer of hydrogenated decene were not primary irritants or corrosives in several rabbit studies. No significant irritation was observed human subjects in a cumulative irritation test of ethylene/octene copolymer and sodium acrylate copolymer (30%-50%) in a trade name mixture. No adverse effects were reported in human subjects following irritation studies of a formulation containing 8% hydrogenated polyisobutene and hydrogenated polyisobutene at 100%. No adverse effects were reported following dermal exposure to formulations containing hydrogenated polydecene with equal amounts of cetyl ethylhexanoate and pentaerythrityl tetraethylhexanoate tested at total concentrations up to 35% in a study in human subjects.

Ethylene/octene copolymer and sodium acrylate copolymer (30%-50% in a trade name mixture was minimally/slightly irritation to rabbit eyes. Polyisobutene and hydrogenated polyisobutene at 100% were not irritating to rabbit eyes in respective irritation studies. Two primary eye irritation studies in rabbits found undiluted hydrogenated polydecene not to be an ocular irritant, while another study found the material to be moderately irritating.

The dermal, ocular, and mucous membrane irritation data that were presented in the original reviews of polybutene, polyethylene, polyisobutene, and hydrogenated polyisobutene are summarized below and not in the tables. All previously reviewed data will be removed from this safety assessment prior to report publication.

Dermal

Polybutene

In primary skin irritation studies, polybutene in formulations including lipsticks produced no abnormalities or irritation in rabbits at concentrations up to 15%; however, mild irritation was observed at concentrations greater than 15%.[3] Average molecular weights were not specified. Human primary irritation tests of a lipstick formulation containing 20% polybutene produced no irritation. The average molecular weight was not specified.

Polyethylene

Dermal irritation studies on rabbits in which 0.5 g of polyethylene (average molecular weight of 450) was administered in 0.5 ml of water caused no irritation or corrosive effects.[1] When the same procedure was used to test polyethylene with an average molecular weight of 655, a primary irritation index score of 0.2 was found and polyethylene was classified as a mild irritant.

Hydrogenated Polyisobutene

A skin irritation study in six rabbits using four patches each containing 0.5 g/patch of a hydrogenated polyisobutene mixture caused no reactions in any of the animals on intact or abraded skin.[2] The primary irritation index was 0.0. There was a primary irritation index score of 1.8 for rabbits treated with undiluted hydrogenated polyisobutene on the intact or abraded skin. Rabbits dosed dermally with 0.5 ml hydrogenated polyisobutene) on intact and abraded skin exhibited a primary irritation index of 0.38; not a dermal irritant. In a similar study, hydrogenated polyisobutene produced a primary irritation index of 0.96; also not a dermal irritant. Average molecular weights were not specified in these studies.

In humans, no primary skin irritation was produced in a 72-h primary skin irritation patch test study with 100% hydrogenated polyisobutene in 25 male and female participants.[2] There was no irritancy observed in humans during a 24-h single-insult patch test with a lip gloss containing 66.11% hydrogenated polyisobutene. Average molecular weights were not specified in these studies.

Ocular

Polybutene

Rabbits suffered only minimal eye irritation when polybutene at concentrations up to 75% was instilled into the eyes with and without washouts.[3] Average molecular weights were not specified.

Polyethylene

Polyethylene (molecular weight of 450) was tested as a solid material (66 mg) in the eyes of rabbits.[1] The test substance caused a maximum group mean score of 11.0 and was classified as a mild irritant. All treated eyes appeared normal 48 hours after application. The same procedure, with 55 mg of polyethylene of average molecular weight of 655, was carried out on white rabbits. The mean maximum group score produced by polyethylene was 11.7 and it was classified as a mild irritant. All treated eyes appeared normal 72 h after treatment. When white rabbits were tested with 13% polyethylene beads, the maximum ocular score was 8/110 with resolution after 48 h and no corneal abrasions were observed.

Polyisobutene

Irritant and corrosive effects were examined following a single instillation of polyisobutene into rabbit eyes.[2] No corneal or iridial damage was recorded in the study. One eye had irritation to the conjunctivae by 72 h, which was present as slight hyperemia. The average molecular weight was not specified.

Hydrogenated Polyisobutene

When 0.1 ml hydrogenated polyisobutene was instilled into the conjunctival sac of rabbit eyes, the test material caused slight conjunctival irritation in 33% of eyes which cleared up by day 2.[2] The authors determined that hydrogenated polyisobutene is not an eye irritant. Another study of hydrogenated polyisobutene under similar test conditions produced the same results. No signs of ocular irritation were observed in a Draize study of three rabbits exposed to a facial lotion containing 3% hydrogenated polyisobutene. In a 7-day eye irritation study on rabbits, no eye irritation was observed in washed or unwashed eyes following treatment with 0.1 ml hydrogenated polyisobutene. An unknown concentration of hydrogenated polyisobutene instilled into the right eyes of six rabbits

produced a score of 1 on the Draize scale. No other effects were observed. Average molecular weights were not specified in these studies.

In human, no adverse reactions or ocular irritation were reported in 59 subjects in a 29 day in-use study of 3 different formulations of cosmetic foundations/concealer products that contained hydrogenated polyisobutene.[2] The concentration of hydrogenated polyisobutene was not specified in 2 of the 3 formulations, while the third contained 4% hydrogenated polyisobutene. Average molecular weights were not specified.

Mucous Membrane

Polybutene

Undiluted polybutene produced no irritation or signs of systemic toxicity when applied to the vaginas of rabbits.[3] Average molecular weight was not specified.

Sensitization

Non-human and human sensitization studies are presented in Table 12.[5,11,12,43,47] Ethylene/octene copolymer was not sensitizing in a guinea pig maximization test or in a local lymph node assay (LLNA) Hydrogenated polydecene was not a dermal sensitizer in guinea pig maximization tests at concentrations up to 100%. The dimer of hydrogenated decene was not a dermal sensitizer guinea pig maximization studies. The trimer of hydrogenated decene in propylene glycol was a slight sensitizer according to an LLNA. The stimulation indices were 1.56, 1.89, and 3.54 for the test concentrations of 25%, 50%, and 100%, respectively. Ethylene/octene copolymer was not a sensitizer in a human repeat insult patch test (HRIPT). Polyisoprene was not a sensitizer according to the results of a human repeat insult patch test (HRIPT) at 12.33% in a lip gloss.

The sensitization data that were presented in the original reviews of polybutene, polyethylene, and hydrogenated polyisobutene are summarized below and not in the tables. All previously reviewed data will be removed from this safety assessment prior to report publication.

Polybutene

Repeated insult patch tests of 3.1-50% polybutene in formulations produced no sensitization.[3] Average molecular weights were not specified.

Polyethylene

Polyethylene (average molecular weight of 450) did not cause dermal sensitization in guinea pigs tested with 50% polyethylene (w/w) in arachis oil BP.[1] In a repeat insult patch test of 201 volunteers, a product containing 13% polyethylene beads was tested in a series of nine consecutive administrations. There was no irritation observed with any of the induction patches. Challenge patches produced only a slight response in one subject and the investigators concluded that polyethylene has a low irritation and sensitization potential.

Hydrogenated Polyisobutene

Hydrogenated polyisobutene was intradermally injected in an area of the skin on the back and flanks of guinea pigs.[2] Erythema and edema were observed after most inoculations, but no sensitization reactions were observed. Hydrogenated polyisobutene injections (5%) in guinea pigs using a maximization procedure resulted in no observed reactions and an irritation index of 0.0 in both challenge phases I and II. Average molecular weights were not specified in these studies.

Repeat-insult patch tests performed to evaluate the primary irritancy/sensitization potential of formulations containing 1.44% or 4% hydrogenated polyisobutene in 54 male and female subjects found no reactions greater than slight erythema.[2] In a modified repeat-insult patch test under double-blind conditions, no irritation or sensitization was found in human skin patched with a makeup remover containing 51% hydrogenated polyisobutene. Hydrogenated polyisobutene at up to 100% was not sensitizing in a Draize repeat insult patch in 200 subjects. Average molecular weights were not specified.

Phototoxicity

Polybutene

Photo patch tests of formulations with concentrations ranging from 15% to 50% polybutene produced no reactions.[3] Average molecular weights were not specified.

Hydrogenated Polyisobutene

The phototoxic potential of cosmetic foundations/concealer products containing 4% hydrogenated polyisobutene or 1.44% hydrogenated polyisobutene, and a blank patch under UVA light source (320 to 400 nm) was studied in 26 fair-skinned volunteers.[2] No significant reactions were reported. Formulations containing 1.44% or 4% hydrogenated polyisobutene were evaluated to determine their potential to induce a photoallergic reaction in the skin of 30 subjects. No response was reported at induction, rest, or challenge. Average molecular weights were not specified.

Comedogenicity

Polyisobutene

The comedogenic potential of polyisobutene was studied using adult New Zealand White rabbits.[2] The test material was applied to the right ear of each animal daily on 5 consecutive days per week for 3 weeks. There were no signs of hyperkeratosis or comedone formation during weeks 1 and 2. By the third week, two treated ears exhibited signs of hyperkeratosis. The ear of the third rabbit, however, remained clear. Histological examination showed no signs of follicular hyperkeratosis on the treated, untreated, or control ears of any rabbits. The average molecular weight of polyisobutene was not specified.

CLINICAL STUDIES

Polyethylene

There have only been a few cases of reactions to the implantation of polyethylene in humans.[1] In the three published accounts, polyethylene strips used for breast augmentation caused increased histological activity around the implant. There have also been occupational case reports on ocular irritation and systemic sclerosis in workers exposed to polyethylene. Such workers are also exposed to other irritants. Clinical testing of intrauterine devices made of polyethylene failed to conclusively identify statistically significant adverse effects, although squamous metaplasia was observed in treated women.

SUMMARY

Data from earlier CIR safety assessments on polybutene, polyethylene, polyisobutene, and hydrogenated polyisobutene have not been summarized here. Only new data are summarized below.

The polyene ingredients in this report are simple polyolefins that are the polymerization products of vinyl-type monomers. The polyenes reviewed in this report cover a wide range of molecular weights, but have very similar structures and reaction starting materials (monomers). Polyenes function mainly as film formers and/or viscosity increasing agents-nonaqueous in cosmetic products.

According to the 2015 VCRP survey data, polyethylene is reported to be used in 2773 formulations; the single category with the most reported uses was lipstick with 885. Hydrogenated polyisobutene is reported to be used in 1963 formulations; the single category with the most reported uses was lipstick with 865. Most of the other in-use ingredients are mainly used in leave-on products and lipsticks. The results of the concentration of use survey conducted in 2013 and 2014 by the Council indicate hydrogenated polyisobutene has the highest reported maximum concentration of use; it is used at up to 95% in lipsticks.

For the ingredients that were previously reviewed by the CIR Expert Panel, concentrations of use for polybutene and hydrogenated polyisobutene have remained about the same, with the highest maximum use concentration in hydrogenated polyisobutene at 95% in lip products. The highest maximum use concentration for polyethylene has increased from 24% (eye shadow) to 67.6% (skin cleansing agents), while the highest maximum use concentration for polyisobutene has decreased from 76% to 40% (both concentrations in lip products. Uses for all four ingredients have increased by several fold since their original reviews.

Many of the polyene ingredients have been approved by the FDA for use as food additives and in medical devices.

An oral study that assessed the absorption potential of undiluted hydrogenated polydecene in rats found that the majority of the test compound was excreted into the feces without being absorbed (> 92%). Urinary excretion was low (< 1%), and very little of the dose was recovered in the bile (0.01%).

In acute oral toxicity studies in rats, the LD_{50}s of diisobutylene, and triisobutylene were > 2000 mg/kg/body weight each. The oral LD_{50}s of di-n-butene, tributene, and tetrabutene (containing 30% pentabutene) in rats were > 10,000 mg/kg each. The oral LD_{50} values for ethylene/octene copolymer, undiluted hydrogenated polydecene and undiluted hydrogenated polydodecene were > 5000 mg/kg in rat studies. The LD_{50} of undiluted polyisobutene was > 15,400 mg/kg in an oral rat study.

Acute dermal studies of diisobutylene and hydrogenated polydodecene found the LD_{50} values > 2000 mg/kg in rats. In rabbit studies, the dermal LD_{50} values for ethylene/octene copolymer, hydrogenated decene dimer, hydrogenated polyisobutene, and polyisobutene were > 5000 mg/kg, > 3000 mg/kg, >2000 mg/kg, and >25,000mg/kg, respectively.

In acute inhalation studies, the LC_{50} of diisobutylene vapor in albino rats was > 4185 ppm (19,171 mg/m^3) after a 4- hour, single, whole-body exposure. The LC_{50} for an aerosol of hydrogenated polydecene was > 5.2 mg/L in rats. The LC_{50} for the dimer of hydrogenated decene was 1.17 mg/L in rats. In another acute inhalation study of the dimer of hydrogenated decene, the LC_{50} could not be determined in rats tested at 5 mg/L because 9/10 animals died within 3 days of administration of the test material. The LC_{50} for hydrogenated polydodecene was > 5.06 mg/L. The LC_{50} for 100% hydrogenated polyisobutene was > 5 mg/l.

No treatment-related gross of microscopic changes were observed following exposure to 100% polyisobutene in a 90-day dietary study ofrats and 2-year dietary studies in rats or dogs. No adverse effects were observed in oral repeated dose studies of hydrogenated polydecene, with the no observed adverse effect levels (NOAELs) determined to be 1000 mg/kg/day in one 90-day rat study and over 4000 mg/kg/day in another. In a 4-week oral repeated dose study, the NOAEL for hydrogenated polydecene was 6245 mg/kg/day in males and 6771 mg/kg/day in females. Gross necropsy, histopathology, and microscopic findings did not reveal any significant treatment-related findings. The NOAEL for the oral administration of the trimer of hydrogenated dodecene in two respective oral repeated dose toxicity studies in rats was 1000 mg/kg/day. Treatment-related effects in mortality, clinical signs, body weight, food consumption, hematology, clinical chemistry, organ weights, or gross and histologic pathology were not observed in either study. In a 4-week dermal study in rats, 100% hydrogenated polyisobutene produced minimal to mild dermal irritation in the majority of treated animals. Histopathologic examinations of the high-dose group found effects limited to the application site and included minimal to mild epidermal hyperplasia and hyper-keratosis with reactive hyperplasia of the underlying inguinal lymph nodes.

In rat reproductive studies of hydrogenated polydecene and the trimer of hydrogenated polydodecene, the NOAELs for parental systemic and reproductive effects and for offspring were 1000 mg/kg body weight/day for the respective studies. No treatment-related effects were observed on clinical signs, body weight, or gross pathology in the parental generation or in the pups. There were no treatment related effects on reproduction or pup viability. In a 3-generation reproductive dietary toxicity study, an unreported number of Charles River rats received 0, 800, or 20,000 ppm 100% polyisobutene produced no treatment-related reproductive effects in any generation of the treated groups when compared to controls.

A trade name mixture containing 30%-50% ethylene/octene copolymer and sodium acrylate copolymer was not mutagenic in an Ames test or in an in vitro chromosomal aberration test Hydrogenated polydecene at concentrations up to 10 mg/plate was not mutagenic in Ames assays, with or without metabolic activation. The trimer of hydrogenated polydodecene was not clastogenic to human lymphocytes nor was it mutagenic in CHO cells (HGPRT locus assay) in vitro when tested at concentrations up to 5000 µg/mL.

IARC determined that polypropylene is not classifiable as to its carcinogenicity to humans (Group 3). Polyisobutene (100%) was not carcinogenic in rats (dosed up to 20,000 ppm) or dogs (dosed up to 1000 mg/kg) in oral studies.

Ethylene/octene copolymer and sodium acrylate copolymer (30%-50% in a trade name mixture was minimally/slightly irritation to rabbit skin. Polyisobutene and hydrogenated polyisobutene at 100% were not irritating to rabbit skin in respective irritation studies. Hydrogenated polydecene and the trimer of hydrogenated decene were not primary irritants or corrosives in several rabbit studies. No significant irritation was observed human subjects in a cumulative irritation test of ethylene/octene copolymer and sodium acrylate copolymer (30%-50%) in a trade name mixture. No adverse effects were reported in human subjects following irritation studies of a formulation containing 8% hydrogenated polyisobutene and hydrogenated polyisobutene at 100%. No adverse effects were reported following dermal exposure to formulations containing hydrogenated polydecene with equal amounts of cetyl ethylhexanoate and pentaerythrityl tetraethylhexanoate tested at total concentrations up to 35% in a study in human subjects.

Ethylene/octene copolymer and sodium acrylate copolymer (30%-50% in a trade name mixture was minimally/slightly irritation to rabbit eyes. Polyisobutene and hydrogenated polyisobutene at 100% were not irritating to rabbit eyes in respective irritation studies. Two primary eye irritation studies in rabbits found undiluted hydrogenated polydecene not to be an ocular irritant, while another study found the material to be moderately irritating.

Ethylene/octene copolymer was not sensitizing in a guinea pig maximization test or in a local lymph node assay (LLNA) Hydrogenated polydecene was not a dermal sensitizer in guinea pig maximization tests at concentrations up to 100%. The dimer of hydrogenated decene was not a dermal sensitizer in one guinea pig

maximization study and was given a grade 1 response in another. The trimer of hydrogenated decene in propylene glycol was a slight sensitizer according to an LLNA. The stimulation indices were 1.56, 1.89, and 3.54 for the test concentrations of 25%, 50%, and 100%, respectively. Ethylene/octene copolymer was not a sensitizer in a human repeat insult patch test (HRIPT). Polyisoprene was not a sensitizer according to the results of a human repeat insult patch test (HRIPT) at 12.33% in a lip gloss.

DISCUSSION

The Panel considered the available data on polyenes, including the previous safety assessments on polybutene, polyethylene, polyisobutene, and hydrogenated polyisobutene, and noted low systemic toxicity at high doses in single-dose and repeated-dose animal studies, no teratogenic effects in animal studies, and no genotoxicity in in vitro and in vivo studies. The Panel noted that use concentrations were as high as 95% in lipsticks, but a human dermal sensitization study of 100% hydrogenated polyisobutene in the previous safety assessment of this ingredient was negative and no irritation or sensitization was observed multiple tests of some of the other polyene ingredients. The Panel recognized that polyenes are approved for use in foods (directly and indirectly) and drug and medical devices.

The Panel also noted that although molecular weights are in the range that could be dermally absorbed, the lack of heteroatom functional groups dramatically limits solubility and would prevent significant absorption. The lack of functional groups also limits interactions with other biomolecules and probably accounts for the apparent biological inertness of these ingredients.

The Panel noted gaps in the available safety data for some of the polyenes in this safety assessment. The data available for many of the ingredients are sufficient, and can be extrapolated to support the safety of the entire group because of the similarities in the chemical structures, physicochemical properties, use concentrations, and reported functions across the group.

The Panel recognized that there were no data available on the UV absorption of polyenes; however, because none of the polymer ingredients are chromophores, the Panel felt that there was no concern that these ingredients would cause adverse effects from UV exposure.

The Panel discussed the issue of incidental inhalation exposure in pump and aerosol hair sprays, underarm deodorant sprays, face and neck sprays, body and hand sprays, and aerosol suntan products. The limited data available from inhalation studies, including acute exposure data, suggest little potential for respiratory effects at relevant doses. The Panel considered pertinent data indicating that incidental inhalation exposures to polyenes in such cosmetic products would not cause adverse health effects, including data characterizing the potential for polyenes to cause systemic toxicity, ocular or dermal irritation or sensitization, and other effects. The Panel noted that 95% – 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount. The potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs. In principle, inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions of the respiratory tract may cause toxic effects depending on their chemical and other properties. However, coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

CONCLUSION

The CIR Expert Panel concluded that the following polyene ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment:

butene/propylene copolymer*
butylene/ethylene copolymer
butylene/ethylene/propylene copolymer
decene/butene copolymer
ethylene/octene copolymer*
ethylene/propylene copolymer
hydrogenated poly(C6-12 olefin)
hydrogenated poly(C6-14 olefin)
hydrogenated poly(C6-20 olefin)
hydrogenated polybutene*
hydrogenated polydecene
hydrogenated polydodecene*
hydrogenated polyisobutene
isobutylene/isoprene copolymer*
isoprene/pentadiene copolymer*
polybutene
poly(C4-12 olefin)*
poly(C6-14 olefin)*
poly(C20-28 olefin)*
poly(C30-45 olefin)
polydecene
polyethylene

polyisobutene
polyisoprene
polypentene*
polypropylene

**Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.*

TABLES

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[48]
(The idealized copolymer structures herein present a depiction of block copolymers only for the sake of simplicity and are not intended to suggest that block is the dominant form)

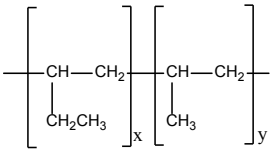
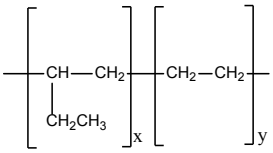
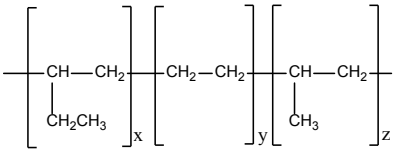
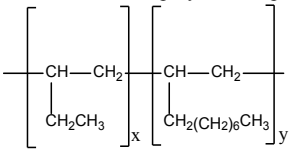
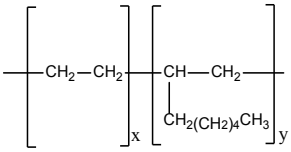
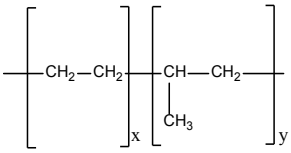
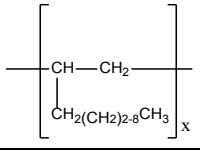
Ingredient CAS No.	Definition & Structure	Function(s)
Butene/Propylene Copolymer 29160-13-2	Butene/Propylene Copolymer is a copolymer of butene and propylene monomers. 	film formers; slip modifiers; viscosity increasing agents-nonaqueous
Butylene/Ethylene Copolymer	Butylene/Ethylene Copolymer is a copolymer of butylene and ethylene monomers. 	viscosity increasing agents-nonaqueous
Butylene/Ethylene/Propylene Copolymer	Butylene/Ethylene/Propylene Copolymer is a copolymer of butylene, ethylene and propylene monomers. 	film formers
Decene/Butene Copolymer	Decene/Butene Copolymer is a polymer of butene and decene monomers. 	viscosity increasing agents-nonaqueous
Ethylene/Octene Copolymer	Ethylene/Octene Copolymer is a copolymer of ethylene and 1-octene monomers. 	film formers; viscosity increasing agents-nonaqueous
Ethylene/Propylene Copolymer 9010-79-1	Ethylene/Propylene Copolymer is the copolymer of ethylene and propylene monomers. 	film formers; viscosity increasing agents-nonaqueous
Hydrogenated Poly(C6-12 Olefin)	Hydrogenated Poly(C6-12 Olefin) is a series of low molecular weight polymers of olefin monomers, each containing 6 to 12 carbon atoms. 	skin-conditioning agents-occlusive; viscosity increasing agents-nonaqueous

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[48]
(The idealized copolymer structures herein present a depiction of block copolymers only for the sake of simplicity and are not intended to suggest that block is the dominant form)

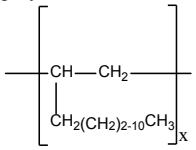
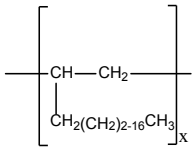
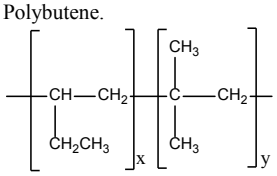
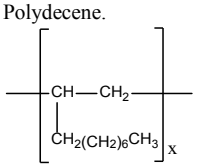
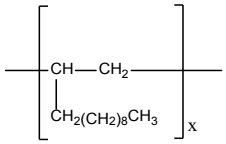
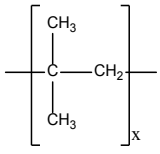
Ingredient CAS No.	Definition & Structure	Function(s)
Hydrogenated Poly(C6-14 Olefin)	Hydrogenated Poly(C6-14 Olefin) are a series of low molecular weight polymers of olefin monomers, each containing 6 to 14 carbon atoms. 	skin-conditioning agents-occlusive; viscosity increasing agents-nonaqueous
Hydrogenated Poly(C6-20 Olefin) 69430-35-9	Hydrogenated Poly(C6-20 Olefin) is a polymer synthesized from hydrogenated C6-20 olefins. 	epilating agents
Hydrogenated Polybutene	Hydrogenated Polybutene is the end-product of the controlled hydrogenation of Polybutene. 	viscosity increasing agents-nonaqueous
Hydrogenated Polydecene 68037-01-4	Hydrogenated Polydecene is the end-product of the controlled hydrogenation of Polydecene. 	fragrance ingredients; hair conditioning agents; skin-conditioning agents-emollient; skin-conditioning agents-misc.; solvents
Hydrogenated Polydodecene	Hydrogenated Polydodecene is the hydrogenated homopolymer of Dodecene. 	binders; hair conditioning agents; skin-conditioning agents-emollient; solvents; viscosity increasing agents-nonaqueous
Hydrogenated Polyisobutene 68937-10-0	Hydrogenated Polyisobutene is the polymer that conforms generally to the formula: 	skin-conditioning agents-emollient; viscosity increasing agents-nonaqueous

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[48]
(The idealized copolymer structures herein present a depiction of block copolymers only for the sake of simplicity and are not intended to suggest that block is the dominant form)

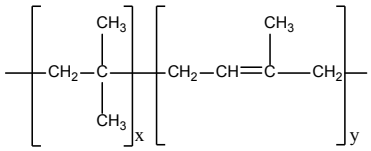
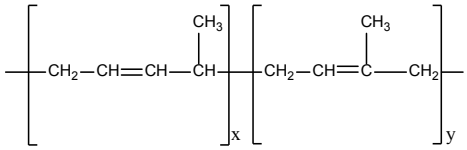
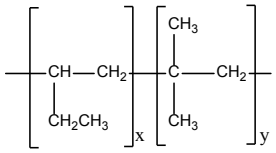
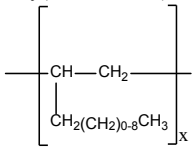
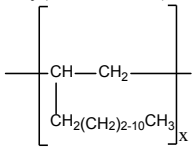
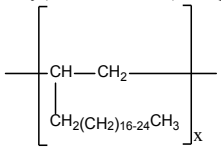
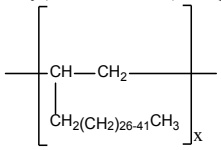
Ingredient CAS No.	Definition & Structure	Function(s)
Isobutylene/Isoprene Copolymer 9010-85-9	Isobutylene/Isoprene Copolymer is a copolymer of isobutylene and isoprene monomers. 	viscosity increasing agents-nonaqueous
Isoprene/Pentadiene Copolymer	Isoprene/Pentadiene Copolymer is a copolymer of isoprene and 1,3-pentadiene monomers. 	viscosity increasing agents-nonaqueous
Polybutene 9003-28-5 9003-29-6	Polybutene is the polymer formed by the polymerization of a mixture of iso- and normal butenes. 	binders; epilating agents; viscosity increasing agents-nonaqueous
Poly(C4-12 Olefin)	Poly(C4-12 Olefin) is a polymer synthesized from C4-12 olefins. 	skin-conditioning agents-occlusive
Poly(C6-14 Olefin)	Poly(C6-14 Olefin) is a polymer synthesized from C6-14 olefins. 	viscosity increasing agents-nonaqueous
Poly(C20-28 Olefin) 64743-02-8	Poly(C20-28 Olefin) is a polymer synthesized from C20-28 olefins. 	binders; film formers; skin-conditioning agents-occlusive; surface modifiers; viscosity increasing agents-nonaqueous
Poly(C30-45 Olefin)	Poly(C30-45 Olefin) is a polymer synthesized from C30-45 olefins. 	film formers

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[48]
(The idealized copolymer structures herein present a depiction of block copolymers only for the sake of simplicity and are not intended to suggest that block is the dominant form)

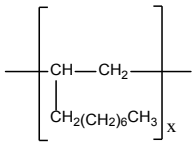
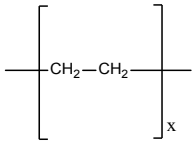
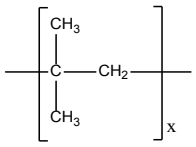
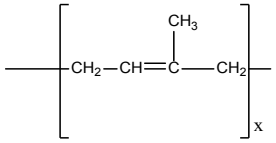
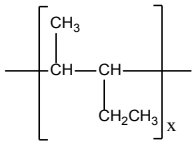
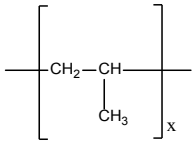
Ingredient CAS No.	Definition & Structure	Function(s)
Polydecene 25189-70-2 37309-58-3	Polydecene is the polymer formed by the polymerization of decene. It conforms to the formula: 	skin-conditioning agents-occlusive
Polyethylene 9002-88-4	Polyethylene is a polymer of ethylene monomers that conforms generally to the formula: 	abrasives; adhesives; binders; bulking agents; emulsion stabilizers; film formers; oral care agents; viscosity increasing agents-nonaqueous
Polyisobutene 9003-27-4	Polyisobutene is the homopolymer of isobutylene that conforms generally to the formula: 	binders; film formers; viscosity increasing agents-nonaqueous
Polyisoprene 9003-31-0	Polyisoprene is the polymer of isoprene that conforms generally to the formula: 	viscosity increasing agents-nonaqueous
Polypentene 9078-70-0	Polypentene is the polymer formed by the polymerization of pentene. It conforms to the formula: 	film formers; viscosity increasing agents-nonaqueous
Polypropylene 9003-07-0	Polypropylene is a polymer of propylene monomers that conforms generally to the formula: 	bulking agents; viscosity increasing agents-nonaqueous

Table 2. Physical and chemical properties of polyenes

Property	Value	Reference
	Polybutene	
Physical Form	Light colored, nondrying, sticky viscous liquid	49-51
Solubility	Insol. in water, sol. in hydrocarbon and chlorinated hydrocarbon solvents	49-51
Melting point ºC	124-130	49-51
Density g/cm^3	0.92	49-51
	Polyethylene	
Odor	odorless	52
Melting point ºC	85-110	1
Flammability (flash point) ºC	221	1
Density g/cm^3	0.910-0.925	1
Maximum λ (nm)	161.5	53
	Polyisobutene	
Physical Form	White to yellowish or pale rubbery solid	2
Odor	Slight rubber/petroleum odor	2
Flash point ºC	165	2
Solubility	Insol. in water	2
Specific gravity g/cm^3	0.92	2
	Hydrogenated Polyisobutene	
Physical Form	Clear liquid	54
Odor	Odorless	54
log K_{ow}	13.27	2
Solubility	Negligible in water	2
Boiling point ºC	35	55
Freezing point ºC	Below -30	54
Specific gravity at 20 ºC (g/cm^3)	0.819-0.830	54
	Hydrogenated Polydecene	
Physical Form at 20 ºC and 1013 hPa	Clear liquid	5
Odor	Odorless	5
log K_{ow}	> 6.5	5
Solubility in water at 20 ºC (mg/l)	< 0.1	5
Vapor pressure at 20 ºC	< 0.545	5
Freezing point ºC at 1013 hPa	-57	5
Specific gravity at 15.6 ºC (g/cm^3)	0.82 to 0.83	5

Table 3. Molecular weight ranges of polyenes

Ingredient	Molecular Weight	Reference
Ethylene/Octene Copolymer	24,038 (number average), 52,743 (weight average) with 0.06% below 500 and 0.29% below 1000	[10]
Hydrogenated Polydecene	367-596	[20-23,43]
Hydrogenated Polyisobutene	average 430, 187-468	[2,9,16-19,39-42]
Polyethylene	198-500,000	[1,56]
Polyisobutene	900 minimum, 654-2168	[2,14,15,37,38]

Table 4. Frequency (2015) and concentration of use (2013) according to duration and type of exposure for polyene ingredients.[24-26]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Butylene/Ethylene Copolymer		**Butylene/Ethylene/Propylene Copolymer**		**Decene/Butene Copolymer**		**Ethylene/Propylene Copolymer**	
Totals†	**1**	**1.5**	**14**	**4.5**	**3**	NR	**107**	**0.0063-12.5**
Duration of Use								
Leave-On	1	NR	14	4.5	3	NR	107	0.0063-12.5
Rinse Off	NR	1.5	NR	NR	NR	NR	NR	2
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	2	NR	1	NR	11	0.0063-4
Incidental Ingestion	1	NR	8	NR	2	NR	72	0.0097-12.5
Incidental Inhalation-Spray	NR	NR	spray: NR possible: 1[a]	NR	NR	NR	spray: 4 possible: 6[a]; 1[b]	spray: 0.11 possible: 0.21[a]
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	powder: 1 possible: 1[b]	NR
Dermal Contact	NR	1.5	5	4.5	NR	NR	32	0.0063-4
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	3	2
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	1.5	8	NR	2	NR	72	0.0097-12.5
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	Hydrogenated Poly(C6-14 Olefin)[c]		**Hydrogenated Poly(C6-20 Olefin)**		**Hydrogenated Polybutene**		**Hydrogenated Polydecene**	
Totals†	**82**	**0.25-58**	**NR**	**10**	**51**	**NR**	**713**	**0.005-59**
Duration of Use								
Leave-On	79	58	NR	10	47	NR	681	0.035-59
Rinse Off	3	0.25-1	NR	NR	4	NR	32	0.005-49
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	35
Exposure Type								
Eye Area	9	NR	NR	NR	14	NR	77	2-38
Incidental Ingestion	16	58	NR	10	26	NR	188	5.2-59
Incidental Inhalation-Spray	spray: NR possible: 10[a]; 14[b]	NR	NR	NR	NR	NR	spray: 17 possible: 224[a]; 115[b]	spray: 1.8-42 possible: 0.88-5[a]
Incidental Inhalation-Powder	powder: 2 possible: 14[b]	NR	NR	NR	NR	NR	powder: 4 possible: 115[b]	powder: 0.9-10.5
Dermal Contact	66	NR	NR	NR	24	NR	482	0.035-49
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	not spray: 2-13.8
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	38	0.005-36
Hair-Coloring	NR	0.25-1	NR	NR	NR	NR	2	1-11
Nail	NR	NR	NR	NR	NR	NR	1	NR
Mucous Membrane	16	58	NR	10	28	NR	191	5.2-59
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 4. Frequency (2015) and concentration of use (2013) according to duration and type of exposure for polyene ingredients.[24-26]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Poly (C30-45 Olefin)		**Polydecene**		**Polyisoprene**		**Polypropylene**	
Totals†	**2**	**0.6-26.1**	**156**	**0.098-47.9**	**28**	**0.098-47**	**24**	**0.05-68.6**
Duration of Use								
Leave-On	2	0.6-26.1	129	0.098-47.9	26	0.098-47	20	0.05-68.6
Rinse Off	NR	NR	27	25	2	1.8	4	0.2-66
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	1	NR	8	0.098-6	2	0.49-47	6	0.4-68.6
Incidental Ingestion	NR	NR	75	10.2-47.9	3	2-12.2	NR	4
Incidental Inhalation-Spray	NR	spray: 26.1	spray: 1 possible: 12[a]; 8[b]	NR	spray: NR possible: 9[a]; 6[b]	NR	spray: NR possible: 2[a]; 6[b]	NR
Incidental Inhalation-Powder	NR	NR	powder: 7 possible: 8[b]	NR	powder: 3 possible: 6[b]	NR	powder: NR possible: 6[b]	powder: 2.8
Dermal Contact	2	0.6-26.1	63	0.098-25	25	0.098-47	18	0.05-66
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	2	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	16	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	1	NR
Mucous Membrane	NR	NR	75	10.2-47.9	3	1.8-12.2	1	4-66
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

NR = Not reported.

† Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

[a.] It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.

[b.] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

[c.] Hydrogenated C6-14 Olefin Polymers is a synonym for Hydrogenated Poly(C6-14 Olefin). The VCRP database has entries for both names and the data has been added together.

Table 5. Current and historical frequency and concentration of use according to duration and exposure.[1-324,26]

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Polybutene				**Polyethylene**			
	2015	**1976**	**2013**	**1976**	**2015**	**2002**	**2013**	**2004**
Totals†	**1823**	**85**	**0.1-82.4**	**>1->50***	**2773**	**717**	**0.0097-67.6**	**0.09-24**
Duration of Use								
Leave-On	1808	83	0.1-82.4	>1->50	2271	615	0.0097-52.6	0.09-24
Rinse-Off	15	2	8-20	>5-10	501	92	0.05-67.6	0.3-11
Diluted for (Bath) Use	NR	NR	NR	NR	1	10	10	4-18
Exposure Type								
Eye Area	239	10	0.5-13.1	>1-5	734	382	0.06-21	3-24
Incidental Ingestion	1322	70	6-82.4	>1->50	885	67	0.0097-18.9	3-16
Incidental Inhalation-Spray	spray: 2 possible: 12[a]; 8[b]	spray: NR possible: 2[a]	spray: 0.1 possible: 20[a]	spray: NR possible: >1-25[a]	spray: 17 possible: 120[a]; 70[b]	spray: 1 possible: 23[a]; 17[b]	spray: 0.5-52.6 possible: 0.47-12[a]	spray: 3-5 possible: 0.5-10[a]; 1-16[b]
Incidental Inhalation-Powder	powder: 11 possible: 8[b]	NR	powder: 0.92-4	NR	powder: 82 possible: 70[b]	powder: 32 possible: 17[b]; 1[c]	powder: 4-30	powder: 3-10 possible: 1-16[b]
Dermal Contact	425	13	0.1-73	>1-25	1765	603	0.03-67.6	0.2-24
Deodorant (underarm)	NR	NR	NR	NR	possible spray: 8	NR	spray: 1.6 possible spray: 9.6-12[a] not spray: 1	possible spray: 7
Hair - Non-Coloring	4	2	NR	>5-10	19	5	0.26-6	2
Hair-Coloring	NR	NR	NR	NR	2	3	5-6	NR
Nail	NR	NR	8	NR	32	NR	0.42-15	0.09-3
Mucous Membrane	1327	70	6-82.4	>1->50	1185	93	0.0097-18.9	0.3-18
Baby Products	NR	NR	NR	NR	NR	1	NR	3

	Polyisobutene				**Hydrogenated Polyisobutene**			
	2015	**2005**	**2013**	**2005**	**2015**	**2005**	**2013**	**2005**
Totals†	**310**	**30**	**0.24-40**	**0.3-76**	**1963**	**654**	**0.00055-95**	**0.001-96**
Duration of Use								
Leave-On	295	29	0.24-40	0.3-76	1916	639	0.001-95	0.001-96
Rinse-Off	15	1	1.1-3.5	4	47	15	0.00055-51	2-85
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	3-85
Exposure Type								
Eye Area	108	11	0.45-36.3	1-30	227	78	0.09-67.7	0.1-40
Incidental Ingestion	54	12	6-40	4-76	865	318	0.29-95	0.001-96
Incidental Inhalation-Spray	spray: 6 possible: 42[a]; 30[b]	spray: 2 possible: 1[a]	spray: 5.5-7 possible: 0.5[a]	spray: NR possible: 0.5[a]	spray: 10 possible: 196[a]; 219[b]	spray: 5 possible: 39[a]; 18[b]	spray: 0.048-31 possible: 0.53-58.9[a]	spray: 10 possible: 3-15[a]; 0.5-42[b]
Incidental Inhalation-Powder	powder: 4 possible: 30[b]	NR	NR	NR	powder: 42 possible: 219[b]	powder: 24 possible: 18[b]	powder: 1-4	powder: 0.1-5 possible: 0.5-42[b]; 4[c]
Dermal Contact	186	7	0.24-36.3	0.3-46	1058	325	0.001-93	0.1-85
Deodorant (underarm)	NR	NR	NR	NR	possible spray: 4	NR	NR	possible spray: 2
Hair - Non-Coloring	5	3	NR	NR	15	NR	0.00055-58.9	15-17
Hair-Coloring	NR	NR	NR	NR	3	1	0.048-20	NR
Nail	NR	NR	NR	NR	7	5	23-68.5	0.2-3
Mucous Membrane	54	12	6-40	4-76	871	323	0.29-95	0.001-96
Baby Products	NR	NR	NR	NR	NR	NR	NR	4

NR = Not reported.

† Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

* Earlier CIR safety assessments reported concentrations as ranges, not exact values.

[a] It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.

[b] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

[c] It is possible these products may be powders, but it is not specified whether the reported uses are powders.

Table 6. Polyene ingredients with no reported uses.[25,26,57]

Butene/Propylene Copolymer
Ethylene/Octene Copolymer
Hydrogenated Polybutene
Hydrogenated Polydodecene
Isobutylene/Isoprene Copolymer
Isoprene/Pentadiene Copolymer
Poly (C4-12 Olefin)
Poly(C6-14 Olefin)
Poly(C20-28 Olefin)
Polypentene

Table 7. FDA approved uses of polyenes

Ingredients	Regulation	CFR Reference
	Food Use	
isobutylene/isoprene copolymer; polyethylene; polyisobutene	Food additives permitted for direct addition to food for human consumption – chewing gum base	21 CFR172.615
hydrogenated polyisobutene; isobutylene/isoprene copolymer; polybutene; polyethylene; polyisobutene; polyisoprene; polypropylene; hydrogenated polybutene;	Adhesives approved for use as indirect food additives	21 CFR175.105
polybutene; polyisobutene; polyisoprene;	Pressure-sensitive adhesives approved for use as indirect food additives	21 CFR175.125
hydrogenated polyisobutene; polybutene; polyethylene; polyisobutene; polypropylene; hydrogenated polybutene	Resinous and polymeric coatings - adhesives and components of coatings approved for use as indirect food additives	21 CFR175.300
hydrogenated polybutene	Components of paper and paperboard in contact with aqueous and fatty foods approved for use as indirect food additives	21 CFR176.170
isobutylene/isoprene copolymer; polybutene; polyethylene; polyisobutene; polyisoprene; hydrogenated polybutene	Components of paper and paperboard in contact with dry food approved for use as indirect food additives	21 CFR176.180
polyethylene	Defoaming agents used in coatings approved for use as indirect food additives	21 CFR176.200
polyethylene	Defoaming agents used in the manufacture of paper and paperboard approved for use as indirect food additives	21 CFR176.210
polyethylene; polyisobutene; polypropylene	Cellophane approved for use as indirect food additives	21 CFR177.1200
ethylene/propylene copolymer; isobutylene/isoprene copolymer; polyisobutene	Approved for use in closures with sealing gaskets for food containers – indirect food additives	21 CFR177.1210
isobutylene/isoprene copolymer; polyisobutene	Isobutylene polymers approved for use as indirect food additives	21 CFR177.1420
butylene/ethylene/propylene copolymer; ethylene/octene copolymer; ethylene/propylene copolymer; polyethylene; polypropylene	Olefin polymers approved for use as indirect food additives	21 CFR177.1520
butylene/ethylene copolymer;	Poly-1-butene resins and butene/ethylene copolymers approved for use as indirect food additives	21 CFR177.1570
ethylene/propylene copolymer; isobutylene/isoprene copolymer; polybutene; polyethylene; polyisoprene	Rubber articles intended for repeated use approved for use as indirect food additives	21 CFR177.2600
polybutene; polyethylene; polyisobutene; hydrogenated polybutene	Lubricants with incidental food contact approved as indirect food additives (addition to food not to exceed 10 ppm for polybutene, hydrogenated polybutene, and polyethylene; for use only as a thickening agent in mineral oil lubricants in polyisobutene)	21 CFR178.3570

Table 7. FDA approved uses of polyenes

Ingredients	Regulation	CFR Reference
polyisobutene; hydrogenated polybutene	Plasticizers in polymeric substances approved as indirect food additives	21 CFR178.3740
polyethylene	Reinforced wax approved for use as indirect food additives	21 CFR178.3850
hydrogenated polybutene	Release agents approved for use as indirect food additives	21 CFR 178.3860
polyisobutene; hydrogenated polybutene	Surface lubricants used in the manufacture of metallic articles approved for uses as indirect food additives	21 CFR178.3910
polypropylene	Packaging materials for use during the irradiation of prepackaged foods	21 CFR179.45
polyethylene	Polyethylene – approved as a food additive permitted in feed and drinking water of animals	21 CFR573.780
	Drug/Medical Use	
polypropylene	Intercardiac patch or pledget – cardiovascular device	21 CFR 870.3470
polyethylene	Ear nose and throat devices – prostheses of the ear and mandible	21 CFR874.3430; .3450; .3495; .3620; .3695; .3880; .3930
polypropylene	Nonabsorbable polypropylene surgical suture - general and plastic surgery device	21 CFR878.5010
polypropylene	Approved use as a finger joint polymer constrained prosthesis – orthopedic device	21 CFR888.3230
polyethylene	Approved use as bone cap; ankle joint prosthesis, elbow joint prosthesis; finger joint prosthesis; hip joint prosthesis; knee joint prosthesis; shoulder joint prosthesis; wrist join prosthesis-orthopedic devices	21 CFR888.3000; .3100; .3110; .3120; .3150; .3160; .3200; .3220; .3310; .3340; .3350; .3353; .3358; .3390; .3490; .3500; .3510; .3520; .3530; .3535; .3540; .3550; .3560; .3565; .3640; .3650; .3660; .3670; .3680; .3800; .3810

Table 8. Acute toxicity studies in animals

Ingredient and Concentration/Dose	Method	Results/Conclusions	References
	Oral		
ethylene/octene copolymer (14%-16%) in a trade name mixture	acute oral toxicity study in rats (no further details provided)	LD_{50} > 5000 mg/kg	11
ethylene/octene copolymer and sodium acrylate copolymer (30%-50%) in a trade name mixture	acute oral toxicity study in rats (no further details provided)	LD_{50} > 2000 mg/kg	12
polybutene analog diisobutylene	acute oral toxicity study in rats (no further details provided	LD_{50} > 2000 mg/kg, no mortalities observed	6
polybutene analog triisobutylene	acute oral toxicity study in rats (no further details provided)	LD_{50} > 2000 mg/kg, no mortalities observed	6
polybutene analog di-n-butene	acute oral toxicity study in rats (no further details provided)	LD_{50} > 10,000 mg/kg, 1 animal had partial thickening of the forestomach and another had partial hyperemia of the small intestine membrane, no mortalities observed	6
polybutene analog tributene	acute oral toxicity study in rats (no further details provided)	LD_{50} > 10,000 mg/kg, no mortalities observed	6
polybutene analog tetrabutene (containing 30% pentabutene)	acute oral toxicity study in rats (no further details provided)	LD_{50} > 10,000 mg/kg, no mortalities observed	6
polyisobutene (100%), MW range 654-2168	acute oral toxicity study in rats (no further details provided)	LD_{50} > 15,400 mg/kg	37,38
hydrogenated polyisobutene (100%, MW range 187-468	acute oral toxicity study in rats (no further details provided)	LD_{50} > 5000 mg/kg	39-42
hydrogenated polydecene (undiluted), average MW not specified	acute oral toxicity study in Sprague-Dawley rats (5 rats/sex)	LD_{50} > 5000 mg/kg	5
hydrogenated polydecene (100%), MW range 367-596	acute oral toxicity study in rats (no further details provided)	LD_{50} > 5000 mg/kg	43
hydrogenated polydodecene (undiluted), average MW not specified	acute oral toxicity study in Sprague-Dawley rats (5 rats/sex)	LD_{50} > 5000 mg/kg	5
	Dermal		
ethylene/octene copolymer (14%-16%) in a trade name mixture	acute dermal toxicity study in rabbits (no further details provided)	estimated LD_{50} >5000 mg/kg	11
ethylene/octene copolymer and sodium acrylate copolymer (30%-50%) in a trade name mixture	acute dermal toxicity study in rabbits (no further details provided)	estimated LD_{50} >2000 mg/kg	12
polybutene analog diisobutylene	acute dermal toxicity study in rats; exposure under occlusive patches for 24 h (no further details provided)	LD_{50} > 2000 mg/kg; no mortalities or overt signs of toxicity were observed	6
polyisobutene (100%); MW range 654-2168	acute dermal toxicity study in rabbits (no further details provided)	LD_{50} > 25,000 mg/kg	37,38
hydrogenated polyisobutene (100%); MW range 187-468	acute dermal toxicity study in rabbits (no further details provided)	LD_{50} > 2000 mg/kg	39-42
hydrogenated polydecene analog hydrogenated decene dimer (undiluted); dose tested = 3000 mg/kg	acute dermal toxicity study in New Zealand White rabbits (2 rabbits/sex); material applied to clipped skin on the back for 24 h; occluded and rinsed	estimated LD_{50} > 3000 mg/kg; skin reactions observed at 24 h post-patch removal included pale red erythema and slight to mild edema; by day 14, only slight edema and desquamation were observed; 1 female rabbit that died on day 9 of the observation period was observed to be emaciated prior to death; no other clinical, behavioral, or systemic signs of toxicity were observed; no treatment-related signs of toxicity were observed at necropsy	5
hydrogenated polydodecene (undiluted); concentration tested = 2000 mg/kg; average MW not specified	acute dermal toxicity study in Sprague-Dawley rats (5 rats/sex); material applied to an area of 37 cm^2 clipped skin for 24 h; occluded and rinsed	LD_{50} > 2000 mg/kg; no clinical signs of toxicity or skin irritation were observed; body weight appeared unaffected by treatment and there were no treatment-related signs of toxicity observed at necropsy	5
	Inhalation		
polybutene analog diisobutylene	4-h, single, whole-body inhalation toxicity study in albino rats (no further details provided)	LC_{50} = > 4185 ppm (19,171 mg/m^3), no mortalities or overt signs of toxicity were observed	6
hydrogenated polyisobutene (100%), MW range 187-468	4-h inhalation study in rats (no further details provided)	LC_{50} > 5 mg/l	39-42
hydrogenated polydecene, average MW not specified	4- h, nose-only inhalation toxicity study in Sprague-Dawley-derived rats (6 rats/sex)	LC_{50} > 5.2 mg/L, no mortalities were observed, no significant clinical signs were observed during and after the exposure period, and no treatment-related signs of toxicity were observed at necropsy	5

Table 8. Acute toxicity studies in animals

Ingredient and Concentration/Dose	Method	Results/Conclusions	References
	Inhalation (continued)		
hydrogenated polydecene analog hydrogenated decene dimer, concentrations tested = 0.77, 0.94, 1.1, 1.4, or 5.1 mg/L	4-h inhalation (aerosol/vapor) toxicity study in groups Sprague-Dawley rats (5 rats/sex)	combined LC_{50} = 1.17 mg/L; all animals treated with 5.1 mg/L died within 2 days, 2 to 5 females each from all the remaining treatment groups died, no males in the 0.77 or 0.94 dose groups died but 2 males each in the remaining dose groups died; clinical signs included dyspnea and nasal discharge; body weight gain was reduced in the first week, but within normal parameters the second week; treatment-related effects of the lung were observed during gross necropsy of only the animals that died during the study; Microscopic lesions in the lung were observed in all of the high-dose animals	[5]
hydrogenated polydecene analog hydrogenated decene dimer, concentration tested = 5 mg/L	acute whole-body inhalation toxicity study in Sprague-Dawley rats (5 rats/sex)	LC_{50} not determined; 9/10 treated animals died within 3 days; clinical signs included reduced activity, increased respiration rate, respiratory sounds, labored breathing, irregular breathing, muzzle and abdominal staining, partially closed eyes, hunched back, and lying on the side; in the one female that survived treatment, all respiratory signs were normal by day 5, but muzzle staining persisted until day 9 and marked loss in body weight was observed through day 4; at necropsy, the surviving female had absolute and relative lung and trachea weights greater than the controls and the heart appeared to be affected (no further details); in the animals that died following treatment, treatment-related increases in respiratory findings were observed (no further details)	[5]
hydrogenated polydodecene, average MW not specified	4-h, nose-only inhalation toxicity study in Sprague-Dawley rats (5 rats/sex)	LC_{50} > 5.06 mg/L; clinical signs observed after removal from the exposure chamber included wet fur, hunched posture, piloerection, increased respiration rate, ptosis, and isolated incidents of decreased respiration rate and red/brown stain on the head; 1 h after exposure, the only observable clinical signs included hunched posture, piloerection, and increased respiration rate; by day 2 post-exposure, all animals had recovered and appeared to be normal; no treatment-related changes observed in body weight; no treatment-related signs of toxicity observed at necropsy.	[5]

Table 9. Repeated dose toxicity studies in animals

Ingredient and Concentration/Dose	Method	Results/Conclusions	References
	Oral		
polyisobutene (100%); concentrations tested = 0, 800, 4000, or 20,000 ppm; MW range 654-2168	2-year dietary toxicity study in Charles River rats (no further details provided)	After 12 months, no treatment-related gross or microscopic changes were observed; following 24 months, no treatment-related effects on body weights, feed consumption, mortality, clinical observations, hematology, or urinalysis were observed; in the high dose group, 3 of 6 males that died between weeks 17 and 24 exhibited hematuria while another male in this dose group exhibited similar reactions but recovered within 2 weeks; necropsy of the 3 rats found that 2 of the rats had clotted blood in the urinary tract, bladder, stomach, and intestines while the third rat had no significant gross pathologic changes; no increases in frequency of neoplastic lesions were observed in any dose group	37,38
polyisobutene (100%); doses tested = 0, 40, 200, or 1000 mg/kg; MW range 654-2168	2-year oral toxicity study in Beagle dogs (no further details provided)	No treatment-related effects on body weight, feed consumption, mortality, clinical signs, hematology, blood chemistry, urinalysis, liver function, organ weights, or gross pathologic and histopathologic changes (no further details provided)	37,38
hydrogenated polyisobutene (0% or 5%); MW range 187-468	90-day dietary toxicity study in rats; half of the animal groups were killed at 90 days and the other half were killed 30 days later following a recovery period (no further details provided)	No effects were observed on body weight, body weight gain, urinalysis, hematology, or clinical chemistry parameters; when compared to controls, liver weights were increased in both males and females and kidney weights were increased in males; no organ weight differences between treated and control animals were observed following the recovery period; no treatment-related histopathologic changes were observed (no further details provided)	39-42
hydrogenated polydecene; concentrations tested = 0, 8000, 20,000, or 50,000 ppm (equivalent overall mean daily intakes were 1039, 2538, or 6245 mg/kg/day for males and 995, 2481, or 6771 mg/kg/day for females); average MW not specified	4-week dietary toxicity study in F-344 rats (5 sex/dose)	No observed adverse effect level (NOAEL) = 6245 mg/kg/day in males and 6771 mg/kg/day in females; no clinical signs of toxicity or mortality were observed in any rats during the study; overall body weight gain and feed consumption of females in the 50,000 ppm dose group was higher than the controls; a dose-dependent decrease in mandibular lymph node weights (absolute and relative to body weight) was observed in males and females but these results were statistically significant only for 50,000 pm females and were not considered adverse effects since there were no other findings; gross necropsy, histopathology, and microscopic findings did not reveal any significant treatment-related findings	5
hydrogenated polydecene (100%); doses up to 1000 mg/kg/day ; MW range 367-596	90-day oral toxicity study in rats (no further details provided)	no observed effect level (NOEL) = 1000 mg/kg/day	43
hydrogenated polydecene in polyethylene glycol via gavage at dose levels of 0, 100, 500, or 1000 mg/kg bw/day for 91 days (average molecular weight not specified	90-day oral toxicity study, groups of 20 male and 20 female Sprague-Dawley rats received test material via gavage.	NOAEL = 1000 mg/kg/day; toxicity of the test material was examined in F_1 generation rats following reproduction study ;F_1 generation rats of each dose group, including the vehicle control, had minor gastrointestinal effects; transient changes in body weight, body weight gain, feed consumption, hematology, and organ weights were observed but not considered to be treatment-related; a significant increase in prothrombin time was observed in males of the 1000 mg/kg/day dose group but no corresponding decreases in platelets or macroscopic or microscopic changes were observed so this result was not considered biologically significant; no treatment-related changes in clinical chemistry, mortality, or ophthalmology were observed (no further details provided)	5

Table 9. Repeated dose toxicity studies in animals

Ingredient and Concentration/Dose	Method	Results/Conclusions	References
hydrogenated polydecene; concentrations tested = 0, 1000, 7000, or 50,000 ppm (equivalent to 77.5, 553.7, and 4159.4 mg/kg/day, respectively, in males and 85.5, 611.5, and 4619.9 mg/kg/day, respectively, in females); average MW was not specified	90-day oral toxicity study of F-344 rats (10 rats/sex/dose) ; an additional 5 rats/sex were administered control feed or 50,000 ppm in their diet for 13 weeks and left untreated for the following 4 weeks to examine recovery	NOAEL = 50,000 ppm (4159.4 mg/kg/day in males and 4619.9 mg/kg/day in females); clinical signs of toxicity observed in the 50,000 ppm group included oily and ungroomed coats, soft feces, and brown staining.; hair loss occurred at a greater incidence in treated animals when compared to controls; oily coats continued through the 1st week of the recovery period, particularly in females receiving 50,000 ppm; during recovery weeks 2-4, rats appeared ungroomed and exhibited hair loss; soft feces occasionally observed in the 7000 ppm females; slight increase in feed consumption in the high-dose group compared to controls (8% in males and 10% in females) that continued through the recovery period but there was no effect observed on either body weight or feed efficiency; slight (<5%) but significant increases in erythrocyte counts, hemoglobin, and packed cell volume in males of the 7000 and 50,000 ppm groups with dose-related increase in hemoglobin was not observed at the end of the recovery period; slight (6%) but significant increase in platelet counts in high-dose males and females was not observed at the end of the recovery period; absolute and relative liver weights in treated males were slightly lower but the liver weights were comparable to controls at the end of the recovery period; no treatment-related effects noted in the bone marrow, clinical chemistry, urinalysis, gross pathology, or histopathology	5
hydrogenated dodecene trimer (analog of hydrogenated polydodecene); doses tested = 0 or 1000 mg/kg body weight/day	28-day repeated dose oral toxicity study in Sprague-Dawley CD rats (5 rats/sex/dose: an additional 2 satellite groups (0 and 1000 mg/kg/day) were also maintained without treatment for 14 days following the end of the dosing period	NOAEL was determined to be 1000 mg/kg/day; treatment-related effects in mortality, clinical signs, body weight, feed consumption, hematology, clinical chemistry, organ weights, or gross and histologic pathology were not observed	5
hydrogenated dodecene trimer (analog of hydrogenated polydodecene) in arachis oil; doses tested = 0, 50, 250, or 1000 mg/kg/day	10-week oral gavage repeated dose toxicity study in 3 groups of 10 male and 10 female Sprague-Dawley Crl:CD® (SD) IGS BR strain rats (10 rats/sex/group) .	NOAEL =1000 mg/kg/day; during the dosing period, one rat in the control group and one rat in the 250 mg/kg/day dose group died but deaths were not treatment-related; no signs of clinical toxicity or effects on behavioral and functional performance, sensory reactivity, body weight, or feed and water consumption were observed following treatment with the test material; no significant treatment-related effects were observed in the hematological and clinical chemistry assessments or during the gross pathology examination	5
	Dermal		
hydrogenated polyisobutene (100%); doses tested = 0, 0.5, 1.0, or 1.5 ml/kg for 5 days/week; MW range 187-468	4-week dermal toxicity study in Sprague-Dawley rats (no further details provided)	No mortalities were observed during the study and no statistically significant differences in body weights, body weight gain, hematology, or clinical chemistry parameters were observed between treated and control animals; relative kidney weights were increased in high-dose males and relative heart weights were decreased in low-dose males but these changes were not considered toxicologically significant because the kidney weight changes were not accompanied with any histopathologic effects and the heart weight changes were not decreased in a dose-related manner; minimal to mild dermal irritation consisting of redness, paleness, scaling, rippling and pinpoint scabbing of the skin was observed in the majority of treated animals; histopathologic examinations were performed on the high-dose and control groups only; effects observed in the treated animals were limited to the application site and included minimal to mild epidermal hyperplasia and hyperkeratosis of the application site with reactive hyperplasia of the underlying inguinal lymph nodes	39-42

Table 10. Dermal irritation studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			NON-HUMAN		
ethylene/octene copolymer and sodium acrylate copolymer (30%-50%) in a trade name mixture	concentration/dose not reported	rabbit skin	details not provided	minimally/slightly irritating	[12]
polyisobutene; MW range 654-2168	100%	rabbit skin	details not provided	nonirritating	[37,38]
hydrogenated polyisobutene; MW range 187-468	100%	rabbit skin	details not provided	nonirritating	[39-42]
hydrogenated polydecene; MW range 367-596	0.5 ml of 100%	rabbits	modified Draize primary skin irritation test (no further details provided)	nonirritating, primary irritation index 3.1	[43]
hydrogenated polydecene; average MW not specified	0.5 ml, concentration not reported	6 New Zealand White rabbits	-primary skin irritation study on clipped or abraded skin -test sites occluded -remaining test material was washed off at 24 h -animals were observed for skin reactions at 24 and 72 h	-at 24 h, slight erythema was observed in 4 of the abraded sites and 5 of the intact sites, slight edema was observed on 3 of the abraded sites, edema was observed at an abraded site at the end of treatment, all effects had reversed 2 days post-exposure -after 72 h, the mean erythema score was 0.42 for both the intact and abraded skin, the mean edema score after 72 h was 0.17 for intact skin and 0.08 for abraded skin -based on these results, the study authors calculated a primary dermal irritation index of 0.5 -not a primary irritant or corrosive	[5]
hydrogenated polydecene, average MW not specified	0.5 ml, concentration not reported	6 female New Zealand White rabbits	-primary skin irritation study on clipped or abraded skin -test sites occluded -remaining test material was washed off at 24 h -animals were observed for skin reactions at 24 and 72 h	-over 72 h, the mean erythema score for intact skin was 0.75, mean erythema score for abraded skin was 0.67 -the mean edema score for intact and abraded skin over 72 h was 0.25 and 0.08, respectively -all rabbits had very slight to well-defined erythema on both intact and abraded sites and slight edema on 3 intact and 1 abraded site at the end of treatment -no difference in severity between intact and abraded sites -two days after treatment, only 1 abraded site still had evidence of slight erythema -the primary dermal irritation index was calculated to be 0.9 -not a primary irritant or corrosive	[5]

Table 10. Dermal irritation studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
hydrogenated decene trimer	0.5 ml of undiluted test material	groups of 3 New Zealand White rabbits	-Draize study -test area was 2.5 cm^2 and semi-occluded for up to 4 h -animals observed for 7 days.	-no treatment-related changes in body weight observed -very slight erythema and edema observed in 1 rabbit through 72 h -at 72 h, the skin lost its elasticity and flexibility -at 7 days, slight desquamation observed -no effects observed in the other 2 rabbits -mild irritant according to Draize system but nonirritating according to EU classification system	5
HUMAN					
ethylene/octene copolymer and sodium acrylate copolymer (30%-50%) in a trade name mixture	details not provided	details not provided	cumulative irritation test (no further details provided)	no significant irritation	12
polyisobutene ; MW range 654-2168	100%	details not provided	human skin patch test (no further details provided)	nonirritating	37,38
hydrogenated polyisobutene in formulation, average MW not specified	8%	10 female subjects	single application to the skin (no further details provided)	no adverse effects were reported	46
hydrogenated polyisobutene; MW range 187-468	100%	details not provided	human skin patch test (no further details provided)	nonirritating	39-42
hydrogenated polydecene with equal amounts of cetylethylhexanoate and pentaerythrityl tetraethylhexanoate; average MW not specified.	total concentrations up to 35% in combined product	98 subjects	a study of formulations with differing ratios of polyols and oils on the skin	no adverse effects	45

Table 11. Ocular irritation studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			OCULAR – NON-HUMAN		
ethylene/octene copolymer and sodium acrylate copolymer (30%-50%) in a trade name mixture	details not provided	rabbits	details not provided	minimally/slightly irritating	[12]
polyisobutene; MW range 654-2168	100%	rabbits	details not provided	nonirritating	[37,38]
hydrogenated polyisobutene; MW range 187-468	100%	rabbits	details not provided	nonirritating	[39-42]
hydrogenated polydecene: MW range 367-596	0.1 ml of 100% test material	rabbits	modified Draize primary eye irritation test (no further details provided)	nonirritating (irritation score 0 to 6 out of 110 in individual rabbits)	[43]
hydrogenated polydecene; average MW not specified	0.1 ml of undiluted test material	New Zealand White rabbits, 3/sex	-test material instilled into the conjunctival sac of the right eye of each animal -eyes not rinsed. -animals then observed for 72 h.	-no corneal lesions or iris changes -conjunctival changes included mild erythema in 5 of the 6 rabbits that were still present in 3 of the rabbits at 72 h and swelling occurred in 3 of the rabbits -none of the rabbits had any discharge -individual total scores over the three time points for all changes observed ranged from 0 to 4 out of a possible score of 110 -nonirritating	[5]
hydrogenated polydecene; average MW not specified	0.1 ml, concentration not reported	9 male New Zealand White rabbits	-test material instilled into the conjunctival sac of one eye while the other eye served as control -eyes were examined for ocular irritancy at 1, 24, 48, and 72 h post-treatment -both eyes of 3 of 9 treated rabbits were rinsed with distilled water and the rinsed eyes were examined for ocular irritancy at 1, 24, 48, and 72 h	-none of the rabbits exhibited corneal lesions or iris changes - in unrinsed eyes, moderate to severe conjunctival redness with oily residue was noted at 1 h, but by 24 h, there was only slight redness and the eye was clear by 48 h -in rinsed eyes, there was no to slight conjunctival redness 1 h after treatment with oily residue around the eye; the eyes were clear by 24 h -moderately irritating	[5]

Table 12. Sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			NON-HUMAN		
ethylene/octene copolymer (14%-16%) in a trade name mixture	details not provided	guinea pigs	guinea pig maximization and Buehler assays (no further details provided)	not sensitizing	[11]
ethylene/octene copolymer and sodium acrylate copolymer (30%-50%) in a trade name mixture	details not provided	mice	local lymph node assay (LLNA) (no further details provided)	not sensitizing	[12]
hydrogenated polydecene; MW range 367-596	intradermal induction dose was 5%; topical induction and challenge doses were 10%	guinea pigs	Magnusson and Kligman skin sensitization test (no further details provided)	not sensitizing	[43]
hydrogenated polydecene: average MW not specified	concentrations up to 10% v/v	Hartley guinea pigs, 10 male and 10 females	-guinea pig maximization test -test material administered intradermally at 5.0% v/v in mineral oil -one week after the intradermal induction, treatment groups were induced by topical application of the 10% v/v test material in mineral oil for 48 hours -14 days following topical induction, all animals received a 10% v/v test material in mineral oil challenge application at naïve sites	-one female in the test group exhibited abnormal gait, flaccid body tone and tremors on day 9 of the study and was found dead on day 10 of the study, but the death was not considered treatment-related -no signs of skin irritation, edema, or erythema were observed in any of the remaining male or female treatment or vehicle control group animals throughout the study period -no other signs of clinical toxicity were noticed following administration of the test material. -animals that received the positive control experienced expected results -body weights were comparable to vehicle controls through the study period -not sensitizing	[5]
hydrogenated polydecene in corn oil; average MW not specified.	concentrations up to 100%	20 Dunkin-Hartley guinea pigs	-maximization study -6 intradermal injections of the test material (2 injections at 50% aqueous Freund's Complete Adjuvant, 2 injections of 100% test material, and 2 injections of 100% test material in 25% aqueous Freund's Complete Adjuvant) -control group animals were treated with 6 intradermal injections (2 injections of 50% aqueous Freund's Complete Adjuvant, 2 injections vehicle, and 2 injections of the vehicle in 25% aqueous Freund's Complete Adjuvant) -on test day 6, no irritation was observed so the test sites were treated with 0.5 ml of 10% sodium lauryl sulfate -on test day 7, each test group animal was treated with a topical application of the test material for 48 h -control group received vehicle only -on test day 20, animals were challenged with 100% test material via topical application	-during challenge, 2 test group animals exhibited positive responses (details not provided) to the test material -no positive responses were observed in the control animals -a rechallenge was conducted using 50% and 100% hydrogenated polydecene and a positive response was observed in one animal exposed to 100% hydrogenated polydecene -not sensitizing	[5]
hydrogenated polydecene; average MW not specified	details not provided	10 male Hartley guinea pigs	-animals were patched with Webril pads containing 0.5 ml test material on the midline of the back -a positive control group was patched with DNCB -a challenge dose of 0.5 ml of the test material and the positive control was administered 2 weeks after the final sensitization dose.	-8 of the 10 animals in the treated group had slight erythema and edema -all animals in the positive control group also exhibited slight erythema and edema -not sensitizing	[5]

Table 12. Sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
hydrogenated decene dimer (an analog of hydrogenated polydecene)	induction and challenge concentration s= 5% w/v in spectrum oil	10 male and 10 female Hartley guinea pigs	-delayed contact hypersensitivity study -animals induced 3 times weekly with occlusive 6-h exposures for 3 weeks -following a 2 week rest period, the test animals and a naïve control group were challenged -animals were scored for skin reactions at 24 and 48 h following the challenge phase	-the primary challenge resulted in a grade 1 response, which was of less incidence and severity than the naïve control group. -not sensitizing	5
hydrogenated decene,dimer	intradermally induced with 5% test material in mineral oil; topically chellanged with 10% test material	10 male and 10 female Hartley guinea pigs	-Magnusson-Kligman maximization test protocol -a negative control group was induced with vehicle alone and a positive control group received DNCB.	-no signs of skin irritation, edema, or erythema were observed in any of treated animals or vehicle control group animals throughout the study period -no other signs of clinical toxicity were observed - individual and group mean body weights were comparable to vehicle controls through the study period -not sensitizing.	5
hydrogenated decene trimer in propylene glycol	25%, 50%, and 100%	mice	LLNA (no further details provided	-stimulation indices were 1.56, 1.89, and 3.54 for the test concentrations of 25%, 50%, and 100%, respectively -EC_3 values were not provided -slight sensitizer	5
HUMAN					
ethylene/octene copolymer in a trade name mixture	details not provided	details not provided	human repeat insult patch test (HRIPT; no further details provided)	no irritation or sensitization observed	12
polyisoprene	12.33% in a lip gloss	103 subjects	-HRIPT -0.2 g test material applied to upper back with a 1 in^2 pad and semi-occluded for 24 h -total of 9 induction patches -after 2 week rest, challenge patch applied to naïve site for 24 h and sites were scored 24 and 72 h post-application	no irritation or sensitization observed	47

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Final Report on the Safety Assessment of Polybutene

Polybutenes are the isotactic polymers of isobutene and n-butene. Polybutenes provide viscosity or emulsifiability to more than 80 cosmetic products in concentrations up to 50%.

The results of acute oral and percutaneous toxicity tests of Polybutenes show these materials to be relatively harmless.

Acute skin irritation tests on rabbits showed no or mild irritation. Other test results indicate that Polybutenes are not toxic: (a) there were no observable effects in rats after inhalation at concentrations up to 18.5 mg/l of air; (b) there was only mild, transient eye irritation in rabbits; (c) intravaginal application of concentrated Polybutene daily for 30 days produced no observable effect in rabbits. Chronic oral toxicity in rats fed up to 20,000 ppm for three successive generations showed no impairment in reproduction.

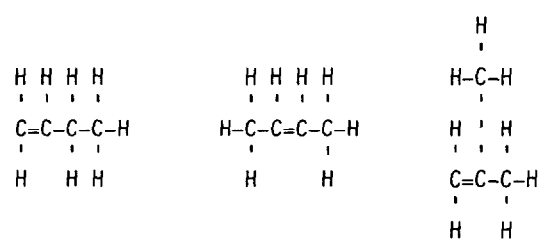
The available human clinical data indicated only very mild effects. Skin tests for sensitization, irritancy, phototoxicity, and photosensitization were limited to cosmetic formulations.

On the basis of the available information, it was concluded that Polybutenes are safe as presently used in cosmetics.

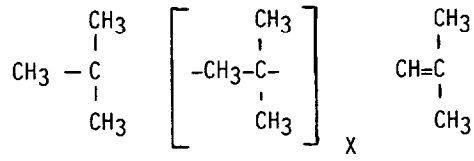
CHEMISTRY

Structure

POLYBUTENE is any one of several isotactic (stereoregular) polymers of isobutene and n-butene; the molecular weights of these polymers vary according to their degree of polymerization. Isobutene chains may contain from 10 to 100 subunits; n-butene monomers can be either 1-butene, 2-butene, or both.[1,2]



The olefin structure of Polybutene is predominantly the trisubstituted type ($R-CH=CR_2$). The major component of Polybutenes can be represented as:[3]



Other names include:[1,2,4] Butene, Homopolymer, Butene, Polymer, Polybutylene, Butene Polymer, Polyisobutylene, Poly (1-butene), and Poly-α-butylene.

Preparation

Passman[5] describes an industrial preparation of Polybutene in which a solution of 1-butene is dried and fed into a reaction chamber. A Zeigler-Natta reagent ($TiCl_3$ and diethyl aluminum chloride) is added to catalyze the polymerization process. The molecular weight of the end product is limited by the reaction temperature used in the chamber.

Properties

Polybutenes are light colored, nondrying, sticky, viscous liquids. They are stable when exposed to light, insoluble in water, and soluble in hydrocarbon and chlorinated hydrocarbon solvents. Polybutene-1 has a density of 0.92 g/cm^3 and a melting range of 124°C–130°C.[2,5,6]

Polybutene is available in a variety of grades. The differences depend on viscosity, which increases directly in proportion to increasing molecular weight.[7,8]

Polybutene films have a high resistance to stress cracking, and low stress deformation.[5]

Reactivity

Polybutenes undergo combustion, pyrolysis, and autoxidation; the latter two can occur during analytical treatment.[2,14,17] Their low polarity, low degree of unsaturation, and their closely packed, branched-chain molecular structure make Polybutenes resistant to chemical reaction.[6]

Analytical Methods

A number of methods for the analysis of Polybutene are available.

McCall and Falcone,[9] Zymonas,[10] and Corno[11] employed nuclear magnetic resonance (NMR) to identify Polybutene, and Mauzac[12] used it in a study tracing ^{13}C-labeled Polybutene. NMR deals with the measurements of energy gaps between states of different energy; this spectroscopic phenomenon requires the presence of an external magnetic field.[13]

Infrared (IR) spectroscopy, far-infrared spectroscopy, and Raman scattering are commonly used in Polybutene analysis. Stivala[14] employed IR methods to observe autoxidation of poly-1-butene, and Goldstein et al.[15] used the longer wavelength far-infrared spectroscopy in determining Polybutene. Using laser excitation, Cornell and Koenig[16] observed the Raman scattering spectrum of polybutene.

Chromatography methods are reported, including gas, gel-permeation, and thin-layer.[6,8,17-21] Thin-layer chromatography is widely employed in determining Polybutene residues on plants and in volatile plant oils.[6,8] Barton[19] describe a gas chromatographic determination of Polybutene which involves flash pyrolysis.

Differential thermal analysis and differential thermogravimetry were employed by Tiunova et al.[22] and Era and Jauhiainen,[23] respectively.

Impurities

A typical analysis of Polybutene contains isoparaffins (less than 5%), vinylidene and terminal

vinyl structures, chloride (20 to 100 ppm), sulfur-containing compounds [(as S) up to 50 ppm], and nitrogen compounds [(as N) up to 45 ppm].[3]

USE

Cosmetic Use

Polybutenes are used in more than 80 cosmetic formulations in concentrations ranging from one to >50% (Table 1).[24] The ingredient commonly adds to the viscosity of a formulation, or it may act as an emulsifier.[2]

Non-cosmetic Use

Polybutenes are components of lube-oil, microscope immersion oil, hot-melt adhesives, sealants, and cable insulation.[2,25,26] They are also used in or as fungicides, bird repellents, rodenticides, herbicides, insecticides and acaricides.[2,6-8,27-33]

BIOLOGICAL PROPERTIES

Polybutenes are used in agricultural sprays to control mildew, leaf mold, various fungi, phytophageous mites, insects, and weeds.[6,7,29,30,33-35] Polybutenes are primarily used as additives that provide complimentary activity to pesticides, as adhesives and as controlled release dispensers.[8,35] The pesticidal action is frequently mechanical trapping. Herne,[7] however, concluded that Polybutenes had a toxic effect on mites and that mechanical trapping was not the only mode of action involved; when applied in concentrations as little as 2.5% (by weight), various grades of Polybutene caused high mortality in mites. Bradbury and Fisher[29] report that the fungitoxic effect of Polybutene emulsions is solely the result of the activity of the emulsifier.

Briggs[36] observed that Polybutene sprays applied to peppermint plants caused premature aging of the leaves and low oil yield. He concluded that Polybutene was unsuitable as a pesticide for plants from which oils are extracted.

Animal Toxicology

Acute

Oral toxicity

The acute oral toxicity of Polybutene, as a single ingredient and in cosmetic formulations, was

TABLE 1. PRODUCT FORMULATION DATA.[a]

Ingredient	*Cosmetic product type*	*Concentration (percent)*	*Number of product formulations*
Polybutene	Eye shadow	>1–5	10
	Hair preparations (non-coloring)	>5–10	2
	Lipstick	>50	8
		>25–50	17
		>10–25	21
		>5–10	13
		>1–5	11
	Other makeup preparations	>10–25	1
	Moisturizing	>1–5	1
	Night	>10–25	1

[a]From Ref. 24.

tested using albino rats. Test methods and results are outlined in Table 2. Samples ranged in concentration from 3.7% to 75% and were delivered by oral intubation. The LD50s ranged from >5 to >50 g/kg and the Polybutene was considered to be relatively harmless. Mild lethargy and diarrhea occurred in some animals at high dosage levels; autopsy data revealed no abnormalities.

Percutaneous systemic toxicity

Test methods and results are noted in Table 3. The percutaneous systemic toxicity of Polybutene samples H-100 (viscosity 93.8 sec Saybolt at 210°F) and H-1500 (viscosity 15,000 sec Saybolt at 210°F), both 75% concentrate, was tested on four groups of four adult New Zealand strain albino rabbits (two male, two female for each dosage level). Twenty-four hours before the sample was applied, the backs of the animals were shaved free of fur to expose 10 percent of the total body area. Skin applications were made in four dosage levels of 3.04, 4.56, 6.83, and 10.25 g/kg (one dose level per group, per rabbit). The test material remained in contact with the skin for 24 h. After 24 h, exposure sites, mortality, and behavior were observed for 14 days. No abnormal behavioral reactions or deaths were noted at any dosage level. The acute percutaneous LD50 of H-100 and H-1500 Polybutene for the albino rabbits was >10.25 g/kg.[37,38]

The acute dermal systemic toxicity of a lipstick formulation containing 15% Polybutene was tested in 10 rabbits. The percutaneous LD50 of the lipstick was found to be greater than 2 g/kg (0.3 g/kg Polybutene) body weight.[39]

Skin irritation studies

Test methods and results are outlined in Table 4. The primary skin irritation of 15% Polybutene in a lipstick formulation was tested on six albino rabbits. The formulation was not a primary irritant; it had a Primary Irritation Index (PII) of 0.0.[40]

A sample containing 20% Polybutene was tested for acute skin irritation according to the Draize method. Six albino rabbits were used. A 0.5 g sample of the test material was applied under surgical gauze for 24 h to shaved intact and abraded skin. Intact skin showed erythema and eschar formation in all rabbits at 24 h; it persisted in two of six until 72 h. Edema occurred in the intact skin of three of six rabbits at 24 h, but cleared at 72 h. The abraded skin showed erythema and eschar formation in all animals through 72 h. Edema occurred in the abraded skin of five out of six animals at 24 h and persisted in three of six to 72 h. The primary skin irritation index was 1.29, indicating that this formulation was a mild irritant.[41]

An acute skin irritation study of a lipstick formulation containing 3.7% Polybutene was conducted according to the Draize method. Of the six rabbits tested, erythema and eschar formation occurred in the intact skin of two animals at 72 h, in the abraded skin of one at 24 h, and in the abraded skin of three at 72 h. Edema occurred in the abraded skin of one rabbit at 24 h and in two at 72 h. The primary skin irritation index was 0.38, and the formulation was considered to be nonirritating.[51]

The primary skin irritation of a product containing 44% Polybutene was tested according to a modification of the Draize method. A 0.5 ml dosage of the product was applied to the intact and abraded skin of six rabbits for three consecutive 24-hour periods. According to the Draize scores, Grade 1 erythema was seen in three of six rabbits on Days 1 and 2, and Grade 1 erythema was observed in two of six rabbits on Day 3. This product was considered to be mildly irritating.[52]

A modified Draize method was used to test a lip oil containing 30% Polybutene for primary skin irritation. Six rabbits were given 0.5 ml dosages for three consecutive 24-hour periods. The samples were applied to intact and abraded skin under open patch conditions. According to Draize scoring criteria, Grade 1 erythema occurred on two of six rabbits on Days 1 and 2 and in one of six on Day 3.[53]

Inhalation toxicity

A group of 10 Sprague-Dawley albino rats was exposed continuously for 4 h to an atmosphere containing an aerosol of a 5% aqueous emulsion of Polybutene (H-100). During the exposure period, the concentration of the test material was approximately 17.3 mg/L (expressed in terms of active ingredient). No deaths occurred and no abnormal behavioral reactions were noted.[54]

The same time exposure was used to test the acute inhalation toxicity of an atmosphere containing

TABLE 2. ORAL TOXICITY.

No. of rats	Conc. (Percent)	Dose/kg	Route	Study time (Days)	LD50/kg	Comments	Ref.
Acute							
10	15	–	Oral intubation	–	>5.0 g	Nontoxic, Lipstick product	42
6	24	0.0 ml	Oral intubation	14			43
18	24	20.0–40.0 ml	Oral intubation	14	>40.0 ml	Mild lethargy for 24 h following intubation	
24	30	10.0–40.0 ml	Oral intubation	14	>40.0 ml	One death at 10.0 ml/kg at 24 h	44
10	30	50.0 ml	Oral intubation	–	>50.0 ml	No deaths. Mild diarrhea for 72 h. Lip product.	45
10	44	20.0 ml	Oral intubation	–	>20.0 ml	No abnormalities. Lip product.	46
16 albino	75	10.3–34.6 g	Oral intubation	14	>34.6 g	No deaths or abnormal behavior Polybutene H-100	47
16 albino	75	10.3–34.6 g	Oral intubation	14	>34.6 g	No deaths or abnormal behavior Polybutene H-1500	48
20	[a]	5.0–40.0 g	Oral intubation	7	>40.0 g	No deaths. Lip product.	49
20	[b]	5.0–40.0 g	Oral intubation	7	>40.0 g	One death at 40.0 g/kg level on Day 1. Lip product.	50

[a]20% in product. Product administered as a 50% solution in corn oil.
[b]3.7% in product. Product administered as a 50% solution in corn oil.

TABLE 3. ANIMAL TOXICOLOGY PERCUTANEOUS SYSTEMIC TOXICITY.

No. or rabbits	Conc. (Percent)	Dose/kg	Route	Study time (Days)	LD50/kg	Comments	Ref.
Acute							
16 albino	75	3.0–10.3 g	Shaved back	14	>10.3 g	No deaths or abnormal reactions. Polybutene H-100	37, 38
10 rabbits	15	2 g (of product)	–	–	>2.0 g	15% in formulation	39

18.5 mg/L of Polybutene (H-1500) on 10 Sprague-Dawley rats. Neither behavioral changes nor deaths occurred among the exposed rats.[55]

Eye irritation

Test methods and results are listed in Table 5. A group of five albino New Zealand rabbits was used to evaluate the eye irritation of undiluted Polybutene H-100 (75% concentration). This test was patterned after the Draize method, in which 0.1 ml of the test material was instilled into the conjunctival sac of the right eye of each animal while the left eye serves as a control. The Draize scoring system was used to grade irritation at 1, 24, 48, 72, and 96 h and 7 days after instillation. A zero score indicates no irritation; a score of 110 shows maximal irritation and tissue damage. In four rabbits, mild irritation (average score of 3.8) persisted to 48 h, after which time all irritation cleared for the remainder of the seven-day observation.[56]

Undiluted Polybutene H-1500 (75% concentration) was tested according to the Draize method for ocular irritation in a group of five albino rabbits. The product produced mild irritation in all animals at 24 h (average score 11.4), in four of the five animals at 48 h (score 7.4), and in three of them at 72 h (score 5.6). After 72 h, the eyes remained free of irritation for the rest of the seven day observation.[57]

A lipstick formulation containing 15% Polybutene caused no ocular toxicity in six rabbits after 24-, 48-, or 72-hour intervals.[58]

A red lipstick paste containing 20% Polybutene was tested for ocular irritation in six rabbits. A dose of 0.1 g/ml of the test materials was instilled with no washout into the right eye of three of the animals. Observations were made after Days 1, 2, 3, and 7. In the second group, the test material was instilled into the eye with a washout four seconds later. All rabbits were observed on Days 1, 2, 3, and 7. All animals in the first group developed conjunctival effects which cleared during the seven-day period. Their average Draize scores after 24, 48, and 72 h were 3.3, 2.0, and 1.6, respectively. The rabbits in the second group displayed conjunctival effects which disappeared at 48 h. Their average Draize scores for the same time intervals were 3.3, 0.0, and 0.0, respectively. The material was found to be a mild, transient irritant both when it was washed out and when it was not.[59]

A sample of 24% Polybutene was tested on nine albino rabbits in a Modified Draize Eye Irritation Study. A 0.1 ml sample of the substance was instilled into the right eye, and observations were made at 24, 48, and 72 h, and seven and 14 days. The six rabbits with unwashed eyes had an average Draize score of 0.222 out of a possible 110. The three rabbits with eyes washed immediately following instillation had an irritation score of 0.0. Thus, the substance was nonirritating.[60]

A lip product containing 55.2% Polybutene was tested for ocular irritation on six New Zealand rabbits. This product caused no irritation.[61]

Another lip product containing 44.0% Polybutene was tested by the Federal Hazardous Substances Act (FHSA) method on six rabbits. When a 0.1 sample of the product was instilled into the eye without a washout, no irritation resulted.[62]

A third lip product containing 30% Polybutene was tested according to the FHSA method on six rabbits. A 0.1 ml sample was instilled into the left eye, and no washout followed. At 24 h, mild conjunctivitis was observed in all six animals; all eyes were clear at 72 h. The product was considered nonirritating.[63]

Subchronic

Dermal systemic toxicity

The effect of Polybutene on hepatic drug-metabolizing enzymes and on skin benzo(a)pyrene hydroxylase was studied in rats. The Polybutene was applied to rat skin in a 10 μl volume (dissolved in mineral oil) daily for six days. It did not affect liver weight, microsomal protein, cytochrome P-450 or drug metabolizing enzyme activity of the liver. Similarly, it did not affect hepatic or skin enzymatic activities.[26]

Mucous Membrane Irritation

Undiluted Polybutene was applied to 12 female New Zealand white rabbits to study its subchronic mucous membrane irritation potential. Six of the rabbits were injected intravaginally daily for 30

TABLE 4. SKIN IRRITATION.

No. of rabbits	*Conc. (Percent)*	*Dose/kg*	*Route*	*Comments*	*Ref.*
Acute					
6 albino	15	–	–	– PII = 0.0 in a formulation	40
6 albino	20	0.5 g	Shaved intact and abraded skin	72 h PII = 1.29	41
6 albino	3.7	0.5 g	Shaved intact and abraded skin	72 h PII = 0.38	51
6 albino	44	0.5 ml	Shaved intact and abraded skin	Grade 1 erythema in 3/6 rabbits on Day 2; in 2/6 on day 3. Mildly irritating.	52
6 albino	30	0.5 ml	Shaved intact and abraded skin	Grade 1 erythema in 2/6 on Day 2; in 1/6 on Day 3.	53

TABLE 5. ANIMAL TOXICOLOGY EYE IRRITATION.

No. of rabbits	*Conc. (Percent)*	*Dose (ml)*	*Route*	*Study time (Days)*	*Comments*	*Ref.*
Acute						
5 albino	75	0.1	Eye instillation	7	Draize score at 48 h = 3.8 Polybutene H-100	56
5 albino	75	0.1	Eye instillation	7	24 h score–11.4; 48 h score–7.4; 72 h score–5.6 Polybutene H-1500	57
					Product Formulation	
6	15	–	Eye instillation	3	No ocular toxicity, 15%	58
6	20	0.1	Eye instillation	7	Unwashed eyes–24, 48, 72 h score = 3.3, 2.0, 1.6 Washed eyes–24, 48, 72 h score = 3.3, 0.0, 0.0	59
9	24	0.1	Eye instillation	14	Unwashed eyes–Draize score = 0.222 Washed eyes–Draize score = 0.0	60
6	55.2	–	Eye instillation	–	No irritation	61
6	44.0	0.1	Eye instillation	–	No irritation	62
6	30.0	0.1	Eye instillation	3	Nonirritating	63

consecutive days with 0.2 cc (0.2 ml/kg) of Polybutene. The other six were injected with saline as a control. The test compound produced neither signs of systemic toxicity nor behavioral changes, and all vaginas appeared normal.[64]

Chronic

Oral toxicity

Some of the test methods and the results are listed in Table 6. A two-year chronic oral toxicity study of Polybutene (H-100) (75% concentrate) was conducted on 240 Charles River albino rats. The animals were divided into four groups, each group being comprised of 30 males and 30 females. They were given 0 (control), 800 (0.08%), 4000 (0.40%), or 20,000 (2.0%) ppm Polybutene blended in their basic diets. The rats were checked for body weights, mortality and reactions, tumor incidence, and hematologic, urologic and pathologic changes. After 12 months of testing, five animals from each group were sacrificed for examination; no gross or microscopic pathological changes could be correlated with Polybutene ingestion. After 24 months of feeding, no significant differences were found in body weights or weight of food consumption, hematological results, urology, or tumor formation between the animals fed Polybutene and those that were not.

In the 20,000 (2.0%) ppm group, three of six males that died between weeks 17 and 24 exhibited hematuria. One other male in this group exhibited similar reactions, but completely recovered within two weeks; necropsy of the three rats revealed that two had clotted blood in the urinary tract, bladder, stomach, and intestines. The third animal revealed no significant gross pathologic changes. No abnormal reactions were noted in any other tested animal.[65]

A two-year chronic oral toxicity study of Polybutene H-100 (75% concentrate) was conducted on beagle dogs. The substance was administered orally daily to three test groups, each consisting of eight pure-bred beagle hounds (four male, four female). Each group was given one of the following doses: 40, 200, and 1000 mg/kg of body weight, or 0.045, 0.227, and 1.14 ml of test material. An untreated control group consisted of 5 male and 2 female dogs. Complete hematologic studies, blood chemistry, urinalysis, and liver function tests were conducted on the control and the highest dosage group after 90, 180, and 540 days of testing, and on all four groups after 360 and 720 days of testing. After one year of testing, one male and one female from each test group were sacrificed. At two years, all surviving dogs from all groups were sacrificed and major tissues and organs were examined. This study found that daily oral administration of Polybutene H-100 to pure-bred beagle dogs over a two-year period at the specified dosages caused no abnormalities in body weight, food consumption, survival, behavioral patterns, hematology, blood chemistry, urinalysis, liver function, gross and histopathologic examinations, or organ weights and ratios.[66]

Teratogenicity

Polybutene fed to rats at 1% or 10% in the diet for six months did not affect body weight gain, fertility, or gland weight. There were no teratogenic effects.[67]

Reproduction studies

A three-generation reproduction study was conducted on albino rats to determine the effect of ingesting Polybutene H-100. Three groups of Charles River albino rats (eight males and 16 females per group) were fed Polybutene in the following three dosage levels in the diet: 0 ppm (control), 800 ppm, and 20,000 ppm. Results showed that except for the test (F_2) male parental animals that were fed 20,000 ppm Polybutene, none of the animals in successive generations differed from controls with regard to weight gains. The F_2 male parental animals showed slight weight depression, although their growth patterns were still within the normal range. Differences in mortality or reaction or in gross or microscopic histology could not be correlated with the ingestion of Polybutene. Organ weight and ratio data revealed a few intergroup diffrences which were considered "random effects."

Reproductive performances (mating indices, fertility indices, incidence of pregnancy and parturition, and gestation times) of control and test animals were essentially comparable. Lactation indices ranged from 83% to 94% in the control group and from 89% to 99% in the 20,000 ppm group. In all three generations, there were no significant differences between test and control animals with regard to litter size, the number of stillborn, and the number of viable pups during lactation. The survival, body weights, and reactions of test animals were comparable to those of controls.[68]

TABLE 6. CHRONIC ORAL TOXICITY.

No. and species of animals	*Dose/kg*	*Route*	*Study time*	*Comments*	*Ref.*
Chronic					
				Polybutene H-100	
240 albino rats	0–20,000 ppm	Diet	2 years	3 deaths in 20,000 ppm group No other abnormalities	65
				Polybutene H-100	
6 beagles	Control 0.0 ppm				
24 beagles	40–1,000 ppm or 45–1.14 ml	Diet	2 years	No abnormalities	66
Rats		1.0% in diet	6 months	No teratogenic effects	67
Rats		1.0% in diet	6 months		

Human Clinical Studies

Primary Skin Irritation

The primary irritation potential of a lipstick formulation containing 20% Polybutene was patch-tested on 100 women. The entire upper back of each panelist was thoroughly cleansed with 70% isopropyl alcohol. The formulation was impregnated into one-half inch square blotting paper, applied to the skin and then covered with Patchplaster. After remaining in contact with the skin for 48 h, the paper was removed from the skin. Observations for reactions were made immediately, fifteen minutes later, and at 24 and 48 h. No inflammatory reactions occurred.[69]

The primary irritation potential of a lipstick formulation containing Polybutene (concentration unspecified) was tested on 100 women. Their backs were thoroughly cleansed with alcohol before application of the material. A closed one-half inch square patch was applied to the backs for 48 hours. The test sites were observed at 48 and 72 h after removal of the patches for reactions. No evidence of any inflammatory reaction on the site appeared at any of the observation periods.[70]

Repeated Insult Patch Tests

Test methods and results are listed in Table 7. A lipstick containing 15% Polybutene was tested for irritation by the Schwartz-Peck Prophetic Patch Test. There were "virtually" no reactions in the 195 subjects.[71] When the Draize-Shelanski Repeated Insult Patch Test was used to evaluate this same formulation on 96 subjects, there were "virtually" no reactions.[72]

A Modified Draize-Shelanski Repeated Insult Patch Test was used to determine the potential for irritation and sensitization caused by a lip lotion containing 30% Polybutene. The materials were applied to 50 human volunteers on the same patch sites for one 72-hour period and then for eight alternate 24-hour periods. After a 12-day rest period, challenge 48-hour patches were applied to the same sites on all subjects. Observations were made upon removal of the patch, and challenge sites were read 24 h after patch removal. The product caused neither sensitivity nor significant irritation.[73]

Another lip lotion formulation containing 30% Polybutene was tested according to the protocol just described. In the Modified Draize-Shelanski Repeated Insult Patch Test, the 50 volunteers showed neither sensitivity nor irritation.[74]

A lip lotion containing 24% Polybutene was tested for irritation and allergenicity according to the Modified Draize-Shelanski-Jordan Patch Test. The test material was applied to the upper backs of 50 volunteers for 48 h and then reapplied for 10 alternate 24-hour periods; readings were made at 48 h. After a 13-day rest period, a 48-hour challenge patch was applied, and a second 48-hour patch was applied seven days later. The challenge sites were read 48 and 72 h after application. Neither sensitization nor irritation was observed.[75]

A repeated insult patch test was conducted on a lip gloss containing 3.1% Polybutene in order to assess its irritation and allergic sensitization potential. An application of the material was made under occlusion every 48 h to the 104 panelists until there was a total of 10 applications per site. The site was graded for irritation 15 min after removal of the patch after each 48-hour application. After an 11-day rest period, a challenge patch was applied for 48 h. The site was graded 15 min and 24 h after removal of the patch. Two of the 104 panelists showed positive reactions of unspecified type. The product was considered to show no evidence of irritation or allergic sensitization.[76]

A repeated insult patch test according to the Draize-Shelanski-Jordan Procedure was conducted on a formulation containing 15.5-18.2% Polybutene. Of the 4717 subjects tested, six showed a Grade 1 Draize reaction.[77]

Lip gloss products containing 43.8-44.0% Polybutene were tested in the manner described above. Of the 2545 subjects, two showed a Grade 1 Draize reaction.[77]

Lip products with a 30.0% Polybutene concentration were tested according to the Draize-Shelanski-Jordan Procedure. Of the 7279 subjects who were tested, one showed a Grade 1 Draize reaction.[77]

A Draize-Shelanski-Jordan test of a lip product containing 50% Polybutene caused no irritation in 198 subjects.[77]

In a four-week controled use test, four formulations were tested for irritation potential. A lip gloss

TABLE 7. HUMAN CLINICAL STUDIES.

No. of subjects	*Conc. (Percent)*	*Dose*	*Time*	*Comments*	*Ref.*
Primary Skin Irritation				Product formulations	
100	20	—	48 h contact 3-day observe	No reactions	69
100	—	—	48 h contact 3-day observe	No reactions	70
Repeated Insult					
195	15	—	—	No reactions	71
96	15	—	—	No reactions	72
50	30	—	—	Material applied for one 72 h period; then, eight alternate 24 h periods Caused no irritation or sensitivity	73
50	30	—	—	Same protocol as above Caused no irritation or sensitivity	74
50	24	—	—	Applied for one 48 h period and then for 10 alternate 24 h periods; 13-day rest, then 48 h challenge No irritation or sensitization	75
104	3.1	—	—	Ten 48 h applications; 11-day rest; 48 h challenge patch No irritation or sensitization	76
4717	15.5–18.2	—	—	6/4717 showed Grade 1 Draize reaction	77
2545	43.81–44.0	—	—	2/2545—Grade 1 Draize reaction	77
7279	30.0	—	—	1/7279—Grade 1 Draize reaction	77
198	50.0	—	—	No irritation	77
407	15.5–18.2	—	4 weeks	1/407 showed erythema	78
219	43.81–44.03	—	4 weeks	No reactions	78
817	30.0	—	4 weeks	No reactions	78
25	50.0	—	4 weeks	1/25—blister on lower lip	78
63	15.0	—	28 days	Applications 2 × a day for 28 days. No irritation or sensitization.	79
Phototoxicity					
280	15.8–18.2	—	—	No reactions	80
165	43.81–44.02	—	—	No reactions	80
448	30.0	—	—	No reactions	80
27	50.0	—	—	No reactions	80

product containing 15.5–18.2% Polybutene was tested in 407 individuals. One erythematous reaction occurred. When lip formulations containing 43.8–44.0% Polybutene and 30.0% Polybutene were tested on 219 and 817 subjects, respectively, they produced no irritation. A lip product containing 50% Polybutene was applied to 25 panelists. A blister appeared on the lip of one person. No other reactions occurred.[78]

Sixty-three women panelists applied a lip formulation containing 15 percent Polybutene to test for product-induced irritation. The product was applied to the lips twice a day for 28 days, and the panelists were examined at 0-, 1-, 2-, 3-, and 4-week intervals. The panelists did not exhibit any irritation or sensitization.[79]

Phototoxicity and Photoallergenicity

Three lip gloss formulations, Type A (15.8–18.2% Polybutene), Type B (43.81–44.02% Polybutene), and Type C (30.0% Polybutene) were photopatch tested for phototoxicity and photoallergenicity in 280, 165, and 448 persons, respectively. A Xenon Arc Solar Simulator (150 W), which produces continuous emission spectrum from 290 to 400 nanometers, was used. These three products produced no reactions.[80]

A lip conditioner containing 50.0% Polybutene, tested on 27 individuals, did not induce any reactions.[80]

SUMMARY

Polybutenes are stereoregular polymers of isobutene and n-butene. The polymer chains may contain from 10 to 100 subunits and are prepared by heating 1-butene with catalysts. Polybutenes are light colored, nondrying, sticky, viscous liquids which are stable to light and soluble in hydrocarbon solvents. They undergo combustion, pyrolysis, and autoxidation. Analytical methods include nuclear magnetic resonance spectroscopy (NMR), infrared, far-infrared, and Raman scattering spectroscopy, and gas, gel, and thin layer chromatography. Impurities of Polybutene include isoparaffins, vinylidene, terminal vinyl structures, chloride, and sulfur containing compounds. Polybutenes are used in over 80 cosmetic formulations in concentrations ranging from 1 to >50%. They serve as viscosizers and emulsifiers.

When tested for acute oral toxicity in albino rats, concentrations of Polybutene ranging from 15% to 75% were relatively harmless. In percutaneous systemic dermal toxicity tests and in primary skin irritation studies, Polybutene in formulations produced no abnormalities or irritation in rabbits. Polybutene produced no abnormalities in rats during a 18.5 mg/L inhalation exposure and rabbits suffered only minimal eye irritation when Polybutenes were instilled into the eyes with and without washouts. In subchronic dermal systemic toxicity studies, Polybutenes did not affect hepatic or skin enzymatic activities in rats. It produced no irritation or signs of systemic toxicity when applied to the vaginas of rabbits. Chronic oral toxicity studies of up to 20,000 ppm Polybutene in the diet of rats and up to 1000 mg/kg daily in dogs for two years produced no adverse effects, and no teratogenic effects were found when fed to rats at 1% or 10% in the diet for six months. In three-generation reproductive studies with rats, Polybutene-fed rats showed no significant deviations from the control rats in any generation. Human primary irritation tests of a formulation containing 20% Polybutene produced no irritation, and repeated insult patch tests of 3.1–50% Polybutene in formulations produced, at most, minimal irritation in a small percentage of the test population. The products tested produced no irritation or sensitization. Photo patch tests of formulations with concentrations ranging from 15% to 50% Polybutene produced no reactions.

COMMENTS

Polybutenes are the isotactic polymers of isobutene and n-butene. Their stability in sunlight, low polarity, low degree of unsaturation, and closely packed, branched-chain molecular structure make them chemically inert. Polybutenes provide viscosity or emulsifiability to more than 80 cosmetic products in concentrations of 1% to >50%. They are primarily used in lipstick formultions, at concentrations greater than 10%. In addition, Polybutenes are widely used in lubricants, sealers, adhesives, fungicides, herbicides, and pesticides.

Commercial interest in Polybutenes extends beyond the cosmetic industry. The numbers and variety of animal toxicological studies conducted to establish their safety have been satisfactory. The results of acute oral toxicity tests of Polybutenes, alone and in formulations, show these materials to

be "relatively harmless."[81] When fed to rats at a concentration of 75%, the LD50 was greater than 34.6 g/kg, and a 30% lip lotion formulation had an LD50 greater than 40 g/kg for the formulation. Similarly, in percutaneous toxicity tests, rabbits showed no adverse systemic effects after exposure to Polybutenes.

In acute skin irritation tests, using several different formulations containing Polybutenes, rabbits showed no irritation or mild irritation. Other test results have also indicated that Polybutenes are not toxic: (a) there were no observable effects in rats after inhalation for 4 h in concentrations up to 18.5 mg/l of air; (b) there was only mild, transient eye irritation in rabbits treated with Polybutenes; (c) intravaginal application of concentrated Polybutene daily for 30 days produced no observable effect in rabbits; and (d) applications of Polybutene to the skin of rats produced no systemic effects.

Similar results were obtained in studies on chronic oral toxicity: rats fed up to 20,000 ppm Polybutene for 2 years and dogs fed up to 1,000 mg/kg daily for 2 years showed no disturbances attributable to the ingredient. Rats fed up to 20,000 ppm for three successive generations showed no impairment in reproduction. Ten percent Polybutene fed to rats for 6 months had no effects on their reproduction. It is evident from these animal tests that Polybutenes consistently have very low toxicity even at high doses and concentrations.

The available human clinical data, like the animal data, show very mild effects. Skin tests for sensitization, irritancy, phototoxicity, and photosensitization, however, used cosmetic formulations, and neither the pure ingredients nor the highest concentrations used in cosmetic products were evaluated. Nevertheless, the large numbers of patients used in these tests fulfill some of the requirements of these tests. Thus, notwithstanding the incompleteness of the human clinical tests, the animal toxicological studies have been sufficient to compensate for the deficiency, and their uniformly negative results permit the conclusion that Polybutenes are safe cosmetic ingredients.

CONCLUSION

On the basis of the available information, the Panel concludes that Polybutenes are safe as presently used in cosmetics.

ACKNOWLEDGMENT

Ms. Anne F. Moore, Scientific Analyst and writer prepared the literature review and technical analysis used by the Expert Panel in developing this report.

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Annual Review of Cosmetic Ingredient Safety Assessments—2002/2003[1]

The Cosmetic Ingredient Review (CIR) program Expert Panel has assessed the safety of almost 1200 cosmetic ingredients since its inception in 1976. The very first safety assessments were published in earlier incarnations of this journal—the *Journal of Environmental Pathology and Toxicology* in 1980, and the *Journal of the American College of Toxicology* from 1982 to 1996.

Because information relevant to the safety of ingredients may have become available since these early safety assessments were published, the CIR Expert Panel has initiated a re-review process. If new information is thought to be available or if a long period of time has passed, the CIR Expert Panel may initiate a search for relevant new data.

In some cases, newly available data are largely redundant with the data available in the original safety assessment. In other cases, there are new safety data. If after considering the newly available information, the CIR Expert Panel decides not to reopen a safety assessment, this finding, along with any background material, is summarized and announced publicly. To assure that the scientific community is aware of any new information and the decision not to reopen, this *Annual Review of Cosmetic Ingredient Safety Assessments* is prepared. This annual review covers all ingredients re-reviewed from February, 2002, to June, 2003.

For each original safety assessment the re-review addresses the import of new studies that were considered by the Panel, if any were available. A reference list is provided that updates the references provided in the original safety assessment. The re-review also captures information on the industry's current practices of ingredient use, updating the data available in the earlier report. Although this material provides the opinion of the CIR Expert Panel regarding the new data described, it does not constitute a full safety review.

The ingredients the CIR Expert Panel reconsidered in 2002/2003, and decided not to reopen are:

Acetylated Lanolin
Acetylated Lanolin Alcohol
Almond Meal
Ammonium Laureth Sulfate
Ammonium Lauryl Sulfate
Beeswax
Benzophenone-1, -2, -3, -4, -5, -6, -8, -9, and -11
n-Butane
Butoxyethanol
Butyl Stearate
Ceresin
Cetearyl Ethylhexanoate (formerly Cetearyl Octanoate)
Cetyl Palmitate
Cetyl Stearate
Choleth-24
Copernica Cerifera (Carnauba) Wax
Dibutyl Phthalate
Diethyl Phthalate
Diisopropyl Adipate
Dimethicone PEG-6 Acetate
Dimethicone PEG-8 Adipate
Dimethicone PEG-8 Benzoate
Dimethicone PEG-7 Phosphate
Dimethicone PEG-10 Phosphate
Dimethicone PEG/PPG-7/4 Phosphate
Dimethicone PEG/PPG-12/4 Phosphate
Dimethicone PEG/PPG-20/23 Benzoate
Dimethicone Copolyol
Dimethyl Phthalate
Diethylhexyl Adipate (formerly Dioctyl Adipate)
Emulsifying Wax N.F.
Ethylhexyl Palmitate (formerly Octyl Palmitate)
Ethylhexyl Stearate (formerly Octyl Stearate)
Euphorbia Cerifera (Candelilla) Wax
Hydrogenated Lanolin
Hydroxylated Lanolin
Isobutane
Isobutyl Stearate
Isocetyl Stearate
Isopentane
Isopropyl Myristate
Isopropyl Palmitate
Isopropyl Stearate
Isostearic Acid
Laneth-5, -16, and -25
Laneth-9 and -10 Acetate
Lanolin
Lanolin Oil

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[1]Reviewed by the Cosmetic Ingredient Review Expert Panel.

Lanolin Acid
Lanolin Alcohol
Lanolin Wax
Laureth-4 and -23
Microcrystalline Wax
Montan Wax
Myrtistyl Myristate
Myristyl Stearate
Octyl Palmitate
Octyl Stearate
Ozokerite
Paraffin
PEG-3, -7, -8, -9, -10, -12, -14, and -17 Dimethicone
PEG-2, -6, -8, -12, -20, -32, -40, -50, -100, and -150 Stearate
PEG/PPG-3/10, -4/12, -6/11, -8/14, -14/4, -15/15, -16/2, -17/18, -18/18, -19/19, -20/6, -20/15, -20/23, -20/29, -22/23, -22/24, -23/6, -25/25, and -27/27 Dimethicone
Polyamino Sugar Condensate
Polybutene
Polyquaternium-11
Potassium Cocyl Hydrolyzed Collagen (formerly Potassium-Coco-Hydrolyzed Animal Protein)
Propane
Propylene Glycol Stearate and Propylene Glycol Stearate SE
Prunus Amygdalus Dulcis Oil (formerly Sweet Almond Oil)
Prunus Amygdalus Dulcis Seed Meal (formerly Almond Meal)
Rhus Succedanea Fruit Wax
Sodium Laureth Sulfate
Sodium Lauryl Sulfate
Sweet Almond Oil
Synthetic Beeswax
Synthetic Wax
TEA-Cocoyl Hydrolyzed Collagen (formerly TEA-Coco-Hydrolyzed Animal Protein)
VA/Crotonates Copolymer (formerly VA/CA Copolymer)

ACETYLATED LANOLIN, ACETYLATED LANOLIN ALCOHOL, HYDROGENATED LANOLIN, HYDROXYLATED LANOLIN, LANOLIN (ANHYDROUS), LANOLIN ACID, LANOLIN ALCOHOL, LANOLIN OIL, AND LANOLIN WAX

A safety assessment of Acetylated Lanolin, Acetylated Lanolin Alcohol, Hydrogenated Lanolin, Hydroxylated Lanolin, Lanolin (anhydrous), Lanolin Acid, Lanolin Alcohol, Lanolin Oil, and Lanolin Wax was published in 1980 in which the CIR Expert Panel concluded that these ingredients are safe for topical application to humans in the then present practice of use and concentration (Elder 1980). The Panel reviewed new studies (listed at the end of this section), along with updated information regarding types and concentrations of use. The Panel determined to not reopen this safety assessment.

CIR Expert Panel acknowledged that there are current uses of lanolin compounds that may include aerosols. The effects of inhaled aerosols depend on the specific chemical species, the concentration, the duration of exposure, and site of deposition within the respiratory system. Particle size is the most important factor affecting the location of deposition (Jensen and O'Brien 1993). The mean aerodynamic diameter of pump hair spray particles is $\geq 80\ \mu$ and the diameter of anhydrous spray particles is 60 to 80 μ. Typically, less than 1% are below 10 μ, which is the upper limit for respirable particles (Bower 1999). Based on the particle size, lanolin and related compounds would not be respirable in formulation.

The panel also noted that animal derived products may contain residues present in the plant material ingested by the animal. Manufacturers are reminded that cosmetic products containing plant or animal derived ingredients should be formulated to limit the presence of pesticide/heavy metal residues as follows: lead ≤ 10 ppm, arsenic ≤ 3 ppm, mercury ≤ 1 ppm, total PCB/pesticide contamination ≤ 40 ppm with ≤ 10 ppm for any specific residue (Andersen 1998). In addition, the CIR Expert Panel has recently stressed that animal-derived ingredients must be free of detectible pathogens and/or infectious agents (e.g., prions). Suppliers and users of these ingredients should assure that these ingredients are risk-free. Tests to assure the absence of a pathogenic agent in the ingredients, or controls to assure deviation from pathogen-free sources are two approaches that should be considered.

Data from the 1980 report on frequency of use and concentration of use (circa 1976) is provided in Table 1 along with current frequency and concentration of use and total products in each category as provided by the Food and Drug Administration (FDA) and Cosmetic, Toiletry, and Fragrance Association (CTFA) (FDA 2002; CTFA 2003). Although the total number of products containing lanolin and related compounds has decreased since 1980 (5196 in 1980 versus 2438 in 2002), there has been an increase in the variety of product categories containing these chemicals. In the 1980 report, the highest concentrations of these ingredients were in makeup and eye makeup preparations, skin care, suntan and sunscreen preparations, manicuring products, noncoloring hair preparations, and hair-coloring preparations. In 2003, lipsticks and rouges have the highest use concentrations.

Acetylated Lanolin. Acetylated lanolin is the acetylated ester of lanolin (q.v.) and is used as hair conditioning agent and skin conditioning agent, both emollient and occlusive. It was used in 127 cosmetic products in 1976, with the highest concentration range of >0.1% to 50% in eye and other make-up preparations. Currently Acetylated lanolin is used in 151 products at a maximum use concentration of 7% in makeup foundations. Table 1 provides the available use information.

Acetylated Lanolin Alcohol is the acetyl ester of Lanolin Alcohol (q.v.) and is primarily used as a hair conditioning agent and skin-conditioning agent—emollient and occlusive. It was used in 376 cosmetic products in 1976, with the highest concentration

TABLE 19

Historical and current cosmetic product uses and concentrations for Polyamino Sugar Condensate

Product type	1976 uses (Elder 1982)	2001 uses (FDA 2001)	1976 use concentrations (Elder 1982) (%)	2001 use concentrations (CTFA 2001) (%)
Eye makeup (other)	1	4	≤0.1	—
Shampoos (noncoloring)	1	—	≤0.1	—
Blushers	6	—	≤0.1	—
Face powders	2	—	≤0.1	—
Foundations	8	—	≤0.1–1	—
Leg and body paints	1	—	>0.1–1	—
Lipstick	1	—	>0.1–1	—
Makeup bases	5	—	≤0.1–1	—
Rouges	4	—	≤0.1	—
Makeup fixatives	1	—	≤0.1	—
Makeup (other)	1	—	≤0.1	—
Cuticle softeners	1	—	>0.1–1	—
Nail creams and lotions	1	—	≤0.1	—
Aftershave lotion	2	—	≤0.1–1	—
Skin-cleansing creams, lotions, liquids, and pads	6	2	>0.1–1	—
Face and neck skin care preparations	12*	1	≤0.1–1*	—
Body and hand skin care preparations		4		—
Moisturizers	26	9	≤0.1–1	—
Night skin care preparations	20	1	≤0.1–1	—
Paste masks/mud packs	3	1	≤0.1–1	—
Skin fresheners	1	—	>0.1–1	—
Skin care preparations (other)	8	2	≤0.1–1	—
Suntan gels, creams, and liquids		1		—
Total uses/ranges for Polyamino Sugar Condensate	**111**	**25**	**≤0.1–1**	**—**

*This category was combined when the original safety assessment was performed and is now two separate categories.

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Wenninger, J. A., R. C. Canterbery, and G. N. McEwen. Jr., eds. 2000. *International Cosmetic Ingredient Dictionary and Handbook*, 8th ed., 1114–1115. Washington, DC: CTFA.

POLYBUTENE

In 1982, CIR issued a Final Report that Polybutenes are safe as presently used in cosmetics (Elder 1982). One new inhalation toxicity study was reported since then (Skyberg et al. 1990). This new study, along with the updated information below regarding types and concentrations of use, were considered by the CIR Expert Panel. The Panel determined not to reopen this safety assessment.

In 1976 Polybutene was reported to be used in 84 cosmetic preparations, with the largest single use occurring in lipstick at concentrations of >1% to >50%. As reported to the FDA (FDA 2001), Polybutene is currently used in 253 products, with lipstick again the largest category and highest concentration, according to an industry survey (CTFA 2001). Table 20 presents the available use information.

The Panel noted that use concentration has increased overall and may currently be as high as 92% in some lipstick products, but that the available data demonstrate that this ingredient is not absorbed in the skin or the gut. The levels of Polybutene that are toxic via an inhalation route are not reached in cosmetics, and there are no aerosolized cosmetic products that contain Polybutene.

REFERENCES

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[21]Available from the Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036.

TABLE 20
Historical and current cosmetic product uses and concentrations for Polybutene

Product type	1976 uses (Elder 1982)	2001 uses (FDA 2001)	1976 use concentrations (Elder 1982) (%)	2001 uses concentrations (CTFA 2001) (%)
Bath preparations (other)	—	—	—	0.002
Eyebrow pencil	—	3	—	3
Eyeliner	—	3	—	4
Eye shadow	10	8	>1–5	8.4–36
Mascara	—	51	—	2–5
Eye makeup (other)	—	6	—	2–36
Fragrance preparations (other)	—	—	—	14
Noncoloring shampoos	2	—	>5–10	0.9
Blushers	—	—	—	10
Face powders	—	1	—	2–3
Foundations	—	5	—	8
Lipstick	70	151	>1–>50	0.6–92
Makeup preparations (other)	—	19	>10–25	6–87
Personal cleanliness products (other)	—	—	—	16
Moisturizers	1	3	>1–5	—
Night skin care preparations	1	—	>10–25	—
Skin care preparations (other)	—	2	—	6–16
Suntan preparations (other)	—	1	—	—
Total uses/ranges for Polybutene	**84**	**253**	**>1–>50**	**0.002–92**

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POLYQUATERNIUM-11

In 1983, CIR issued a Final Report that Polyquaternium-11 is safe as a cosmetic ingredient in the present practices of use (Elder 1983). A review of the recent literature on Polyquaternium-11 uncovered no new studies. Updated information below regarding types and concentrations of use were considered by the CIR Expert Panel. The Panel determined not to reopen this safety assessment.

In 1976 Polyquaternium-11 was reported to be used in 131 cosmetic preparations with the largest single use occurring in hair conditioners at concentrations of ≤25%. As reported to the FDA (FDA, 2001), Polyquaternium-11 is currently used in 254 products, with hair tonics, dressings, etc., as the largest category with a concentration range of 0.05–10%, according to an industry survey (CTFA 2001). Table 21 presents the available use information.

REFERENCES

Cosmetic, Toiletry, and Fragrance Association (CTFA). 2001. Product use concentration information for Polybutene. Unpublished data submitted by CTFA.[22]

Elder, R. L., ed. 1983. Final report on the safety assessment of Polyquaternium-11. *J. Am. Col. Toxicol.* 2:161–178.

Food and Drug Administration (FDA). 2001. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.

POTASSIUM COCOYL HYDROLYZED COLLAGEN AND TRIETHANOLAMINE COCOYL HYDROLYZED COLLAGEN

A Safety Assessment of Potassium-Coco-Hydrolyzed Animal Protein and Triethanolamine-Coco-Hydrolyzed Animal Protein was published in 1983 (Elder 1983). Based on the data available at that time, the Panel concluded that these compounds were "safe as cosmetic ingredients in the present practices of use."

The names these two compounds as listed in the *International Cosmetic Ingredient Dictionary and Handbook* have been

[22]Available from the Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

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Final Report on the Safety Assessment of Polyethylene[1]

Polyethylene is an ethylene polymer used for a variety of purposes in cosmetics as an abrasive, adhesive, binder or bulking agent, an emulsion stabilizer, a film former, an oral care agent, and as a nonaqueous viscosity-increasing agent. Polyethylene is also used in food packaging materials and medical products, including prosthetics. The molecular weight of Polyethylene as used in cosmetics varies over a wide range. The lowest reported molecular weight is 198 Daltons and the highest is 150,000. In any given polymer preparation, there can be a broad range of molecular weights. Cellular and tissue responses to Polyethylene, determined as part of implant biocompatibility testing, include fibrous connective tissue build-up around the implant material that varies as a function of the physical form of the implant material. Specific assays for osteoblast proliferation and collagen synthesis demonstrated a reduction as a function of exposure to Polyethylene particles that is inversely related to particle size. The effect of Polyurethane particles on monocyte-derived macrophages, however, had a stimulatory effect, prolonging the survival of these cells in culture. The LD_{50} for Polyethylene, with an average molecular weight of 450, in rats was >2000 mg/kg. For Polyethylene with an average molecular weight of 655, the LD_{50} was >5.0 g/kg. Toxicity testing in rats shows no adverse effects at Polyethylene (molecular weight not given) doses of 7.95 g/kg or at 1.25%, 2.50%, or 5.00% in feed for 90 days. Dermal irritation studies on rabbits in which 0.5 g of Polyethylene (average molecular weight of 450) was administered in 0.5 ml of water caused no irritation or corrosive effects; Polyethylene with an average molecular weight of 655 was a mild irritant. Polyethylene (average molecular weight of 450) did not cause dermal sensitization in guinea pigs tested with 50% Polyethylene (*w/w*) in arachis oil BP. Polyethylene, with a molecular weight of 450 and a molecular weight of 655, was a mild irritant when tested as a solid material in the eyes of rabbits. Rabbit eyes treated with a solution containing 13% Polyethylene beads produced minimal irritation and no corneal abrasions. No genotoxicity was found in bacterial assays. No chemical carcinogenicity has been seen in implantation studies, although particles from Polyethylene implants can induce so-called solid-state carcinogenicity, which is a physical reaction to an implanted material. Occupational case reports of ocular irritation and systemic sclerosis in workers exposed to Polyethylene have been difficult to interpret because such workers are also exposed to other irritants. Clinical testing of intrauterine devices made of Polyethylene failed to conclusively identify statistically significant adverse effects, although squamous metaplasia was observed. The Cosmetic Ingredient Review (CIR) Expert Panel did not expect significant dermal absorption and systemic exposure to large Polyethylene polymers used in cosmetics. The Panel was concerned that information on impurities, including residual catalyst and reactants from the polymerization process, was not available. The Panel considered that the monomer unit in Polyethylene polymerization is ethylene. In the United States, ethylene is 99.9% pure. The other 0.1% includes ethane, propylene, carbon dioxide, carbon monoxide, sulfur, hydrogen, acetylene, water, and oxygen. The Panel believed that the concentration of these impurities in any final polymer would be so low as to not raise toxicity issues. Safety tests of cosmetic-grade Polyethylene have consistently failed to identify any toxicity associated with residual catalyst. Although it was reported that one process used to cross-link Polyethylene with an organic peroxide, this process is not currently used. In addition, cosmetic-grade Polyethylene is not expected to contain toxic hexanes. The Panel was concerned that the only genotoxicity data available was nonmammalian, but taking this information in concert with the absence of any chemical carcinogenicity in implant studies suggests no genotoxic mechanism for carcinogenicity. The solid-state carcinogenicity effect was not seen as relevant for Polyethylene as used in cosmetics. The available data support the conclusion that Polyethylene is safe for use in cosmetic formulations in the practices of use and concentrations described.

INTRODUCTION

Polyethylene is a polymer of ethylene monomers used in cosmetics as an abrasive, adhesive, binder, bulking agent, emulsion stabilizer, film former, oral care agent, and nonaqueous viscosity-increasing agent. It is also a commonly used plastic in food packaging and prosthetics. This review presents information relevant to the safety of Polyethylene as a cosmetic ingredient.

CHEMISTRY

Definition and Structure

The *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2004) lists Polyethylene (CAS no. 9002-88-4) as a polymer of ethylene monomers that conforms generally to the empirical formula $(C_2H_4)_x$.

Polyethylene has the following technical/other names:

- ethene homopolymer,
- high melting point polyethylene powder,
- polyethylene powder,
- polyethylene wax, and
- synthetic wax.

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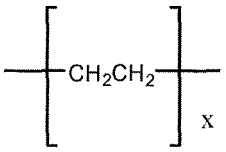
[1]Reviewed by the Cosmetic Ingredient Review Expert Panel. Address correspondence to Valerie C. McLain, Scientific Analyst and Writer, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036, USA.

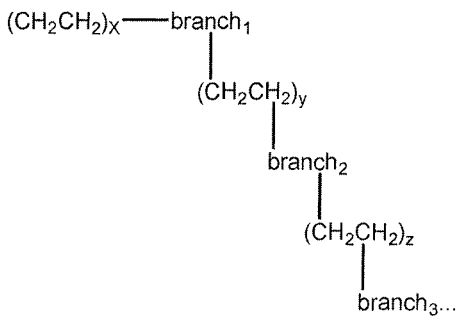
The structural formula from Gottschalck and McEwen (2004) is



where x determines the polymer size.

At least 19 manufacturers supply trade name products that are their own versions of Polyethylene for use in cosmetics and an equal number supply Polyethylene as part of a trade name mixture (Gottschalck and McEwen 2004).

According to Kissin (1999), Polyethylene is a generic name for a large family of semicrystalline polymers used mainly as commodity plastics. A majority of polyethylene molecules contain branches in their chains, which can be represented by the following formula, where the x, y, and z values can range from 4 or 5 to over 100:



Because of this branching structure, Polyethylene can be produced with a wide range of molecular weights and branching elements. The number of monomer units in the polymer can vary from small (about 10 to 20 in polyethylene waxes) to very large (over 100,000 for polyethylene of ultrahigh molecular weight).

Physical and Chemical Properties

Table 1 presents the physical and chemical properties of Polyethylene.

Safepharm Laboratories, Ltd. (1997a) tested Polyethylene with an average molecular weight of either 450 or 655 Daltons, finding that neither product was soluble in water. These polymers were described as mainly linear with very little branching, and the manufacturing process had removed all monomers, with no residual ethylene remaining.

Kissin (1999) characterized Polyethylene polymers as shown in Table 2.

Pebsworth (1999) reported the molecular weight of low-density polyethylene, which ranges from waxy products at approximately 500 molecular weight to very tough products at about 60,000 molecular weight. Low-density polyethylene, also known as high-pressure polyethylene, differs from high-density polyethylene and linear low-density polyethylene in that it possesses both long- and short-chain branches along the polymer chain.

This author stated that, traditionally, low-density polyethylene has been described as homopolymer products having a density between 0.915 and 0.940 g/cm^3 (products having a density above 0.940 g/cm^3 are considered to be high-density polyethylenes). In addition, low-density polyethylene has the potential to include a wide range of comonomers that can be polar in nature on the polymer chain. The broad molecular weight distribution in low-density polyethylene is caused by the presence of long branches on the polymer molecule and may have

TABLE 1
Physical and chemical properties of Polyethylene

Molecular weight	198–500,000	Baker Petrolite 2004 NTP Chemical Repository 2001 Lewis 1997
Density	0.910–0.925 g/ml	NTP Chemical Repository 2001
Melting point	85–110°C	NTP Chemical Repository 2001
Flammability (flash point)	221°C	NTP Chemical Repository 2001
Reactivity	Attacked by oxidizing agents such as nitric and perchloric acids, free halogens, benzene, petroleum ether, gasoline and lubricating oils, aromatic and chlorinated hydrocarbons	NTP Chemical Repository 2001
Maximum λ	161.5 nm	IARC 1979
Odor	Odorless	Lewis 1993

TABLE 2
Commercial classification of Polyethylenes (Kissin 1999)

Designation	Acronym	Density (g/cm^3)
High density polyethylene	HDPE	≥0.941
Ultrahigh molecular weight polyethylene[a]	UHMWPE	0.935–0.930
Medium density polyethylene	MDPE	0.926–0.940
Linear low density polyethylene	LLDPE	0.915–0.925
Low density polyethylene[b]	LDPE	0.910–0.940
Very low density polyethylene	VLDPE	0.915–0.880

[a]Linear polymer with molecular weight of over 3×10^6.
[b]Produced in high pressure processes.

molecules that range in length from a few thousand carbons to a million or more carbons.

As molecular weight increases, certain property values of low-density polyethylenes increase as well. These include: melt viscocity, abrasion resistance, tensile strength, resistance to creep, flexural stiffness, resistance to brittleness at low temperature, shrinkage, warpage, and film impact strength. Increased molecular weight results in reduced film transparence, freedom from haze, and gloss; draw-down rate; neck-in and beading; and adhesion. It was noted that molecular weight distributions around an average molecular weight will differ for the two processes, but there will be a definite range in either case, not a single molecular weight (Pebsworth 1999).

According to the Cosmetic, Toiletry, and Fragrance Association (CTFA), as supplied to the cosmetics industry, weight average molecular weight, number average molecular weight, and polydispersity may be given (CTFA 2004d). The number average molecular weight of a given polymer sample is determined by taking the sum of each of the polymer molecular masses multiplied by the number of polymer molecules at that molecular mass. That total is divided by the total number of polymer molecules in the sample to yield the number average molecular weight.

The weight average molecular weight is the sum of the fraction of the total sample mass represented by each type of polymer multiplied by the molecular mass of each type. Polydispersity is determined by the ratio of the weight average molecular weight to the number average molecular weight. The higher the value for polydispersity, the wider the range of molecular weights represented in the sample. Table 3 provides values for these parameters from two suppliers (CTFA 2004d).

In yet another characterization of Polyethylene supplied to the cosmetics industry for use as an abrasive, Induchem specified a molecular weight range (weight average or number average not stated) of 60,000 to 70,000 and particle size of 10 to 800 μm (CTFA 2004c).

Information from Baker Petrolite (2004) indicated that Polyethylenes used in the cosmetics industry have number average molecular weights (Mn) as low as 300 to 400. This company's trade name Polyethylene, PERFORMALENE 400, is a polymer where the molecular mass distribution may have portions as low as 198. The data on PERFORMALENE 400 polyethylene showed no indication of toxicity, irritation or sensitization, therefore a molecular weight limitation was not considered to be suitable in this case. Molecular weights are not normally included in the quality control tests used for specifications, and are also subject to some variation depending upon the testing technique. Baker Petrolite recommends using the value of 198 as the lower limit of PERFORMALENE 400 polyethylene number average molecular weight distribution.

Additional data (CTFA 2005) indicated that a supplier sells Polyethylene to the personal care industry with a molecular weight of 104,000 to 109,000.

TABLE 3
Polyethylene molecular weights and polydispersity data (CTFA 2004c)

Value	Supplier A	Supplier B
Weight average molecular weight (Mw)	152,500	70,200
Number average molecular weight (Mn)	15,600	9,300
Polydispersity (Mw/Mn)	9.8	7.5

Method of Manufacture

Lewis (1997) stated that the preparation of Polyethylene varies. Cross-linked Polyethylene (XLPE) can be made by irradiating linear polyethylene or by using a cross-linking agent, such as an organic peroxide (e.g., benzoyl peroxide catalyst). Low-density (branched) Polyethylene is formed by the oxygen catalyzed polymerization of ethylene or by applying pressures of 100 to 300 psi at less than 100°C. High-density (linear) Polyethylene is prepared using a metallic catalyst to polymerize ethylene.

Cottom (1999) stated that Polyethylene waxes are synthetic waxes. Low-molecular-weight polyethylenes possessing wax-like properties are produced either by high-pressure polymerization or low-pressure (Ziegler-type catalysts) polymerization. Although all the products have the same general structure, the processes yield products with distinctly different properties. Some polyethylenes have moderately low densities as a result of the branching that occurs during the polymerization. Molecular weight distributions also vary widely among the different processes, as does the range of molecular weights available.

Kissin (1999), in the *Kirk-Othmer Encyclopedia of Chemical Technology*, described methods of manufacture that include polymerization (1) in supercritical ethylene at a high ethylene pressure and temperature above the polyethylene melting point (110°C to 140°C), (2) in solution or in slurry at 120°C to 150°C, and (3) in the gas phase (no temperature given). The properties of polyethylene are maintained by controlling the density, molecular weight, and molecular weight distribution, or by cross-linking. Polyethylene resins are produced either in radical polymerization reactions or in catalytic polymerization reactions.

Analytical Methods

Various methods have been used to identify Polyethylene (IARC 1979). Ultraviolet, visible, and infrared spectrometries have been employed to identify polyethylene in paper coatings. Infrared spectrometry has also been used in textiles. Identification can be accomplished by examining the pyrolysis products of Polyethylene by polarography of bromo or nitro derivates; thin-layer chromatography; combining ultraviolet

analysis, color-forming reactions, and thin-layer chromatography; mass spectrometry; and gas chromatography.

Impurities

IARC (1979) stated that ethylene in the United States is 99.9% pure with impurities including ethane, propylene, carbon dioxide, carbon monoxide, sulfur, hydrogen, acetylene, water, and oxygen.

Sheftel et al. (2000) stated that catalyst (ash contents) from production of high-density (low-pressure) Polyethylene can be reduced to 0.002% to 0.003% by washing. Safepharm Laboratories, Ltd. (Safepharm 1997a) stated that the Polyethylene they tested contained no residual ethylene and that the manufacturing process had removed all monomers.

Information regarding Polyethylene from Baker Petrolite (2004) affirmed that their products (PERFOMALENE polyethylenes) do not use any organic peroxides as catalysts. It was also reported that their process was designed to remove the proprietary catalysts that they use. The data submitted on irritation, sensitization, and an Ames test were from studies using typical batches of commercial products. If there were any residual materials that promoted adverse effects, the tests would have been expected to show some indication.

A safety data sheet for evaluation of cosmetic ingredients provided indicated that Polyethylene is a pure component containing 100% active ingredient and no solvents, preservatives, antioxidants, or additives (CTFA 2004c). This data sheet also showed that there is no known residue from manufacturing.

Another company (CTFA 2004d) reported one product with a value of 1200 ppm of carbon hydrogen compounds (C6–C11) and that their Polyethylene waxes (number weight molecular weights between 3000 and 11,000) are free of aromatic solvents. A third company (CTFA 2004d) stated that their Polyethylene is produced using a slurry process in which no organic peroxides were used. The reported number average molecular weight was 957.

USE

Cosmetic

Polyethylene is used in a wide range of cosmetic product types. As shown in Table 4, current industry reports to the Food and Drug Administration (FDA) include 717 uses (FDA 2002b). For each product type, Table 4 gives the total number of products reported to FDA (in parentheses in the first column). For eyeliner products, for example, of the total of 548 products reported, 297 contained Polyethylene.

Table 4 also gives the results of an industry survey (CTFA 2004a) of current use concentrations—overall the use concentration ranged from 0.09% to 24%. That same survey also provided some data on the physical form of Polyethylene as a function of product type containing which.

Noncosmetic

Food Packaging

Schwope et al. (1987) stated that both High-Density Polyethylene (HDPE) and Low-Density Polyethylene (LDPE) are among the most widely used food-packaging materials, both as a film and in containers. When used in food packaging, Polyethylene is regularly compounded with antioxidants to reduce thermal degradation, antiblocking agents to prevent film sticking, and slip additives to reduce friction.

In the Code of Federal Regulations (21CFR177.1600-177.1620), the FDA recognizes the safety of carboxyl-modified, chlorinated, and fluorinated Polyethylenes as a food-contact surface.

Medical Products

The medical uses of Polyethylene include dentistry, plastic stents in the treatment of malignant biliary structures (Catalano et al. 2002), microsutures used in gynecology microsurgery (Gomel et al. 1980), intrauterine contraceptive devices (Ober et al. 1970), strips in breast augmentations (Roberts and Taylor 1990), and orthopedic implants (FDA 1996).

FDA Center for Devices and Radiological Health (CDRH) mandates biocompatibility testing of materials to be implanted, including Polyethylene. Under the provisions of the FDA Modernization Act of 1997, CDRH established guidance on the recognition and use of consensus standards (FDA 1998a).

Under this provision, CDRH has recognized the ISO 10993 series of standards as the basis for biocompatibility testing (FDA 1998a, 1998b, 2002a). Relevant to the use of Polyethylene in cosmetic products, the tests listed below are routinely performed on all medical devices containing Polyethylene requiring premarket approval:

- Cytotoxicity—in accordance with ISO 10993-5, extracts are tested for ability to cause cell lysis or toxicity and compared with negative and positive controls.
- Sensitization—in accordance with ISO 10993-10, guinea pig maximization test.
- Irritation—in accordance with ISO 10993-10, rabbit acute intracutaneous reactivity.
- Toxicity—in accordance with ISO 10993-11, acute systemic toxicity in the mouse.
- Pyrogenicity—in accordance with ISO 10993-11, temperature rise in rabbits over a 3-h observation period.

Accordingly, all medical grade Polyethylene considered in premarket approval applications by CDRH has been found safe for implantation according to these criteria (FDA 1998a, 1998b, 2002a). CDRH's findings on premarket approval applications are prepared in a summary of safety and effectiveness data. One such example for an implantable device containing Polyethylene is a cardiac ablation catheter (premarket approval application number P000020) approved November 29, 2000 (FDA 2000).

TABLE 4
Frequency of use, use concentrations, and physical form of Polyethylene in cosmetics as a function of product categories

Product category (total number of formulations) (FDA 2002b)	Number of products with ingredient (FDA 2002b)	Concentration of use (%) (CTFA 2004a)	Physical form of Polyethylene (CTFA 2004a)
Baby products			
Baby lotions, oils, powders, and creams (60)	1	3	Powder
Other baby products (34)	—	3	Powder
Bath products			
Bath soaps and detergents (421)	4	0.3–8	Not stated
Other bath preparations (196)	10	4–18	Powder or not stated
Eye products			
Eyebrow pencils (102)	16	6	Not stated
Eyeliners (548)	297	6–10	Small ball or not stated
Eye shadow (576)	20	9–24	Powder, small ball, or not stated
Eye makeup remover (100)	6	5–10	Powder or not stated
Mascara (195)	39	3–8	Not stated
Other eye makeup preparations (152)	4	3–16	Powder or wax
Fragrance products			
Fragrance powders (273)	7	—	—
Perfumes	—	5	Not stated
Other fragrance preparations (173)	1	3	Not stated
Noncoloring hair products			
Hair conditioners (651)	1	—	—
Hair tonics, dressings, etc. (598)	4	2	Not stated
Hair-coloring products			
Hair bleaches (120)	2	—	—
Other hair-coloring preparations (55)	1	—	—
Makeup			
Blushers (245)	23	2–10	Powder, small ball, wax, or not stated
Face powders (305)	25	5–10	Powder, small ball, or not stated
Foundations (324)	23	2–11	Powder, small ball, or not stated
Leg and body paints (4)	—	3–8	Not stated
Lipsticks (962)	67	3–16	Powder, small ball, wax, or not stated
Makeup bases (141)	7	—	—
Rouges (28)	4	8–20	Not stated
Makeup fixatives (20)	3	3	Not stated
Other makeup preparations (201)	20	0.2–11	Powder or not stated
Nail care products			
Nail polish and enamel (123)	—	0.09	Not stated
Other manicuring preparations (55)	—	3	Not stated
Personal hygiene products			

(Continued on next page)

TABLE 4
Frequency of use, use concentrations, and physical form of Polyethylene in cosmetics as a function of product categories *(Continued)*

Product category (total number of formulations) (FDA 2002b)	Number of products with ingredient ingredient (FDA 2002b)	Concentration of use (%) (CTFA 2004a)	Physical form of Polyethylene (CTFA 2004a)
Underarm deodorants (247)	—	7	Not stated
Other personal cleanliness products (308)	12	5–10	Not stated
Skin care products			
Skin cleansers (775)	55	2–11	Powder or not stated
Depilatories (34)	—	5	particles (abrasive)
Face and neck creams, lotions, powder, and sprays (310)	5	1–10	Powder, small ball, or not stated
Body and hand creams, lotions, powder, and sprays (840)	12	2–16	Powder or not stated
Moisturizers (905)	12	5–10	Not stated
Night creams, lotions, powder, and sprays (200)	3	—	—
Paste masks/mud packs (271)	11	4	Not stated
Other skin care preparations (725)	18	0.6–5	Powder or not stated
Suntan products			
Suntan gels, creams, and liquids (131)	2	0.5–8	Powder or not stated
Indoor tanning preparations (71)	—	3	Not stated
Other suntan preparations (38)	2	5	Not stated
Total uses/ranges for Polyethylene	**717**	**0.09–24**	

According to Induchem, there is no difference between medical-grade and cosmetic-grade Polyethylene (CTFA 2004c).

Other Uses

Polyethylene containers are used for packaging of materials such as cosmetics, flammable and combustible liquids, and pharmaceuticals. Figge and Freytag (1980) determined that Polyethylene is suitable for packaging cosmetics. Polyethylene is used in agricultural fields or greenhouses as a tarp to contain fumigants in soil to reduce emissions into the atmosphere (Papiernik and Yates 2002). Polyethylene is also used in wire and cable coatings and insulations, as well as pipe and molded fittings (Lewis 1997).

According to Kissin (1999), uses of Polyethylene resins include many film grades of low-density polyethylene, high-density polyethylene, and linear low-density polyethylene for bags and packaging; coatings for paper, metal, wire, and glass; household and industrial containers such as bottles for different fluids like water, food products, detergents, and liquid fuels, etc.; toys; and various types of piping and tubing.

According to Cottom (2004), major uses of polyethylenes include hot-melt adhesives for applications requiring high temperature performance, additives to improve the processing of plastics, slip and rub additives for inks and paints, and cosmetic applications. Some by-product polyethylene waxes have been recently introduced. Uses include additives for inks and coatings, pigment dispersions, plastics, cosmetics, toners, and adhesives.

GENERAL BIOLOGY

Absorption, Metabolism, Distribution, and Excretion

Most studies of the effects of Polyethylene were done using implantation, so data normally found in this section is included in the following section.

Cellular and Tissue Response—Biocompatibility

Bing (1955) summarized early research on tissue reaction to Polyethylene and carried out a series of experiments to confirm past results.

Polyethylene film balls (7 mm diameter) were implanted intraperitoneally in four rats that were subsequently killed after 11 days, 39 days, 3 and 4 months. In each rat, a capsule of connective tissue was observed. Leukocytes, macrophages, and very few giant cells were found surrounding the area of the implant in the rat killed after 11 days. The 3- and 4-month implantations had little inflammatory reaction.

Small pieces of Polyethylene film were also implanted intraperitoneally into four rats that were killed at the same intervals. Again, the Polyethylene was surrounded by fibrous tissue; however, in contrast to the reaction to the Polyethylene ball, there were many foreign-body giant cells surrounding the film.

Pieces of Polyethylene mesh woven from 0.7 mm thick threads at 1 to 3 mm apart were implanted subcutaneously and intraperitoneally in five rats. Animals were killed at 5, 19, about 45, and about 100 days. The Polyethylene, in each case, was

surrounded by connective tissue and polymorphonuclear leucocytes, macrophages, and a few giant cells (Bing 1955).

In a longitudinal study, Gomel (1980) investigated the histologic reaction to nonabsorbable polyethylene sutures (10-0 in weight) in the bicornuate uterus of a New Zealand white rabbit. Sutures were placed in several rows on each uterine horn. After 24 days, the right uterine horn was removed and after 80 days, the left horn was removed. Segments of tissue containing the sutures were trimmed, fixed in formalin, sectioned, and stained. Two reactions were determined; degree of mononuclear histiocyte infiltration and multinucleated giant cell reaction.

After 24 days, histiocyte infiltration varied from none to marked in the 10 samples, with an average of moderate. There were no multinucleated giant cell reactions. After 80 days, all samples showed some histiocyte infiltration, ranging from minimal to moderate while four of the ten samples had giant cells (Gomel 1980).

Rodrigo et al. (2001) investigated the biological effect of Polyethylene particles of different sizes on human osteoblastic cells isolated from the trabecular bone of 17 osteoarthritic patients. Ten osteoblastic marker secretion samples were obtained from subjects aged 68 $\pm$ 7 years. Seven osteocalcin expression samples came from patients aged 65 $\pm$ 5 years. Polyethylene particles of two different sizes (<30 and 20 to 200 μm) were used. The osteoblastic samples were cultured in three different flasks; with <30-μm particles, 20-to 200-μm particles, and a control flask not treated with Polyethylene. Osteoblastic function was evaluated.

Small (<30 μm) Polyethylene particles were shown to have a greater effect on osteoblastic function markers than larger particles (20 to 200 μm). Evidence of inhibition of both osteoblast proliferation and collagen synthesis was observed.

The seven osteocalcin samples were tested in four flasks, two with <30-μm particles and two controls without Polyethylene. The small Polyethylene particles increased osteocalcin expression and secretion, which may be responsible for osteoclast bone resorption, leading to reduced orthopedic implant stability (Rodrigo et al. 2001).

Rodrigo et al. (2002) examined the hypothesis that Polyethylene and other implant materials may cause alteration in osteoblastic function, resulting in bone loss around the implant. The study focused on the effects of high density Polyethylene on interleukin-6 (IL-6) expression in human osteoblastic cells. Cytokines, such as IL-6, are the most important components in cell proliferation, osteoclast formation, and the stimulation of osteoclasts to resorb adjacent bone. Increased release of cytokines can lead to osteolysis in patients with Polyethylene prosthetics. Human osteoblastic cells, obtained from trabecular bone explants of 15 osteoarthritic patients aged 65 $\pm$ 5 years, were incubated with high-density Polyethylene particles (<5 μm).

Polyethylene increased the expression and secretion of IL-6 in human osteoblastic cells (Rodrigo et al. 2002).

Noting that macrophages are often found in the inflamed membrane that commonly surrounds Polyethylene orthopedic implants, Xing et al. (2002) assessed the effect of polyethylene particle phagocytosis on the viability of mature human monocyte-derived macrophages (MDMs). The Polyethylene used has characteristics similar to that of ultra-high molecular weight Polyethylene. Three healthy volunteers (no detailed information was provided) contributed blood, which was centrifuged to isolate monocytes. Particles of high-density polyethylene (HDPE, size 4 to 10 μm) were suspended in soluble type I collagen. The MDMs were incubated in a collagen control, as well as in the collagen-HDPE substrata for 31 days.

Initial contact (seen as early as 2 h after incubation) of the MDMs with the HDPE particles did not cause a toxic effect. After 24 h, most of the particles were associated with the cells, revealing that phagocytosis of the particles had occurred. The HDPE particles did not change the cell viability, as evidenced by similar viability in the control macrophages. The cells associated with particles were activated, rather than necrotic. This was evidenced further at 31 days. The test cells were more viable and had higher DNA values than the control cells.

The authors concluded that phagocytosis of HDPE particles by MDMs prolongs the macrophages' survival, and the authors speculated that this may explain the chronic inflammation surrounding Polyethylene orthopedic implants (Xing et al. 2002).

ANIMAL TOXICOLOGY

Acute Toxicity

Lefaux (1968) stated that attempts to determine the lethal dose (LD_{50}) of low-pressure Polyethylene were unsuccessful. The rats could not be given more than 7.95 g/kg and at this level, the animals did not show signs of poisoning; their weights and histopathological examinations were normal.

Safepharm Laboratories, Ltd. (1997a) investigated the acute oral toxicity of Polyethylene (average molecular weight of 450) in 10 male and female Sprague-Dawley CD strain rats (201 to 223 g). The rats were fasted and then given a single oral dose of Polyethylene as a suspension in arachis oil BP at a dose of 2000 mg/kg body weight. The animals were observed for 14 days and then killed and underwent necropsy.

During the experimental period, no rats died or had signs of systemic toxicity; they did show an expected gain in bodyweight. Necropsy revealed no abnormalities. The LD_{50} was determined to be greater than 2000 mg/kg body weight (Safepharm Laboratories, Ltd. 1997a).

Subchronic Toxicity

Lefaux (1968) fed male and female rats diets of 1.25%, 2.50%, and 5.00% Polyethylene for 90 days. No adverse effects were seen and the molecular weight of polyethylene was not specified for the study.

Dermal Irritation and Sensitization

As noted earlier, Baker Petrolite (2004) stated that their trade name Polyethylene, PERFORMALENE 400, showed no indication of toxicity, irritation, or sensitization.

Dermal Irritation

Safepharm Laboratories, Ltd. (1997b) tested the acute dermal irritation of Polyethylene (average molecular weight of 450) on three New Zealand white rabbits weighing 2.77 to 2.94 kg and 12 to 16 weeks old. Each rabbit was clipped free of fur from the dorsal flank area the day before testing. Polyethylene (0.5g) was administered with 0.5 ml of distilled water to the skin and occluded with a 2.5-cm^2 patch. Four hours after application, the patch was removed and the area was examined 1, 24, 48, and 72 h later. Polyethylene caused a primary irritation index of 0.0, according to the Draize index. No corrosive effects were noted.

Safepharm Laboratories, Ltd. (1997f) also tested the acute dermal irritation of Polyethylene with an average molecular weight of 655 utilizing the same procedure described above. Three New Zealand white rabbits, aged 12 to 16 weeks and weighing 2.40 to 2.75 kg, were tested. Erythema and eschar formation, as well as edema, were evaluated on a scale of 0 to 4. Polyethylene caused slight erythema at one treated site at the 24-h observation. No irritation was observed at the other two treated sites and no corrosive effects were noted during the study. The primary irritation index was calculated as 0.2 and Polyethylene was classified as a mild irritant.

Dermal Sensitization

Safepharm Laboratories, Ltd. (1997d) tested the sensitization potential of Polyethylene (average molecular weight of 450) on 34 female albino Dunkin Hartley guinea pigs (299 to 364 g, 8 to 12 weeks old). The left flank of each animal was clipped of hair. The test group had a cotton lint patch saturated with 50% Polyethylene (*w/w*) in arachis oil BP applied to the left flank for 6 h. Guinea pigs in the control group underwent the same procedure with vehicle alone. The first induction was followed by two more inductions at the same site on days 7 and 14, for a total of three 6-h exposures. Twenty-four hours after each induction, erythema and edema were measured on a scale of 0 to 4. On day 28 of the experimental period, the right flank of each guinea pig was clipped. The same day, a challenge patch saturated with 50% Polyethylene (*w/w*) in arachis oil BP was applied to the left flank for 6 h. Also, a patch with 25% Polyethylene (*w/w*) in arachis oil BP was applied to the right flank. Patches were removed after 6 h and erythema and edema was quantified 24 and 48 h later. No reactions were observed after any of the inductions or after the challenge. Polyethylene did not cause sensitization in any of the guinea pigs tested.

Ocular Irritation

Safepharm Laboratories, Ltd. (1997c) tested the acute eye irritation potential of Polyethylene (average molecular weight of 450) on three New Zealand white rabbits weighing 3.00 to 3.18 kg and ages 12 to 16 weeks old. Approximately 66 mg (0.1 ml) of the solid test material was placed in the conjunctival sac of the right eye and the eyelids were held together for about a second. The left eye of each rabbit was left untreated and served as a control. The rabbits' eyes were assessed at 1, 24, 48, and 72 h, as well as 7 days following treatment. Redness, chemosis, and discharge of the conjunctivae were scored, with a maximum score of 20. The iris irritation was scored for a maximum score of 10; also, the degree and area of opacity of the cornea were scored, for a maximum score of 80.

Corneal effects were seen in only one treated eye; diffuse corneal opacity was observed at 24 and 48 h after treatment. Inflammation of the iris was seen in only one treated eye at 24- and 48-h observations. At 1 h after treatment, moderate conjunctival irritation was noted in all treated eyes. At 24 h, moderate and minimal conjunctival irritation was seen in one and two treated eyes, respectively. Moderate conjunctival irritation was observed in one treated eye at 48 h, which decreased in severity to minimal at the 72-h observation. All treated eyes appeared normal at 48 h and 7 days after application. Polyethylene caused a maximum group mean score of 11.0 and was classified as a mild irritant (Safepharm Laboratories, Ltd. 1997c).

Safepharm Laboratories, Ltd. (1997g) also investigated the acute eye irritation potential of Polyethylene with an average molecular weight of 655. Three New Zealand white rabbits weighing 2.50 to 2.83 kg and 12 to 16 weeks old were tested. Approximately 55 mg (0.1 ml) of the solid test material was placed in the conjunctival sac of the right eye and the eyelids were held together for about a second. The left eye of each rabbit was left untreated and served as a control. The rabbits' eyes were assessed at 1, 24, 48, and 72 h, as well as 7 days following treatment. Redness, chemosis, and discharge of the conjunctivae were scored, with a maximum score of 20. The iris irritation was scored for a maximum score of 10; also, the degree and area of opacity of the cornea were scored, for a maximum score of 80. The total irritation score could range from 0 to 110.

Diffuse corneal opacity was observed in one treated eye at both the 24- and 48-h observations. All treated eyes displayed moderate conjunctival irritation 1 h after treatment. At the 24-h observation, one and two treated eyes suffered from moderate and minimal conjunctival irritation, respectively. Minimal conjunctival irritation was observed in all treated eyes at 48 h and in only one eye at 72 h. All treated eyes appeared normal at the 72-h and 7-day observations. Polyethylene produced a maximum group mean score of 11.7 and was classified as a mild irritant to the rabbit eye (Safepharm Laboratories, Ltd. 1997g).

New Zealand white rabbits were tested with 0.1 ml of a product containing 13% (w/v) polyethylene beads (CTFA 2004b). OECD method 405 was utilized for the study. After 1 h, the maximum ocular score was 8/110 with resolution after 48 h. No corneal abrasions were observed. No further details were provided.

GENOTOXICITY

FDA (1996) has reported on the cytotoxic potential of breakdown products from biomaterials, including Polyethylene. Medical grade Polyethylene was incubated for various times, up to 8 weeks under several model physiologic conditions. Although Polyester urethane breakdown products were cytotoxic, spot tests for mutation induction in *Salmonella* and induction of the SOS response in *Escherichia coli* yielded no measurable genotoxic effect.

Safepharm Laboratories, Ltd. (1997e) investigated the mutagenicity of Polyethylene with an average molecular weight of 450 using *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 as well as *E. coli* WP2uvrA$^-$. Each strain was tested at concentrations of 1, 10, 30, 100, 300, and 1000 μg/plate. Aliquots of 0.1 ml of one of the bacterial cultures were dispensed into test tubes, followed by 2.0 ml of molten, trace histidine/tryptophan, supplemented top agar, 0.05 ml of the test material formulation, vehicle (toluene) or positive control and either 0.5 ml of S9 mix or phosphate buffer. The contents of the test tubes were mixed and evenly distributed on Vogel-Bonner Minimal agar plates. All of the plates were incubated at 37°C for 48 h.

Polyethylene did not increase the mutation frequency above background in any strain at any concentration. No toxicity was observed in any strain of bacteria used (Safepharm Laboratories, Ltd. 1997e).

CARCINOGENICITY

In its 1979 assessment, the International Agency for Research on Cancer (IARC) could not, due to lack of data, draw a conclusion on the carcinogenic effects of Polyethylene on humans (IARC 1979). In 1987, IARC listed Polyethylene as a group 3 agent, all of which are "not classifiable as to carcinogenicity in humans" due, most commonly, to inadequate evidence of carcinogenicity in humans and inadequate or limited evidence in experimental animals (IARC 1987).

Solid State Carcinogenesis

Due to the extensive medical use of Polyethylene, there are numerous studies on the solid state carcinogenic effect of Polyethylene, particularly in rats. Selected studies are described below.

Bering et al. (1955) investigated tumor incidence in rats after implantation of pure Polyethylene. Wistar and Hisaw (originally from Wistar stock) rats were used, 50 of each strain and equal numbers of each sex. An additional 50 Hisaw rats were used as a control group; however, of the original 150 rats, 59 were victims of cannibalism, leaving 91 surviving rats. Of the remaining rats, 28 were controls (14 female, 14 male), and of the test subjects, 37 were Hisaw strain (20 female, 17 male), and 26 were Wistar strain (13 female, 13 male). Pure Polyethylene squares (1.5 to 2 cm^2) were aseptically implanted subcutaneously in the abdominal wall and subgaleally over cranial defects in the test subjects. The control group was subjected to an identical surgical procedure. All surviving rats were killed 25 months after the surgery.

Sixteen tumors developed in the test group. Eight were considered unrelated to the Polyethylene; seven were breast tumors and one was a hepatocarcinoma. Of the eight tumors resulting from the Polyethylene, six were found in the abdomen and two in the skull. Seven of the tumors appeared in the Hisaw strain rats, whereas only one developed in the Wistar rats. Tumors developed in five female test rats and three males. Five rats of the control group also developed tumors: four in the breast and one carcinoma of the bowel. A 12.7% incidence of fibrosarcoma in the test rats was reported (Bering et al. 1955).

Oppenheimer et al. (1961) evaluated the carcinogenic effects of powdered Polyethylene and compared these results to those of Polyethylene films. Glass coverslips (1.8 cm diameter) were imbedded subcutaneously in the right and left abdominal walls of ninety Wistar rats. After 4 months, four test groups were created by either removing the coverslip or leaving it in and/or introducing glass or Polyethylene powder into the pocket created by the glass coverslip. These four groups were Polyethylene powder with coverslip, glass powder with coverslip, Polyethylene without coverslip, glass powder without coverslip. The two control groups included subjects with and without cover slips, all without powder. Although not directly stated, groups were most likely made up of 15 rats in each of the six groups.

Those with Polyethylene powder and the coverslip remaining developed five tumors whereas those with Polyethylene but without the coverslip developed only one tumor. In the glass powder and coverslip group, six tumors occurred, whereas in the glass powder without coverslip group, no tumors developed. The control group with the coverslip had six tumors and those with the coverslip removed developed no tumors. The authors concluded that implantation of Polyethylene powder does not produce tumors, thus plastics do not chemically invoke carcinogenesis. Rather, they stated that tumor production is a physical reaction to imbedded plastic films (Oppenheimer et al. 1961).

Nakamura et al. (1994) compared the tumorgenicity of medical-grade Polyethylene and poly-L-lactide (PLLA) plates. One hundred and forty-five male KBL Wistar rats were used; they were 11 weeks old and averaged 400 g in weight. Implants of Polyethylene and PLLA were prepared, sized at 20 × 10 × 1 mm, and inserted subcutaneously in the back skin. Fifty were implanted with PLLA, 50 with Polyethylene, 30 controls underwent a sham operation, and 15 were used for sequential harvesting of PLLA plates. After 24 months, any survivors were killed and examined.

In the PLLA group, tumors occurred in 22 rats (2 were ectopic and unrelated to the implants) and in the Polyethylene group, 23 developed tumors (2 of these were unrelated to the implants). The control group had no tumors (Nakamura et al. 1994).

CLINICAL ASSESSMENT OF SAFETY

Case Reports

Two cases were discussed by Smahel et al. (1977) on the long-term reaction to Polyethylene strips implanted for breast augmentation. In each case, the fibrin-covered strips were closely packed and were 1.5 to 2 mm wide, up to 1 mm long and 0.07 mm thick. The first case was a 44-year-old woman who had the operation 11 years earlier. She had been healthy until she had fallen on her left breast, and later, her right breast. After the trauma, both breasts were enlarged and deformed. On histological examination dense collagen fibers containing histiocytes surrounded each breast capsule. Between the Polyethylene strips were numerous macrophage and giant cells containing clear vacuoles or amorphous material, signifying the breakdown of Polyethylene.

In the second case, a 34-year-old woman had her augmentation 7 years earlier. Since the surgery, her breasts had been hard and deformed. On histological examination Polyethylene strips were surrounded by dense collagenous tissue and sporadic macrophages and giant cells, indicating a prolonged interaction (Smahel et al. 1977).

Roberts and Taylor (1990) reported a case of adenocarcinoma of the breast associated with Polyethylene strips used for augmentation. A woman who had a bilateral breast augmentation at 25 years of age developed difficulties at 58 years of age. There was no family history of breast disease. She was experiencing discomfort in the right axillary tail and examination revealed a fullness in this area. A sonomammogram detected two small benign nodules, which did not change over the following the 4-month examination period. However, 9 months later, the patient returned with increased discomfort and a more prominent lump. Aspiration cytology revealed malignant cells and a mastectomy was performed. The tumor appeared to be developing next to a fibrous capsule surrounding the Polyethylene strips. On histological examination a ductal carcinoma had passed through the fibrous capsule and came in contact with the Polyethylene strips.

Occupational Exposure Case Reports

Akhmetova (1977) evaluated the eyes of workers at factories producing synthetic ethyl alcohol and high-pressure Polyethylene. The most prominent substances, found at the maximum allowable concentration (MAC; 50 mg/m^3), were unsaturated hydrocarbons of the ethylene series. Eyes of 229 workers, age 20 to 40, were examined and compared to those of 173 workers who did not come into contact with workplace toxicants. Forty percent of the test group showed signs of hyperemia of the palpebral conjunctiva, which was more predominant in full-time permanent workers. The average gauges of the retinal vessels was significantly larger in exposed workers at Polyethylene factories than the control group. The diameter of the vessels increased after a year and then peaked after 4 to 5 years of exposure. Workers in the Polyethylene industry had an average intraocular pressure of 11.9 $\pm$ 0.31 mm Hg compared to controls at 13.2 $\pm$ 0.18 mm Hg. The authors attributed this decrease to a reduction in the production of aqueous humor.

Czirjak et al. (1987) reported progressive systemic sclerosis in patients exposed to chemicals, one of whom was a synthetic materials–processing artisan believed to have been exposed to Polyethylene and ethylene by inhalation. The 59-year-old woman was exposed to these suspected agents from ages 46 to 55. At 57, her first symptoms appeared and continued, including proximal scleroderma, Raynaud phenomenon, joint involvement, pulmonary manifestation, and esophageal involvement.

An initial report of one brain and five lymphopoietic cancer deaths of employees at a petrochemical plant in Texas prompted a series of epidemiological studies to investigate the possible excessive mortality rate (National Toxicology Program [NTP] 1983). A regional case ascertainment did not show any further deaths but other studies showed that these five cases of lymphopoietic cancer (specifically Hodgkin's disease) deaths were in excess. Further, a case-control study revealed a link between the deaths due to Hodgkin's disease and work in an area of the plant dealing with Polyethylene production. All five cases had, at one time, been assigned to either the high- or low-density Polyethylene areas of the plant. Although this association was established, the author pointed out that the last Hodgkin's disease death occurred in 1966 and despite an increased Polyethylene production at the plant, no further cases were reported.

In a later report, Robinson et al. (1982) noted that workers making Polyethylene are often exposed to the fumes from the thermal degradation of Polyethylene. Among these are some allergens and irritants, including acrolein, formaldehyde, hydrocarbons, carbon monoxide and possible free radicals, and soot.

Clinical Testing

Ober et al. (1968) examined the endometrial morphology of 209 women in whom a variety of Polyethylene intrauterine devices (IUDs) had been implanted. All of the women had been using an IUD from 1 day to 105 months. Ninety-six were asymptomatic, with an average age of 32.3 years. There were 112 symptomatic subjects, with an average age of 32.0 years. Of the 209 samples taken, 200 were viable. Of the 93 asymptomatic subjects, 9.7% had significant lesions, 50.5% showed minor changes, and 40% were normal. Significant lesions were "those biopsies in which a diffuse inflammatory process was detected, as well as those biopsies which revealed other intrinsic endometrial abnormalities."

In the 107 biopsies of symptomatic women 25.2% had significant lesions, 45.8% had minor lesions, and 29% were normal. Two patients had squamous metaplasia of the endometrium and one had atypical glandular hyperplasia. The incidence of the human papillomavirus (HPV) was not evaluated. The authors stated that although conclusions from these results cannot be made, the occurrence of squamous metaplasia suggests that long-term observation of women using polyethylene uterine devices would be beneficial (Ober et al. 1968).

In a later study, Ober et al. (1970) investigated the endometrial changes in women after long-term use of a specific Polyethylene IUD, the Lippes loop. Endometrial biopsy specimens were collected from 393 women who had used the Lippes loop for 18 months or longer. Of the 281 asymptomatic women who used the device for 36 months or more, only 2.5% had significant lesions. Of the 54 symptomatic women who used the device for 18 to 35 months, 20.4% of these had significant lesions. The other 58 who were symptomatic used the device for 36 months or more and 41.4% of them had inflammatory lesions. The authors concluded that the role of squamous metaplasia and the possible development of endometrial neoplasms in women with this Polyethylene IUD could not be assessed from these data.

Dermal Sensitization

In a repeat insult patch test, 201 volunteers were induced with nine consecutive administrations of a rinse-off product containing 13% (*w/v*) polyethylene beads (CTFA 2004b). Induction patches were applied for 48 h at a time. There was a rest period of 10 to 14 days between the induction and challenge phases. A challenge patch was applied to the induction site for 48 h and evaluated at 48 and 96 h. At the same time, a 48-h occlusive patch was applied to an untreated site and evaluated at 48 h after application. Irritation was measured on a 0–5 grading scale. No irritation was observed with any of the induction patches. The challenge patch produced a sensitization reaction in one subject with a score of +1; the patch applied to the new site also caused a +1 irritation score. However, a +1 score was not considered clinically significant and the investigators concluded that the product has a low irritation and sensitization potential. No further details were provided.

SUMMARY

Polyethylene is an ethylene polymer used for a variety of purposes in cosmetics, including as an abrasive, adhesive, binder or bulking agent, an emulsion stabilizer, a film former, an oral care agent, and as a nonaqueous viscosity-increasing agent. Polyethylene is also used in food packaging materials and medical products, including prosthetics.

Cellular and tissue responses to Polyethylene, determined as part of implant biocompatibility testing, include fibrous connective tissue build-up around the implant material that varies as a function of the physical form of the impant material. Specific assays for osteoblast proliferation and collagen synthesis demonstrated a reduction as a function of exposure to Polyethylene particles that is inversely related to particle size. The effect of Polyethylene particles on monocyte-derived macrophages, however, had a stimulatory effect, prolonging the survival of these cells in culture.

The LD_{50} for Polyethylene (average molecular weight of 450) in rats (201 to 223 g) was found to be >2000 mg/kg, and in Polyethylene with an average molecular weight of 655, the LD_{50} was determined as >5.0 g/kg. Toxicity testing in rats showed no adverse effects at doses of 7.95 g/kg or at 1.25%, 2.50%, or 5.00% in feed for 90 days.

Dermal irritation studies on rabbits in which 0.5 g of Polyethylene (average molecular weight of 450) was administered in 0.5 ml of water caused no irritation or corrosive effects. When the same procedure was used to test Polyethylene with an average molecular weight of 655, a primary irritation index score of 0.2 was found and Polyethylene was classified as a mild irritant. Polyethylene (average molecular weight of 450) did not cause dermal sensitization in guinea pigs tested with 50% Polyethylene (*w/w*) in arachis oil BP. In a repeat insult patch test of 201 volunteers, a product containing 13% Polyethylene beads was tested in a series of nine consecutive administrations. There was no irritation observed with any of the induction patches. Challenge patches produced only a slight response in one subject and the investigators concluded that Polyethylene has a low irritation and sensitization potential.

Polyethylene (molecular weight of 450) was tested as a solid material (66 mg) in the eyes of rabbits. The test substance caused a maximum group mean score of 11.0 and was classified as a mild irritant. All treated eyes appeared normal 48 hours after application. The same procedure, with 55 mg of Polyethylene of average molecular weight of 655 was carried out on white rabbits. The mean maximum group score produced by Polyethylene was 11.7 and it was classified as a mild irritant. All treated eyes appeared normal 72 h after treatment. When white rabbits were tested with 13% Polyethylene beads, the maximum ocular score was 8/110 with resolution after 48 h and no corneal abrasions were observed.

Genotoxicity testing was negative in two bacterial studies. Numerous investigations on the tumor production of Polyethylene implantation have produced mixed results. Polyethylene causes tumors in rats implanted with squares of the test substance; however, testing involving implanting coverslips and powdered Polyethylene suggest that tumors are caused by the physical reaction to imbedded plastic films and not the Polyethylene itself. IARC lists Polyethylene as "not classifiable as to carcinogenicity in humans." No toxicity was observed in any of the strains tested.

There have only been a few cases of reactions to the implantation of Polyethylene in humans. In the three published accounts, Polyethylene strips used for breast augmentation caused increased histological activity around the implant.

There have also been occupational case reports on ocular irritation and systemic sclerosis in workers exposed to Polyethylene. Such workers are also exposed to other irritants.

Clinical testing of intrauterine devices made of Polyethylene failed to conclusively identify statistically significant adverse effects, although squamous metaplasia was observed in treated women.

DISCUSSION

Because of the mostly large size of the Polyethylene polymers used in cosmetics, the Cosmetic Ingredient Review (CIR)

Expert Panel did not expect significant dermal absorption of and systemic exposure to Polyethylene itself.

The Panel was concerned that information on impurities pertaining to residual reactants from the polymerization process were not available. The Panel considered the processes by which low-density Polyethylene is made from the catalyzed polymerization of ethylene. In the United States, ethylene is 99.9% pure. The other 0.1% includes ethane, propylene, carbon dioxide, carbon monoxide, sulfur, hydrogen, acetylene, water, and oxygen. The Panel believed that the concentration of these impurities, or potentially toxic hexanes, in any final polymer would be so low as to not raise toxicity issues. Although it was reported that one process used to cross-link Polyethylene uses an organic peroxide, this process is not currently used, so there is no safety concern regarding the possible presence of organic peroxides. Safety tests of cosmetic-grade Polyethylene have consistently failed to identify any toxicity associated with residual catalyst.

The Panel was concerned that the only genotoxicity data available were nonmammalian, but taking this information in concert with the absence of any chemical carcinogenicity in implant studies suggests no genotoxic mechanism for carcinogenicity. The solid state carcinogenicity effect was not seen as relevant for Polyethylene as used in cosmetics. The available data support the conclusion that Polyethylene is safe for use in cosmetic formulations in the practices of use and concentrations described.

CONCLUSION

The CIR Expert Panel concluded that Polyethylene is safe for use in cosmetic products in the practices of use and concentration as described in this safety assessment.

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Final Report of the Cosmetic Ingredient Review Expert Panel on the Safety Assessment of Polyisobutene and Hydrogenated Polyisobutene as Used in Cosmetics[1]

Polyisobutene and Hydrogenated Polyisobutene are homopolymers of isobutene. These ingredients are produced in a wide range of molecular weights. Polybutene is a chemically related cosmetic ingredient previously determined to be safe as used in cosmetic products. Polyisobutene is used in cosmetic products as a binder, film former, and nonaqueous viscosity-increasing agent. Hydrogenated Polyisobutene functions as a skin-conditioning agent—emollient and nonaqueous viscosity-increasing agent with a wide range of uses in cosmetic formulations. The estimated octanol water partition coefficient for Hydrogenated Polyisobutene and Polybutene is log K_{ow} of 13.27 and the estimated water solubility was 5.6×10^{-3} ng/L for Hydrogenated Polyisobutene and Polybutene. Acute oral toxicity testing demonstrated no effects other than lethargy in one rat study. The oral LD_{50} was >5.0 g/kg in rats. No short-term or subchronic animal toxicity data were available. A 2-year chronic oral toxicity study of Polybutene revealed no gross or microscopic pathological changes, and no changes in body weights or food consumption, hematological results, urology, or tumor formation that could be correlated with Polybutene ingestion, except that in the 20,000 ppm group, three out of six males that died between weeks 17 and 24 exhibited hematuria. In a 2-year chronic oral toxicity study of Polybutene in Beagle dogs, no abnormalities in body weight, food consumption, survival, behavioral patterns, hematology, blood chemistry, urinalysis, liver function, gross and histopathologic examinations, or organ weights and ratios were reported. In a three-generation reproductive study in Charles River albino rats that ingested Polybutene, none of the animals in successive generations differed from controls with regard to weight gain, litter size, the number of stillborn, and the number of viable pups during lactation. The survival, body weights, and reactions of test animals were comparable to those of controls. Neither Polyisobutene nor Hydrogenated Polyisobutene were ocular irritants, nor were they dermal irritants or sensitizers. Polyisobutene was not comedogenic in a rabbit ear study. Polyisobutene did not induce transformation in the Syrian hamster embryo (SHE) cell transformation assay, but did enhance 3-methylcholanthrene–induced transformation of C3H/10T1/2 cells. In a carcinogenicity study in mice, Polyisobutene was not carcinogenic, nor did it promote the carcinogenicity of 7,12-dimethylbenz(α)anthracene. Clinical patch tests uncovered no evidence of dermal irritation and repeat-insult patch tests with a product containing 4% Hydrogenated Polyisobutene or 1.44% Hydrogenated Polyisobutene found no reactions greater than slight erythema. These products also were not phototoxic or photoallergenic. The product containing 4% Hydrogenated Polyisobutene was not an ocular irritant in a clinical test. The Cosmetic Ingredient Review (CIR) Expert Panel recognized that there are data gaps regarding use and concentration of these ingredients. However, the overall information available on the types of products in which these ingredients are used and at what concentrations indicate a pattern of use, which was considered by the Expert Panel in assessing safety. Although there is an absence of dermal absorption data for Polyisobutene and Hydrogenated Polyisobutene, the available octanol water partition coefficient data and the low solubility in water suggest very slow absorption, so additional data are not needed. Gastrointestinal absorption is also not a major concern due to the low solubility of these chemicals. Although one in vitro study did report that Polyisobutene did promote cellular transformation, a mouse study did not find evidence of tumor promotion. Because lifetime exposure studies using rats and dogs exposed to Polybutene failed to demonstrate any carcinogenic or tumor promotion effect, and a three-generation reproductive/developmental toxicity study produced no adverse effects, the CIR Expert Panel does not believe these large, mostly insoluble polymers present any risks in the practices of use and concentration as described in this safety assessment.

INTRODUCTION

This report presents available information pertinent to the assessment of the safety of Polyisobutene and Hydrogenated Polyisobutene as cosmetic ingredients.

An earlier safety assessment of the chemically related ingredient, Polybutene, was published in 1982 (Elder 1982) and was re-reviewed in 2002, at which time a "safe as used" conclusion for this ingredient was confirmed (Andersen 2005). Information on Polybutene has been added to this report in further support of the safety of Polyisobutene and Hydrogenated Polyisobutene, based on its similarities in definition and structure to the isobutene isomer.

CHEMISTRY

Definition and Structure

Polyisobutene

Iversen (1990) stated that Polyisobutene is a pentamer of isobutylene, a highly branched molecule. Parslew et al. (1996) characterized Polyisobutene as the polymer of isobutene,

[1]Reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel. This report was prepared by CIR staff person Valerie C. McLain. Address correspondence to her at Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036, USA.

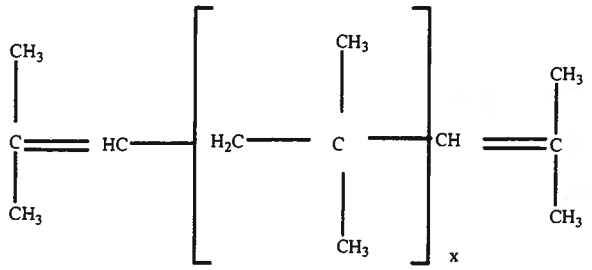

FIGURE 1
Polyisobutene.

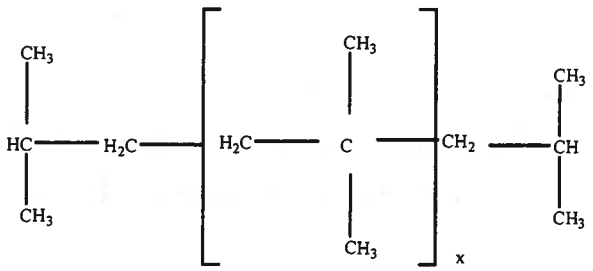

FIGURE 2
Hydrogenated Polyisobutene.

a long chain aliphatic hydrocarbon, with varying molecular weights.

Polyisobutene (CAS no. 9003-27-4) is defined in the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2006) as the homopolymer of isobutylene. Polyisobutene conforms generally to the structure shown in Figure 1. Technical/other names for Polyisobutene include

- Isobutene Homopolymer;
- Isobutylene Homopolymer;
- 2-Methyl-1-Propene, Homopolymer;
- Permethyl 108A;
- Polyisobutylene;
- 1-Propene, and
- -2-Methyl-, Homopolymer.

Trade names (manufacturer) include

- AEC Polyisobutene (A & E Connock);
- Creasil IC (C.I.T.);
- Creasil I.P. (C.I.T.);
- ESP PIB 0611 (Earth Supplied Products);
- ESP PIB 731 (Earth Supplied Products);
- ESP PIB 5011 (Earth Supplied Products);
- Permethyl 104A (Presperse);
- Permethyl 106A (Presperse);
- Permethyl 108A (Presperse); and
- Rewopal PIB 1000 (Degussa Care Specialties).

Trade name mixtures containing Polyisobutene include: Fancorsil P (Fanning) and Simulgel EPG (SEPPIC).

Hydrogenated Polyisobutene

In the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2006), Hydrogenated Polyisobutene (CAS no. 68937-10-0) is defined as a branched-chain aliphatic hydrocarbon. Hydrogenated Polyisobutene conforms generally to the structure shown in Figure 2. Trade names (manufacturer) for Hydrogenated Polyisobutene include

- AEC Hydrogenated Polyisobutene (A & E Connock);
- CREASIL ISO 20 (C.I.T.);
- CREASIL ISO 30 (C.I.T.);
- CREASIL ISO 40 (C.I.T.);
- CREASIL ISO 50 (C.I.T.);
- Fancol Polyiso 200 (Fanning);
- Fancol Polyiso 250 (Fanning);
- Fancol Polyiso 275 (Fanning);
- Fancol Polyiso 300 (Fanning);
- Fancol Polyiso 450 (Fanning);
- Fancol Polyiso 800 (Fanning);
- Keteol S (Prod'Hyg);
- MC 300 (Sophim);
- Panalane H-25E (Amoco Chemical);
- Panalane H-300E (Amoco Chemical);
- Panalane L-14E (Amoco Chemical);
- Panalane L-14E (Lipo);
- Panalane H-300 (Lipo);
- Polysynlane (NOF);
- PRISORINE 3758 (Uniqema Europe); and
- Squatol S (LCW).

Trade name mixtures containing Hydrogenated Polyisobutene include

- Cellini Blue (Engelhard Corp.);
- Cellini Coral (Engelhard Corp.);
- Cellini Green (Engelhard Corp.);
- Cellini Red (Engelhard Corp.);
- Cellini Yellow (Engelhard Corp.);
- Covascreen TI (LCW);
- Covascreen TIYO (LCW);
- Creagel RT PA/ISO (C.I.T.);
- CREASIL ISO 10 (C.I.T.);
- CREASIL ISO 170 (C.I.T.);
- CREASIL ISO 300 (C.I.T.);
- CREASIL ISO 325 (C.I.T.);
- CREASIL ISO 3400 (C.I.T.);
- CREASIL ISO 5000 (C.I.T.);
- DS-TAPS solution (5%) (Doosan);
- Emulzome (Exsymbol);
- Heliogel (Advanced Beauty);
- Jeechem HPIB (Jeen);
- Liant TW 406 (LCW);
- Liant TW 729 (LCW);
- Liant TW 876 (LCW);

- Oxyde de Zinc micropur Covasil S/Squatol S (LCW);
- PEC- 1414 (Sud-Chemie, United Catalysts);
- Polymoist Mask (Cognis Deutschland);
- Polysynlane Gel (Collaborative Labs);
- PW Covasil S1/Squatol S (LCW);
- Questamix H (Quest International);
- Versagel ME (Penreco); and
- Vitaphyle ACE (LCW).

Polybutene

According to the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2004), Polybutene (CAS no. 9003-28-5 or 9003-29-6) is defined as the polymer formed by the polymerization of a mixture of iso- and normal butenes. It conforms to the empirical formula: $(C_4H_8)_x$. Indopol® is a trade name for polybutene.

Physical and Chemical Properties

Polyisobutene

According to the *Kirk-Othmer Concise Encyclopedia of Chemical Technology* (Kresge1999), Polyisobutene is produced in a wide range of molecular weights. However, this author did not provide the specific molecular weight ranges.

In a review article, Tan et al. (1999) stated that polyisobutenes have a regular structure of a carbon-hydrogen backbone with only terminal unsaturation, which results in chemical inertness and good resistance to weathering, aging, heat, and chemicals. Polyisobutene is soluble in typical aliphatic and aromatic hydrocarbon solvents due to their highly paraffinic and nonpolar nature, but are insoluble in common alcohols, esters, ketones, and other oxygenated solvents. It was also stated by these authors that the higher the molecular weight of the polyisobutenes, the lower the permeability; however, no further details were mentioned. The low-molecular-weight polyisobutenes are very viscous, soft, and tacky semiliquids, and the high-molecular-weight grades are tough and elastic rubbery solids.

Infrared transmission values for Polyisobutene are shown in Table 1 (Nakano et al. 2001).

According to AzoM™ (2004), Polyisobutene, also known as butyl rubber, is a synthetic rubber or elastomer first commercialized in 1943. Key properties of Polyisobutene include air tight and gas impermeable; flexibility; good weathering resistance; resistance to ozone; good vibration damper; and biocompatible.

Additional reported physical and chemical properties of Polyisobutene are presented in Table 2.

Presperse Incorporated (2004) stated specifications for Permethyl 104A, a trade name for Polyisobutene, as shown in Table 3.

Unpublished data from the Cosmetic, Toiletry, and Fragrance Association (CTFA) (2006b) provided physical and chemical properties of Polybutene (Indopol® ; molecular weight varies from 910 for grade H-100 to 1300 for grade H-300E) and Hydrogenated Polyisobutene (Panalane® ; lowest molecular weight of 370 for Panalane L-14E), including their lack of water solubility and extreme hydrophobicity of the substances. The water solubility for these polybutenes was estimated at 5.6×10^{-9} mg/L. The log K_{ow} is estimated to be 13.27, which categorizes these substances as super hydrophobic and therefore biologically unavailable. Note, Indopol® and Panalane® conform to the requirements of the European Cosmetics Directive 76/768/EEC and its amendments.

TABLE 1
Infrared transmission values for Polyisobutene (Nakano et al. 2001).

Peak no.	Wave number	Transmittance (%)
1	924	49.08
2	951	46.85
3	1165.1	58.79
4	1230.7	15.4
5	1365.8	8.83
6	1388.9	13.07
7	1471.9	11.39
8	2681.4	75.41
9	2716.1	69.9
10	2733.5	68.37
11	2897.4	7.07
12	2953.4	5.07
13	4334.6	74.39

Hydrogenated Polyisobutene

Davis (1976) described a trade name polymer, Polysynlane (Hydrogenated Polyisobutene), as a novel synthetic substitute for squalene. Selectively polymerizing isobutene results in a saturated isoparaffin that contains virtually no ring structures. After hydrogenating and refining, the product is mainly the polymer ($C_{24}H_{50}$), which closely resembles natural squalene in both physical and chemical properties.

TABLE 2
Physical and chemical properties of Polyisobutene.

Property	Description	Reference
Appearance	White to yellowish or pale rubbery solid	Woods 1999
Odor	Slight rubber/ petroleum odor	Woods 1999
Specific gravity	0.92	Woods 1999
Solubility in water	Insoluble	Exxon Mobil Chemical Co. 2003
Viscosity	120	Amoco Chemical Company 2005

TABLE 3
Specifications for Permethyl 104A (Polyisobutene) (Presperse Incorporated 2004).

Appearance	Water-clear
Color Pt/Co	70 max.
Flash point	165°C or 329°F min.
Kinematic viscosity at 100°C	210–250 cSt
MW number average	900 min.
Water	50 mg/kg max.

Like natural squalene, the synthetic material is a colorless, odorless, tasteless liquid, miscible with vegetable and mineral oils, organic solvents, and lipophilic substances. It is also nonrancid, nondrying, nonoxidizing, and noncongealing. It is easily emulsified and combines good spreading and penetrating properties with an excellent feel. For the perfumer, according to this author, it has exceptionally good oxidation and chemical stability. Table 4 describes the compatibility of Polysynlane (Hydrogenated Polyisobutene) with other materials and Table 5 compares properties of Polysynlane and squalene (Davis 1976).

According to Buekens et al. (1998), Polyisobutene decomposes by both end-chain scission (broken up from the end groups successively yielding the corresponding monomers) and random-chain scission (broken up randomly into fragments of uneven length).

Uniquema (2004) provided a product specification sheet on Prisorine 3758 Squalene (Synthetic), which is a trade name for Hydrogenated Polyisobutene, data from which are given in Table 6.

Sophim (2004) reported that Hydrogenated Polyisobutene is available in two grades—Sophim MC 30 (liquid) and Sophim MC 300 (viscous). MC 300 is an effective waterproofing agent and MC 30 has excellent spreadability and fast penetration into the skin. Table 7 describes the suppliers specifications for these trade name Hydrogenated Polyisobutenes. In addition, this supplier indicated that these trade name Hydrogenated Polyisobutenes are soluble in many sunscreen filters, miscible with lipophilic substances, totally stable versus oxidation, stable across the pH range of use, and have a soft, nongreasy feel.

TABLE 4
Compatibility of Polysynlane (Hydrogenated Polyisobutene) with various materials (Davis 1976).

	Polysynlane		
Materials	10%	50%	90%
Castor oil	C[a]	IC[b]	IC
White oil	C	C	C
Soybean oil	C	C	C
Stearic acid	C	C	C
Soybean oil fatty acid	C	C	C
Beeswax	C	C	C
Coconut oil fatty acid	C	C	C
Polyethylene glycol	IC	—[c]	—

[a]C, compatible; [b]IC, incompatible; [c]—, not determined.

NOF Corporation (2005) reported that Parleum/Polysynlane (Hydrogenated Polyisobutene) has a molecular weight of 350, with the level of molecular weight less than 1000 daltons as 100%. This company provided no data on the level of monomers, because the monomer is in the form of a gas and it is believed there is no remaining monomer in the product. Also, no data were provided on the stability of the product at acidic pH.

Additional reported physical and chemical properties of Hydrogenated Polyisobutene are presented in Table 8.

The Fanning Corporation (2005), a manufacturer of various Hydrogenated Polyisobutene products, sold under the Fancol™ trade name, reported the average molecular weights as presented in Table 9.

CTFA (2006a) reported that Panalane L-14E has a number average (M_n) molecular weight of 370.

CTFA (2006b) also reported that Panalane® trade name products include Hydrogenated Polyisobutene products Panalane® L-14E and H-300E. Panalane® L-14E would be the grade with the lowest molecular weight. The typical number average (M_n) molecular weight for L-14E by a gel permeation chromatography method is 370. The M_n value for the higher molecular weight H-300E was 1300.

Panalane® is a hydrophobic compound whose accurate measurement of water solubility under experimental conditions is impractical. Therefore, determinations of water solubility and of log K_{ow} are more practically made by modeling with programs. For a discrete unit ($C_{28}H_{56}$) representing both the smallest and average molecular weight (392 dalton) of a polymerized chain of five subunits, the water solubility was estimated at 5.6×10^{-9} mg/L, or 5.6×10^{-6} μg/L, or 5.6×10^{-3} ng/L (0.0056 parts per trillion).

The octanol-water partition coefficient (log K_{ow}) also was modeled. The same assumption as in the modeling of water solubility applied in this case: model of the lowest molecular weight unit (392 daltons) to represent the lowest log K_{ow} calculated at 13.27 (CTFA 2006b).

Polybutene

CTFA (2006b) also reported that Indopol® includes products such as Indopol Polybutene H-100, H-300, and H-1900. The M_n values for the higher molecular weight grades were stated as: H-100, -910; H-300, -1300; and H-1900, -2500.

Hydrogenated Polyisobutene (Panalane®) also is a hydrophobic compound whose accurate measurement of water solubility under experimental conditions is impractical. The water solubility modeled for a discrete unit ($C_{28}H_{56}$) representing both the smallest and average molecular weight (392 dalton) of a

TABLE 5
Properties of Polysynlane (Hydrogenated Polyisobutene) and squalene (Davis 1976).

Properties	Polysynlane, specified	Polysynlane, typical	Natural squalene
Specific gravity (20°C)	0.810–0.830	0.8260	0.805–0.812
Refractive index (n20/D)	1.450–1.460	1.4580	1.4520–1.4525
Freezing point (°C)	Below–30	−50	Approx.−38
Acid value	Below 0.1	0.0	0.25
Saponification value	Below 0.5	0.0	5.0 max
Iodine value	Below 3.5	1.0	5.0 max.

polymerized chain of five subunits was estimated at 5.6×10^{-9} mg/L, or 5.6×10^{-6} μg/L, or 5.6×10^{-3} ng/L (0.0056 parts per trillion).

The octanol-water partition coefficient (log K_{ow}) was modeled using the same assumption as in the modeling of water solubility to yield a calculated log K_{ow} at 13.27 (CTFA 2006b).

Reactivity

One material safety data sheet (MSDS) states that Polyisobutene is stable, incompatible with strong oxidizers, produces CO, CO_2, and hydrocarbons on burning, and should be stored in a cool, dry area (Woods 1999). This MSDS goes on to state that the primary route of entry is dermal and that inhalation and ingestion are unlikely.

A MSDS from BASF Corporation (2003) stated that Polyisobutylene is noncorrosive and is not an oxidizer.

In an MSDS, Amoco Chemical Company (2005) stated that Hydrogenated Polyisobutene is stable, except to note that burning can produce carbon monoxide and/or carbon dioxide and other harmful products.

Method of Manufacture

According to Iversen (1990), commercial, low-viscosity Polyisobutenes are manufactured by polymerization of isobutylene in the presence of a catalyst. The type of catalyst used was not mentioned.

TABLE 6
Prisorine 3758 Squalene (Synthetic) specifications (Uniquema 2004).

	Units	Min/Max
Acid value	mg KOH/g	0.1
Saponification value	mg KOH/g	0.5
Iodine value	g/100 g	3.0
Color APHA	Hazen	20
Viscosity (25°C)	mPa·s	20–70
Odor	—	PASS
Density (20/20°C)	g/cm^3	0.810–0.875
Typical refractive index (N25/D)	—	1.455

According to AzoM™ (2004), Polyisobutene is derived from the monomer isobutylene via cationic vinyl polymerization.

CTFA (2006b) reported that Indopol® and Panalane® polybutenes are synthetic hydrocarbon liquid polymers made by the polymerization of C_4 olefins (primarily isobutene mixed with some n-butene) and are available in a wide range of viscosities for use in numerous applications.

Kresge (1999) described a highly complex mechanism of cationic polymerization of isobutylene (a.k.a. isobutene) and copolymerization of isobutylene with isoprene with Lewis acids. Friedel-Crafts Lewis acid and Bronstead acid coinitiators at low temperatures give an extremely high polymerization rate in hydrocarbon or halogenated hydrocarbon diluents. Isobutylene polymerizes in a regular head-to-tail sequence to produce a polymer having no asymmetric carbon atoms. The glass transition temperature is approximately −70°C.

AzoM™ (2004) reported that Polyisobutene polymers are formed by highly exothermic cationic vinyl polymerization. The use of an initiator or cation was involved, which attracted a pair of electrons from the carbon-carbon double bond, therefore forming a single bond with the initiator. One of the previously double-bonded carbons is then positively charged and will react with another monomer, similarly to the initiator. The process is repeated and the polymer is formed. The polymerization reaction

TABLE 7
Specifications of trade name Hydrogenated Polyisobutenes (Sophim 2004).

Property	MC 30	MC 300
Appearance	colorless, odorless, tasteless	clear, odorless, tasteless
Specific gravity	0.810–0.830	0.880–0.910
Refractive index	1.4500–1.4600	1.4950–1.4990
Viscosity at 40°C	15–25	—
Viscosity at 100°C	—	590–630
Acid value	0.1 max	0.1 max
Iodine value	1.0 max	4.0 max
Saponification	0.5 max	1.0 max

TABLE 8
Physical and chemical properties of Hydrogenated Polyisobutene (Amoco Chemical Company 2005).

Property	Description
Appearance	Clear liquid
Specific gravity	0.88 to 0.93
Solubility in water	Negligible, below 0.1%
Viscosity	636–690 cSt at 210°F (99°C)
Stability	Stable
Boiling point	95°F (35°C)

is usually carried out at temperatures in the range of −100°C to control the reaction rate.

Analytical Methods

According to Powles (1956), the proton magnetic resonance absorption in Polyisobutene has been measured over the temperature range −196°C to 90°C. Due to the close approach of the methyl groups on alternate carbon atoms, there is an unusually large width of the absorption line at the lowest temperatures. The usual reduction in line width associated with reorientation of methyl groups about their C_3 axis is notably absent and supports arguments that the methyl groups are severely interlocked. A reduction in the second moment of the absorption line, which sets in over a range of temperature near −10°C, is associated with chain motion.

Impurities

Parslew et al. (1996) mentioned a Polyisobutene with a molecular mass of 85,000 (Oppanol B 15) with ash content less than 100 ppm (a majority of the ash contains the oxides and silicates of iron, potassium, and sodium). The total heavy metal content was reported to be <1 ppm. A stabilizer (2,6-di-tert-butyl-4-methylphenol), at a concentration of 400 ppm, prevents oxidation.

TABLE 9
Average molecular weights for Fancol™ Polyiso products (Fanning Corporation 2005).

Product	Average molecular weight
Fancol Polyiso 200-CG	216
Fancol Polyiso 250-CG	261
Fancol Polyiso 275-CG	268
Fancol Polyiso 300-CG	326
Fancol Polyiso 450-CG	456
Fancol Polyiso 800-CG	806
Fancol Polyiso 1200-CG	1242

AzoM™ (2004) indicated on its Web site that the typical composition of butyl rubber is 98% Polyisobutene, with the balance being 2% isoprene.

The Fanning Corporation (2005) reported that there are no known impurities (monomers or residual catalysts) in any of the following Fancol™ Polyiso ingredients: Fancol Polyiso 200-CG, Fancol Polyiso 250-CG, Fancol Polyiso 275-CG, Fancol Polyiso 300-CG, Fancol Polyiso 450-CG, Fancol Polyiso 800-CG, and Fancol Polyiso 1200-CG.

NOF Corporation (2004) reported that Parleam, Parleam 4, Parleam LITE, Parleam V, Parleam HV, and Parleam SV (all product names for Hydrogenated Polyisobutene) do not contain the impurities, such as: pesticides, polycyclic aromatic hydrocarbons, dioxine, 1,4-dioxane, ethylene oxide, nitrosamine, free amines, diethanoleamine, triethanolamine, monomers, formaldehyde, sulphite, dimethyl sulphate, ethylene chlorohydrine, monochloro/dichloro acetic acid, octamethylcyclotetrasiloxane (D4), dibutylphthalate, and diethylhexylphthalate.

USE

Cosmetic

According to Davis (1976), Polysynlane (Hydrogenated Polyisobutene) has found wide use as a squalene substitute in both Europe and Japan and is now finding approval in the United States. It is also being considered as an additive to improve the feel of and generally upgrades the spreading and penetrating properties of lotions based on mineral oil and petrolatum and offered on the mass market. This author described uses of this trade name Hydrogenated Polyisobutene in moisturizing skin milk at 6.0%, night cream at 15.0%, and vanishing cream at 7.0%.

Sophim (2004) reported some possible uses of Hydrogenated Polyisobutene in hydrating creams, after shave balms, antiperspirants, color cosmetics, acne creams, hair grooms, sunscreen formulations, lipsticks, hair relaxers, baby care, cleansing creams, and shaving gels.

According to the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and McEwen 2006), Polyisobutene functions as a binder, film former, and nonaqueous viscosity-increasing agent with uses in product categories such as lipsticks and mascara, and Hydrogenated Polyisobutene functions as a skin-conditioning agent—emollient and nonaqueous viscosity-increasing agent with uses in a wide variety of cosmetic product categories.

The most recently available frequency of use data provided by industry to the Food and Drug Administration (FDA 2006) under the voluntary cosmetic registration program (VCRP) are given in Table 10. Concentration of use information in Table 10 was based on an industry survey (CTFA 2006a) of current practice.

Polyisobutene has 30 uses, and a high concentration of 76% in lipsticks as obtained from an industry-wide survey provided by CTFA (2005a). The lowest reported concentration for this ingredient is 0.3% in blushers and foundations.

TABLE 10
Uses and concentrations of Polyisobutene and Hydrogenated Polyisobutene in cosmetics.

Product category (FDA 2006a)	2005 ingredient uses (total number of products in each category [FDA 2006])	2005 concentrations (CTFA 2005a) (%)
	Polyisobutene	
Eye makeup preparations		
Eye shadow	1 (576)	5–25
Eye lotions	—[a] (25)	30
Mascara	8 (195)	5–13
Other eye makeup preparations	2 (152)	1[b]–25
Noncoloring hair preparations		
Hair sprays/aerosol fixatives	2 (275)	—[c]
Shampoos	1 (884)	—[c]
Makeup preparations		
Blushers	1 (245)	0.3
Foundations	—[a] (324)	0.3–3
Lipsticks	12 (962)	4–76
Makeup bases	—[a] (141)	1
Other makeup preparations	2 (201)	4–46
Shaving preparations		
Shaving cream	—[a] (134)	4
Skin care preparations		
Night skin care preparations	1 (200)	—[c]
Suntan preparations		
Suntan gels, creams, and liquids	—[a] (131)	0.5
Total uses/ranges for Polyisobutene	30	0.3–76
	Hydrogenated Polyisobutene	
Baby products		
Lotions, oils, powders, and creams	—[a] (60)	4
Bath preparations		
Oils, tablets, and salts	—[a] (143)	85
Bubble baths	—[a] (215)	3
Soaps and detergents	1 (421)	40
Eye makeup preparations		
Eyebrow pencils	3 (102)	4–38
Eyeliners	29 (548)	0.1–39
Eye shadow	18 (576)	3–40
Eye lotions	1 (25)	—[c]
Eye makeup remover	1 (100)	—[c]
Mascara	5 (195)	0.5–15
Other eye makeup preparations	21 (152)	4–24
Fragrance preparations		
Perfumes	—[a] (235)	10
Powders	—[a](273)	0.8
Other fragrance preparations	5 (173)	—[c]
Noncoloring hair preparations		
Hair tonics, dressings, etc.	—[a] (598)	15
Other noncoloring hair preparations	—[a](277)	17[d]
Hair-coloring preparations		
Other hair-coloring preparations	1 (55)	—[c]

(Continued on next page)

TABLE 10
Uses and concentrations of Polyisobutene and Hydrogenated Polyisobutene in cosmetics. *(Continued)*

Product category (FDA 2006a)	2005 ingredient uses (total number of products in each category [FDA 2006])	2005 concentrations (CTFA 2005a) (%)
Makeup preparations		
Blushers	14 (245)	2–30
Face powders	24 (305)	0.1–5
Foundations	16 (324)	2–47
Lipsticks	318 (962)	0.001–96
Makeup bases	1 (141)	4
Makeup fixatives	5 (20)	—[c]
Rouges	70 (28)	16–50
Other makeup preparations	36 (201)	17–77
Nail care products		
Creams and lotions	1 (15)	3
Polishes and enamels	4 (123)	0.2–0.4
Personal hygiene products		
Underarm deodorants	—[a] (247)	2
Other personal hygiene products	4 (308)	24
Shaving preparations		
Aftershave lotions	1 (231)	4
Shaving cream	2 (134)	4
Other shaving preparations	3 (63)	—[c]
Skin care preparations		
Skin cleansing creams, lotions, liquids, and pads	1 (775)	4–85
Depilatories	—[a] (34)	6
Face and neck skin care preparations	13 (310)	0.8–42
Body and hand skin care preparations	5 (840)	0.5–37
Foot powders and sprays	—[a] (35)	4
Moisturizers	26 (905)	3–4
Night skin care preparations	4 (200)	3–6
Paste masks/mud packs	2 (271)	2–7
Other skin care preparations	10 (725)	8
Suntan preparations		
Suntan gels, creams, and liquids	6 (131)	15
Indoor tanning preparations	1 (71)	—[c]
Other suntan preparations	2 (38)	—[c]
Total uses/ranges for Hydrogenated Polyisobutene	654	0.001–96

[a]No uses reported to FDA in the VCRP.
[b]1% in a concealer.
[c]No use concentrations reported in industry survey.
[d]A hair shine product.

Hydrogenated Polyisobutene has 654 reported uses (FDA 2006) with a wide concentration range of 0.001% to 96% in lipsticks; use concentrations in other product categories fall within that range (CTFA 2005a).

Also given in Table 10 are the current data from the VCRP on the total number of products in each product category, allowing the reader to determine how frequently these ingredients are used in a particular product category. For example in Table 10, 12 of the 962 lipstick products reported to be on the market contain Polyisobutene.

Although uses were voluntarily reported to the FDA VCRP (FDA 2006), in some cases no use concentrations were reported

in the industry survey (CTFA 2006a). For example in Table 10, uses of 4 Polyisobutene were voluntarily reported to the FDA but no use concentrations were reported in the industry survey.

In addition, the industry survey (CTFA 2006a) reported use concentrations in product categories for which no reports had been submitted to the FDA VCRP (FDA 2006). For example in Table 10, no uses were reported in shaving cream, yet a use concentration of 4% was identified. This information suggests that at least one currently marketed shaving cream contains polyisobutene.

CTFA (2006c) provided an indication of the molecular weight of Polyisobutene and Hydrogenated Polyisobutene used in certain product categories as shown in Table 11 (CTFA 2006c).

Polybutene

For comparison purposes, the functions of the related ingredient, Polybutene, include binder, epilating agent, and nonaqueous viscosity-increasing agent (Gottschalck and McEwen 2006). Its reported uses are in lipsticks primarily, but also in mascara, makeup preparations (not eye), eye shadow, eye makeup preparations, foundations, eyebrow pencils, eyeliners, and moisturizing preparations at concentrations ranging from 0.002% to 96%.

Noncosmetic

Iversen (1990) reported that the higher branched polyisobutenes are the most widely used polyolefins in electrical

TABLE 11

Polyisobutene and Hydrogenated Polyisobutene molecular weights as a function of product category (CTFA 2006c).

Ingredient	Product category	Average molecular weights
Polyisobutene	Lipstick	950
Polyisobutene	Shaving cream (aerosol, brushless, and lather)	950
Polyisobutene	Suntan gels, creams, and liquids	950
Hydrogenated Polyisobutene	Baby lotions, oils, powders, and creams	350
Hydrogenated Polyisobutene	Bath oils, tablets, and salts	350
Hydrogenated Polyisobutene	Eyebrow pencil	400; 2650
Hydrogenated Polyisobutene	Eyeliner	350; 2650
Hydrogenated Polyisobutene	Eye shadow	350; 2650
Hydrogenated Polyisobutene	Mascara	350; 920–1000; 1300; 2650
Hydrogenated Polyisobutene	Other eye makeup preparations	400
Hydrogenated Polyisobutene	Perfumes	350
Hydrogenated Polyisobutene	Powders (dusting and talcum)	400
Hydrogenated Polyisobutene	Tonics, dressings, and other hair-grooming aids	350
Hydrogenated Polyisobutene	Other hair preparations (noncoloring)	370
Hydrogenated Polyisobutene	Blushers (all types)	350–400; 2650
Hydrogenated Polyisobutene	Face powders	2650
Hydrogenated Polyisobutene	Foundations	350; 1000; 2650
Hydrogenated Polyisobutene	Lipstick	350–400; 1000; 1300–1345; 2650
Hydrogenated Polyisobutene	Makeup bases	1345
Hydrogenated Polyisobutene	Rouges	1000
Hydrogenated Polyisobutene	Other makeup preparations	1000; 2650; 1300
Hydrogenated Polyisobutene	Nail creams and lotions	350
Hydrogenated Polyisobutene	Nail polish and enamel	350
Hydrogenated Polyisobutene	Aftershave lotions	220; 350
Hydrogenated Polyisobutene	Shaving cream (aerosol, brushless, and lather)	350
Hydrogenated Polyisobutene	Skin cleansing (cold creams, cleansing lotions, liquids, and pads)	350–363
Hydrogenated Polyisobutene	Depilatories	363
Hydrogenated Polyisobutene	Face and neck creams, lotions, and powders	220; 350–370; 400 - 600; 1000
Hydrogenated Polyisobutene	Body and hand creams, lotions, and powders	220; 350–370
Hydrogenated Polyisobutene	Night creams, lotions, and powders	220; 363
Hydrogenated Polyisobutene	Paste masks (mud packs)	350–370
Hydrogenated Polyisobutene	Other skin care preparations	370
Hydrogenated Polyisobutene	Suntan gels, creams, and liquids	350

equipment. In addition, they may be used as raw material for detergents and as lubricants.

Tan et al. (1999) reported that low-molecular-weight Polyisobutene polymers are mainly used as tackifiers to provide tack to the high-molecular-weight Polyisobutene or other adhesive polymers. High-molecular-weight Polyisobutene is used to impart internal strength and flow resistance of pressure-sensitive adhesives.

According to the *Kirk-Othmer Concise Encyclopedia of Chemical Technology* (Kresge 1999), Polyisobutylene has a variety of uses. The low-molecular-weight polybutenes are used as adhesives, sealants, coatings, lubricants, plasticizers, and for the impregnation of electrical cables. Moderate weight Polyisobutylene was among the first viscosity-index modifiers for lubricants. The high-molecular-weight Polyisobutylene is used in the production of unpreserved rubbery compounds, and as an impact additive for thermoplastics.

According to the Household Products Database (2004), John Deere Universal 2 Cycle Oil is an auto product that in liquid form contains 15% to 25% Polyisobutene.

Pharmaceutical Capsules

Nixon et al. (1982) described the effects of Polyisobutene on the properties of ethyl cellulose-walled microcapsules of phenobarbitone sodium. It was concluded that the size and wall thickness changed as the proportion of Polyisobutene increased, which affected the first-order release kinetics of the drug.

Kawashima et al. (1984) reported on a study in which Adriamycin hydrochloride was microencapsulated with ethylcellulose by a phase separation method for developing a controlled release dosage form. The authors also studied the effect of Polyisobutene in the production of a liquid phase and in the drug release properties of the microcapsules. With increasing concentration of Polyisobutene (1% to 3%), the average diameter of the microcapsules decreased. At the low concentration, the resultant microcapsules were agglomerated, which resulted in increasing the size. The microcapsules prepared with 2% Polyisobutene prolonged the drug release from the capsule.

Das (1991) investigated the in vitro drug release profile of theophylline from microcapsules prepared with Polyisobutene as protective colloid, with a view to developing a controlled release dosage form of theophylline. It was found that an optimum concentration of 5% w/w of Polyisobutene gives satisfactory controlled theophylline release profile.

Kristl et al. (1991) described the preparation of ethylcellulose microcapsules containing bacampicillin in which a saturated solution of Polyisobutene in cyclohexane was used in the synthesis. Polyisobutene lowers the solubility of ethylcellulose in cyclohexane. The aggregation of microcapsules decreases by increasing molecular weight of Polyisobutene. When Polyisobutene of high molecular weight is used in the process of microencapsulation, smaller liquid phase droplets are formed and larger liquid phase volume is produced.

Sveinsson et al. (1991) prepared naproxen microcapsules from ethylcellulose and Polyisobutene.

The role of Polyisobutene used as a liquid phase inducing agent in the preparation and assessment of Eudragit RS (ERS) microcapsules (MCs) in trichloroethane (TCE) was studied with isoniazid (INH) as the core material (Barick et al. 1994). Polyisobutene improves the overall efficiency of microencapsulation and in vitro release patterns.

Guo (1994) investigated the surface properties and bioadhesion of buccal patches. Using a two-roll milling method, a new bioadhesive polymer patch formulation for drug controlled delivery, which consisted of Carbopol 934P (CP), Polyisobutene (PIB), and polyisoprene (PIP) was prepared.

Pressure-Sensitive Adhesives

Chiang et al. (1998) described a transdermal delivery system for ketotifen that utilized Polyisobutene as an adhesive with liquid parafin and fatty acids making up the rest of the patch. Adjusting the relative proportion of the paraffin can be used to control the rate of drug delivery.

A review article by Tan et al. (1999) discussed pressure-sensitive adhesives (PSAs) for transdermal drug delivery systems, noting that Polyisobutenes are excellent for use in such devices because of their stability, inertness, and broad acceptance in FDA-regulated applications. Table 12 lists products marketed in the U.S. that use Polyisobutenes as the pressure-sensitive adhesive.

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, Excretion

No data were available on the absorption, distribution, metabolism, or excretion.

Bioaccumulation

According to CTFA (2006b), polybutenes are not bioconcentrated or bioaccumulated by organisms due to their poor water solubility and/ or poor solubility in various organic solvents/dissolved organic matter. Also, the log K_{ow}, estimated from a modeling program, of the lowest molecular weight was approximately 13.27 and the molecular size of 392 Da decreases

TABLE 12

Transdermal drug delivery products that use Polyisobutenes as the pressure-sensitive adhesive (Tan et al. 1999).

Drug	Product	Developer/marketer
Clonidine	Catapres-TTS®	Alza/Boehringer Ingelheim
Estradiol	Estraderm®	Alza/Novartis
Nicotine	Nicoderm®	Alza/SmithKline Beecham
Nitroglycerin	Deponit®	Lohmann/Schwarz Pharma
Scopolamine	Transdermal-Scop®	Alza

the likelihood that these compounds become bioavailable. It is widely accepted that the bioavailability of superhydrophobic chemicals (compounds with log K_{ow}'s greater than 6), such as in these polybutenes, is largely insignificant. Therefore, these authors concluded that polybutene compounds are nonhazardous to the environment.

Biocompatibility

Bergdahi et al. (1974) reported on the biological compatibility of Polyisobutene as a possible new root canal sealer.

Test material was filled into Teflon tubes. A total of 96 soft tissue implants of either Polyisobutene, gutta percha, or AH26 were inserted into the backs of guinea pigs for 3 and 8 weeks. Also, 62 implants of either Polyisobutene or AH26 were placed into the mandible of guinea pigs. After 2 or 12 weeks, the animals were killed.

All three materials exhibited mild tissue irritation after implantation in subcutaneous tissue. However, Polyisobutene was found to be less irritating than the other materials. Following bone tissue implantation, AH26 showed an acceptable tissue compatibility whereas Polyisobutene was rated excellent. The authors concluded that Polyisobutene had very low toxicity and negligible irritating effects of tissues in vivo after implantation (Bergdahi et al. 1974).

ANIMAL TOXICOLOGY

Acute Oral Toxicity

Davis (1976) stated that acute oral toxicity testing using mice resulted in no deaths with a maximum of 89.6 g/kg of Polysynlane (Hydrogenated Polyisobutene).

Product Safety Labs (1987a) evaluated the oral toxicity of a single dose of 5 g/kg Hydrogenated Polyisobutene (Permethyl 104A/105A Blend Aliphatic Hydrocarbon; 900 minimum number average molecular weight). Five male and five female albino Wistar rats, weighing 237 to 270 g, were used in this study. Each rat received the undiluted test material by gavage using a stainless steel intubation needle. The rats were observed at 1, 2, 4, and 6 h after administration and at least once daily thereafter for signs of toxicity and mortality. Body weights were recorded initially and at termination on day 14. No mortalities were observed during the study period; however, all of the animals appeared lethargic after dosing. Overall, all the rats appeared active and healthy from 2 h to termination on day 14. At 1 h, one rat developed irregular respiration and facial staining on days 1 and 2. By day 3, these signs disappeared. All of the animals gained weight during the course of the study.

The Fanning Corporation (1998a) studied the single dose oral toxicity in 10 male Wistar albino rats. The animals were orally dosed with Hydrogenated Polyisobutene (Poly Iso 6-50-DN, clear liquid) at 5.0 g/kg body weight. Mortality and systemic observations were recorded 3 to 4 h after dosing and once daily thereafter for 14 days. The body weights were recorded prior to testing (212 to 242 g). All of the animals survived the 5.0 g/kg oral dose. There were instances of wetness of the anogenital area observed on the day of dosing only. The animals were not examined for gross pathology. The authors concluded that the LD_{50} is greater than 5.0 g/kg body weight. Therefore, the Poly Iso 6-50-DN is nontoxic as defined in 16 CFR 1500.3 (c)(2)(I).

The Fanning Corporation (1998d) studied the single-dose oral toxicity in 10 male Wistar albino rats administered 5.0 g/kg body weight Hydrogenated Polyisobutene (Poly Iso 4-50-EN). The maximum amount of liquid given at one time did not exceed 2.0 ml/100 g of body weight. Mortality and systemic observations were recorded 3 to 4 h post dose and once daily thereafter for 14 days. The animals were not examined for gross pathology. Body weights were recorded pretest (213 to 286 g). All animals survived the 5.0 g/kg oral dose. Wetness of the anogenital area was noted on the day of dosing only. All animals appeared normal from day 1 through day 14. The LD_{50} is greater than 5.0 g/kg of body weight. Therefore, the authors noted that the test material is nontoxic as defined in 16 CFR 1500.3 (c)(2)(I).

Short-Term/Subchronic Toxicity

No short-term or subchronic animal toxicity data were available.

Chronic Toxicity

Polybutene

In the Cosmetic Ingredient Review (CIR) safety assessment of the chemically related ingredient, Polybutene (Elder 1982), a 2-year chronic oral toxicity study of Polybutene H-100 (75% concentrate) in Charles River albino rats was presented. The animals were separated into four groups of 60 (30 males and 30 females per group). The animals were given 0 (control), 800 (0.08%), 4000 (0.40%), or 20,000 (2.0%) ppm Polybutene blended into their regular diets. The rats were monitored for their body weights, mortality and reactions, tumor incidence, and hematologic, urologic, and pathologic changes. After 12 months of testing, five animals from each group were killed for evaluation. No gross or microscopic pathological changes could be correlated with Polybutene ingestion. No significant differences were found after 24 months of feeding in the body weights or weight of food consumption, hematological results, urology, or tumor formation between the animals fed Polybutene and those that were not.

In the 20,000 (2.0%) ppm group, three out of six males that died between weeks 17 and 24 exhibited hematuria. Another male in this group showed similar reactions, but recovered completely within 2 weeks. Necropsies of the three rats revealed that two had clotted blood in the urinary tract, bladder, stomach, and intestines. The third animal, however, revealed no significant gross pathologic changes. No abnormal reactions were noted in any other tested animal.

A 2-year chronic oral toxicity study of Polybutene H-100 (75% concentrate) in Beagle dogs was also summarized by this author. The substance was orally administered daily to three test

groups, each consisting of eight pure-bred Beagle hounds (four males, four females). Each group was given one of the following doses: 40, 200, and 1000 mg/kg body weight (bw), or 0.045, 0.227, and 1.14 ml of test material. An untreated control group consisted of 5 male and 2 female dogs. Complete hematologic studies, blood chemistry, urinalysis, and liver function tests were conducted on the control and the highest dosage group after 90, 180, and 540 days of testing, as well as on all four groups after 360 and 720 days of testing.

Following 1 year of testing, one male and one female from each group were killed. At 2 years, all surviving dogs from all groups were killed and the major tissues and organs were examined. The authors of this study found that daily oral administration of Polybutene H-100 to pure-bred Beagle dogs over a period of 2 years at the specified dosages caused no abnormalities in body weight, food consumption, survival, behavioral patterns, hematology, blood chemistry, urinalysis, liver function, gross and histopathologic examinations, or organ weights and ratios (Elder 1982).

Ocular Irritation

CTFA (1973b) submitted an eye irritation study in 9 rabbits using Polysynlane (Hydrogenated Polyisobutene). The rabbits were treated once and then observed for 7 days. One-tenth of a milliliter of the test material was instilled in one eye of each animal. The other eye remained untreated and served as the control. Two seconds after instillation of the test material, a washout was performed in three other rabbits using 30 ml of warm water. Four seconds after instillation of the test material, washout was performed in three additional rabbits using 20 ml of warm water. No eye irritation was observed in any of the washed or unwashed rabbit eyes. The material was therefore considered to be nonirritating.

Product Safety Labs (1987b) investigated the irritant and/or corrosive effects of a single installation of Permethyl 104A/105A Blend Aliphatic Hydrocarbon (Hydrogenated Polyisobutene) into the eyes of rabbits. Six healthy, New Zealand white rabbits were used for this experiment. The conjunctival sac of the right eye of each rabbit was treated with 0.1 ml of the test material. The opposite eye remained untreated and served as the control. The treated eyes were scored for irritation at 24, 48, and 72 h following administration using the Draize scale. No corneal or iridial damage was observed during the study. At 24 h, five of the six eyes had a slight to moderate hyperemia and all had a slight to moderate discharge. Three eyes were clear of irritation by 48 h and the remaining three had moderate hyperemia. Only one eye had irritation to the conjunctivae by 72 h present as slight hyperemia.

Data submitted by CTFA (1976) included rabbit eye irritation scores using the test material Prisorine 3758 (Hydrogenated Polyisobutene). Six rabbits were used in the study. The test material was administered into the right eye of each animal; the left eye served as the control. Mild redness was observed in 3 of the rabbits with a score of 1 on the Draize scale. No other effects were reported. No further details were provided on this study.

Fanning Corporation (1998c) examined the irritation potential of Poly Iso 6-50-DN (clear liquid) when instilled into the eye of the rabbit. Six New Zealand white rabbits were given 0.1 ml of the test substance into the conjunctival sac of one eye of each rabbit. The contralateral eye served as a control. On days 1, 2, and 3, the eyes were examined and scored using the Draize method. The primary eye irritation score for each rabbit and each day was calculated. Body weights were recorded pretest (2.0 to 2.5 kg).

Four of the six eyes appeared normal at each period of observation. Slight conjunctival irritation, observed in two out of six eyes, cleared up by day 2. There was one instance of soiling of the anogenital area, which was the only abnormal systemic sign noted during the observation period. The authors stated that Poly Iso 6-50-DN is not an eye irritant (Fanning Corporation 1998c).

Fanning Corporation (1998f) investigated the primary eye irritation of Poly Iso 4-50-EN in rabbits. The test material (0.1 ml) was used to dose six female New Zealand white rabbits. The Poly Iso 4-50-EN was placed into the conjunctival sac of one eye of each rabbit. The contralateral eye served as a control. The eyes were examined and scored according to the Draize method at 1 h post administration and on days 1, 2, and 3. Sodium fluorescein was used to determine the corneal effects on day 1. The eyes were washed with 20 ml of distilled water following the 24-h observations. Prior to testing, the body weights were recorded (2.3 to 2.6 kg). The primary eye irritation score for each rabbit was calculated everyday, as well as the mean total scores for each time period.

Four out of six eyes appeared normal on days 1, 2, and 3. Slight conjunctival irritation, observed in two out of six eyes, cleared by day 2. There were no abnormal systemic signs noted during the observation period. The authors concluded that Poly Iso 4-50-EN is not an eye irritant based on the results of this study (Fanning Corporation 1998f).

A Draize eye irritation study was performed with a facial lotion (12F) containing 3.0% Hydrogenated Polyisobutene (CTFA 1987). The right eyes of three rabbits were tested and according to the data sheet, no signs of irritation were observed. No further details were provided on this study.

According to CTFA (2006b), irritation tests with approved surrogate systems/animals have shown that Indopol® polybutenes are not likely to be more mild than eye irritants (the maximum primary eye irritation score [PEIS] of 3.0/110 with complete disappearance of effects in 72 h for the lighter grades; maximum PEIS score of 8.0/110 with complete disappearance of effects in 72 h for the heavier grades).

Dermal Irritation

CTFA (1973a) reported on a skin irritation study in rabbits using Polysynlane. Six rabbits were patched with four patches, each containing 0.5 g/patch of the test material. There were no

reactions in any of the animals on intact or abraded skin. The primary irritation index was 0.0.

Davis (1976) found that Polysynlane (Hydrogenated Polyisobutene) was not irritating to intact or abraded rabbit skin when using synthetic squalene on four patches on each of the six animals. Specific concentrations were not provided by this author.

Product Safety Labs (1987c) studied the irritant and/or corrosive effects of a single 24-h exposure of Permethyl 104A/105A Blend Aliphatic Hydrocarbon (Hydrogenated Polyisobutene) on the intact and abraded skin of rabbits. The undiluted test material was a clear, viscous liquid. Six healthy New Zealand albino rabbits were clipped free of hair over approximately 10% of their body surface (dorsal and ventral surfaces from scapular to pelvic area). Two 2.5-cm^2 test sites were delineated; one remained intact and the other was abraded with a needle.

Test material (0.5 ml) was placed on each site and occluded for 24 h. The patches were then removed and the test sites were wiped clean to prevent further exposure. The sites were evaluated 24 and 72 h after initial exposure. At 24 h, all abraded and intact sites had well-defined erythema. By 72 h, the degree of erythema was reduced to very slight on two abraded and one intact site. One intact site was clear of irritation. No edema was observed in any of the animals. All animals appeared active and healthy throughout the study. The primary skin irritation score was 1.8 (Product Safety Labs 1987c).

Fanning Corporation (1998b) investigated the primary dermal irritation and corrosion in rabbits. Six female New Zealand white rabbits were dosed dermally with 0.5 ml Poly Iso 6-50-DN (clear liquid). The left side of each animal was abraded with a bent tip needle. Three abrasions, about 2 to 3 cm apart, extending the length of the exposure site were made. The abrasions were deep enough to penetrate the stratum corneum, but not deep enough to cause bleeding. The right side of each animal remained intact. The test substance was applied to one intact and one abraded site on the clipped back of each rabbit for a total dose of 1.0 ml per rabbit. The sites were occluded for 24 h, followed by evaluations for skin reactions by the Draize method at 24 and 72 h after dosing. The body weights were recorded pretest (2.0 to 2.4 kg).

Erythema and edema was recorded as absent to very slight at 24 h post dose, and were absent at 72 h. There were no abnormal systemic signs noted during the observation period. The primary irritation index was 0.38, therefore, the authors concluded that the test substance is not a dermal irritant as defined in 16 CFR 1500.41 and 16 CFR 1500.3 (c)(4) (Fanning Corporation 1998b).

Fanning Corporation (1998e) determined the irritation potential of Poly Iso 4-50-EN (clear liquid) in 6 New Zealand white rabbits. The backs and sides of each animal were clipped free of hair. The left side of each animal was abraded. Three abrasions, about 2 to 3 cm apart, were made that extended the length of the site. The abrasions were deep enough to penetrate the stratum corneum, but not enough to cause bleeding. The material was applied to one intact and one abraded site on the clipped back of each rabbit at a dose of 0.5 ml. Therefore, the total per rabbit was 1.0 ml. For 24 h, the sites were occluded and skin reactions were evaluated using the Draize scale at 24 and 72 h following dosing. The primary irritation index was calculated to be 0.96. Animal body weights were recorded pretest (2.2 to 2.7 kg).

Erythema, absent to very slight at 24 h post dose, was absent by 72 h. Edema, absent to slight at 24 h post dose, was absent by 72 h. Diarrhea, noted in one animal, was the only abnormal systemic sign found during the observation period. Therefore, the authors concluded that the Poly Iso 4-50-EN is not a dermal irritant as defined in 16 CFR 1500.41 and 16 CFR 1500.3 (c)(4) (Fanning Corporation 1998e).

Dermal Sensitization

CTFA (1973c) submitted unpublished data on sensitivity testing in guinea pigs using Polysynlane. Ten male white guinea pigs, weighing 300 to 500 g, were used in the study. The test substance was injected intradermally in an area of skin on the back and flanks that were clipped free of hair. The first dose was 0.05 ml of a 0.1 dispersion in sesame oil. The following nine injections were 0.1 ml, given three times weekly, for a total of 10 doses. After a 14-day rest period, the animals were then given a challenge dose of 0.05 ml. Twenty-four hours after each injection, the reactions were observed. Erythema and edema were observed after most inoculations. The author(s) of this study concluded that under the test conditions described, Polysynlane is not a sensitizing material.

Davis (1976) stated that Polysynlane (Hydrogenated Polyisobutene) was nonsensitizing when injected intradermally in guinea pigs after 10 injections given over a week followed by a challenge injection after 14 days.

CTFA (1981) determined the allergic contact sensitization potential of Hydrogenated Polyisobutene on the skin of female guinea pigs. The Magnusson-Kligman maximization procedure consisted of four or five stages—induction phase, dose range phase, booster phase, challenge phase I, and challenge phase II (if necessary). The vehicle used for induction was mineral oil.

A week after the 5.0% induction injections, a topical booster with a slightly irritating concentration of test material in petrolatum was administered. The control animals received petrolatum only. Sodium lauryl sulfate (SLS) (10% in petrolatum), if necessary, was applied to the induction site of animals in groups with nonirritating test material 24 h prior to material booster. Two weeks later, the animals were challenged with a subirritating concentration of the test material, as well as a level 50% of the subirritating concentration at specific sites. Petrolatum was the challenge vehicle. The guinea pigs were all shaven 3 h before grading. The second challenge occurred 1 week after challenge phase I. Only those guinea pigs that were sensitized, as well as the appropriate controls, were challenged with 100% concentration of the test material. The authors concluded that

Hydrogenated Polyisobutene is a nonsensitizer. There were no reactions observed and the irritation index was 0.0 in both challenge phases I and II (CTFA 1981).

According to CTFA (2006b), laboratory tests with approved surrogate systems/animals revealed that skin contact testing showed only slight irritation (primary dermal irritation score [PDIS] of 1.5/8.0). There were no observed sensitivity reactions. Also, acute dermal irritation testing indicated that polybutenes are practically nontoxic because the LD_{50} is greater than 10, 250 mg/kg. Lastly, polybutenes are relatively nontoxic when tested in an acute oral test (LD_{50} > 34,600 mg/kg, rat).

Comedogenicity

Product Safety Labs (1987d) studied the comedogenic potential of Permethyl 104A/105A Aliphatic Hydrocarbon (Hydrogenated Polyisobutene). Three adult New Zealand white rabbits were treated with the undiluted test material following an 8-day adaptation period. The test material was applied to the internal base of the right ear of each animal daily on 5 consecutive days per week for 3 weeks. The left ear was untreated and served as the negative control. The test material was applied at approximately the same time each day. The negative-control ears were scored for hyperkeratosis and comedone formation. There were no signs of hyperkeratosis or comedone formation during weeks 1 and 2. At week 3, two treated ears showed signs of hyperkeratosis. One ear remained clear. Histological examination revealed no signs of follicular hyperkeratosis on the treated, untreated, or control ears of any rabbits.

GENOTOXICITY

Aarsaether et al. (1987) studied the ability of different insulating fluids to induce transformation in the Syrian hamster embryo (SHE) cell transformation assay and to enhance 3-methylcholanthrene–induced transformation of C3H/10T1/2 cells. Cultures were grown in Dulbeccos's modified Eagle's medium (DMEM), supplemented with 10% fetal bovine serum at 37°C in a 10% CO_2 atmosphere.

A feeder layer of 6×10^4 lethally x-irradiated SHE cells (4500 rad) was seeded in 3 ml complete medium (DMEM supplemented with 15% fetal bovine serum [FBS], 2 μg/ml insulin, no antibiotics). The next day, 150 target cells in 1 ml medium were added. After 24 h, the chemical to be studied was added in 4 ml medium and the cells were incubated for 5 days. The medium was then removed, the dishes were rinsed with phosphate-buffered saline (PBS), and the same chemical was added in 6 ml complete medium. Two days later, the dishes were washed with PBS, and the colonies fixed with methanol and stained with Giemsa before counting and examination.

Morphological transformation is defined as altered colony morphology consisting of criss-crossing and piling up of cells. A test was considered positive when a transformation frequency higher than 1% was obtained.

In the C3H/10T1/2 transformation assay, the mouse embryo fibroblast cell line was obtained and cells between passages 7 and 12 were used. These cells are highly susceptible to postconfluent inhibition of cell division and do not form tumors in mice under normal test conditions. The cells were grown in basal Eagle's medium supplemented with 10% heat-inactivated FBS and incubated at 37°C in a humidified atmosphere of 5% CO_2 in air.

The cells harvested from logarithmically growing stock cultures were used to innoculate petri dishes. After 24 h of incubation, 0.37 μM 3-methylcholanthrene (MCA) was added to the dishes. The medium was removed and new medium added after 24 h. The cells were then exposed to an oil-containing Polyisobutene dissolved in acetone from day 5 throughout the remaining test period. The cell culture medium was changed twice weekly. The cells were fixed and stained after 6 weeks of incubation. The Polyisobutene used was primarily composed of branched isomers of dodecene, hexadecene, and eicosene. The T3700 fluid was a mixture of a polyisobutene-based oil and a mineral oil. The fluids were dissolved in acetone. The final acetone concentration was always less than 0.2% in the SHE cell transformation assay and 0.5% in the C3H/10T1/2 assay. These concentrations of acetone have been shown not to affect the transformation frequencies.

Table 13 gives the cytotoxic effects of Polyisobutene and T3700 fluid for both SHE cells and C3H/10T1/2 cells. The authors concluded that there was low cytotoxicity.

Table 14 gives the transformation data using SHE cells. The authors concluded that there was no transformation activity of Polyisobutene and T3700 fluid.

In the two-stage transformation assay of 3-methylcholanthrene–induced transformation of C3H/10T1/2 cells, promoter activity was obtained with a Polyisobutene-based oil as shown in Table 15 (Aarsaether et al. 1987).

TABLE 13
Cytotoxic effects of Polyisobutene and T3700 fluid in cell transformation study (Aarsaether et al. 1987).

Treatment		Relative plating efficiency (% ± SD)	
Agent	Concentration (μg/ml)	SHE cells	C3H/10T1/2 cells
Control	—	100 ± 10	100 ± 15
Polyisobutene A	67	105 ± 9	—
	200	105 ± 6	—
	50	—	100 ± 37
T3700[a]	67	100 ± 14	—
	200	90 ± 5	—
MCA	0.37 μM	—	72 ± 30
	3.70 μM	—	50 ± 22

[a]Mixture of a Polyisobutene-based oil and a mineral oil.

TABLE 14
Transformation of SHE cells by Polyisobutene and T3700 fluid (Aarsaether et al. 1987).

Treatment	Concentration (μg/ml)	Number of colonies	Plating efficiency	Transformed colonies	Transformation frequency (%)
Control	—	283	21	0	0.0
Polyisobutene A	67	297	22	0	0.0
	200	297	22	0	0.0
T3700	67	283	21	3	1.1
	200	256	19	0	0.0
Benzo [a]pyrene[a]	0.005	338	25	4	1.2
	0.05	216	16	6	2.8

[a]Positive control.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Polybutene

Elder (1982) reported on a three-generation reproductive study in Charles River albino rats that ingested Polybutene H-100. The animals were divided into three groups (8 males and 16 females per group) and fed Polybutene in the following three dosage levels in the diet: 0 ppm (control), 800 ppm, and 20,000 ppm. Except for the test (F_2) male parental animals that were fed 20,000 ppm Polybutene, none of the animals in successive generations differed from controls with regard to weight gains. The F_2 male parental animals showed slight weight depression, although their growth patterns were still within the normal range. Differences in mortality or reaction or in gross or microscopic histology could not be correlated with the ingestion of Polybutene. Organ weight and ratio data revealed a few intergroup differences, which were considered "random effects."

Reproductive performances (mating indices, fertility indices, incidence of pregnancy and parturition, and gestation times) of control and test animals were essentially comparable. Lactation indices ranged from 83% to 94% in the control group and from 89% to 99% in the 20,000 ppm. In all three generations, there were no significant differences between test and control animals with regard to litter size, the number of stillborn, and the number of viable pups during lactation. The survival, body weights, and reactions of test animals were comparable to those of controls (Elder 1982).

CARCINOGENICITY

Polyisobutene

Iversen (1990) conducted a study to determine the tumor promotion effects of certain oils used for the impregnation of paper-insulated power cables and their synthetic alternatives, including Polyisobutene.

Male and female *hr/hr* Oslo strain mice (32 mice in each treatment group) were used in one of two protocols. In a two-stage protocol, 7,12-dimethylbenz(α)anthracene (DMBA) in acetone (either 51.2 or 25.6 μg of DMBA) was applied to the skin of these hairless mice one time, followed by application twice per week for 18 months of 40% or 20% Polyisobutene in acetone. In a complete tumorigenesis protocol, 80%, 40%, or 20% Polyisobutene was applied to the mouse skin twice a week for 18 months. The

TABLE 15
Promoter activity of insulation oils in two-stage transformation of C3H/10T1/2 cells (Aarsaether et al. 1987).

Treatment			Transformation		
MCA[a] concentrations (μM)	Promoter	Component concentration	Total no. of dishes scored	Total no. of dishes with type III foci	Dishes with type III foci (%)
		Controls			
0	Acetone	0.5%	96	1	1
3.7	Acetone	0.5%	72	9	12.5
0.37	Acetone	0.5%	86	2	2.4
0.37	TPA	0.17 μM	85	43	50
		Polyisobutene			
0.37	Polyisobutene-based oil	50 μg/ml	41	11	26.8

[a]MCA = 3-methylcholanthrene.

TABLE 16
Final number of tumors and lesions in mice given DMBA followed by Polyisobutene (Iversen 1990).

Type of tumor/lesion	51.2 μg DMBA once (normalized to 32 mice)	51.2 μg DMBA then Polyisobutene 2×/ week for 18 months		25.6 μg DMBA once (normalized to 32 mice)	25.6 μg DMBA then Polyisobutene 2×/ week for 18 months	
		40%	20%		40%	20%
Papillomas	17/9	5/4	18/8	2/2	0	6/5
Carcinomas	1/1	2	1	1	0	2
Sarcomas	1/1	0	0	0	0	0
B cell lymphoma	0	2	0	0	1	1
Lymphoma NOS	0	1	0	0	1	1
Reticulosis	0	1	0	1	1	2
Lung adenomas	1/1	1/1	3/3	1/1	4/4	4/4
Lung adenocarcinoma	1	0	0	0	0	0
Hepatoma	0	0	1	0	0	0
Ovary adenocarcinoma	0	0	1	0	0	0
Teratoma of the ovary	0	0	0	0	0	0
Kidney adenocarcinoma	0	0	0	0	0	0
Spindle cell carcinoma	0	0	0	0	0	0
Amyloidosis	1	0	1	1	3	0
Skin toxicity	0	0	(++)	0	(+)	(+)
Mast cell hyperplasia	0	0	(+)	0	(+)	0
Pigment leakage	0	0	0	0	0	0
Pronounced hyperplasia	0	0	(+)	0	(+)	(+)

Polyisobutene (Polyisobutylene, as given by the author) used had an average molecular weight of 250 and a viscosity of 5 mm^2/S (at 50°C).

Controls received acetone alone twice a week for 50 weeks (32 animals—negative control), acetone alone one time (32 animals—second negative control), 51.2 μg DMBA alone (48 animals—positive control), or 25.6 μg DMBA alone (48 animals—positive control). In controls and treatment groups, the application volume was 100 μl. Data were also reported on 128 positive, historical control hairless mice that had received 51.2 μg DMBA alone.

After treatment, animals were returned to their cages, where they were observed to lick each other. Also a noticeable odor attributed to vapor from the fluid painted on the skin was present in the cages for 2 to 4 h.

Table 16 shows the final number of tumors and lesions in mice given DMBA once followed by chronic exposure to Polyisobutene in acetone. The author concluded that treatment with Polyisobutene oil alone had no tumerogenic or carcinogenic effect. In the studies with DMBA pretreatment followed by Polyisobutene exposure, the author stated that no evidence of tumor promotion was found, and that 40% Polyisobutene oil may have reduced the number of tumors in comparison with DMBA alone or DMBA and 20% Polyisobutene oil.

The author also stated that Polyisobutene increased the death rate at higher doses, but no data were provided. Although the original study design was to evaluate skin tumor formation only, observations of skin irritation at the site of application, amyloidosis, and swelling of the lymph nodes caused the author to begin recording these findings and conducting necropsies on all the animals. However, upon reviewing the amended experimental design, the CIR Expert Panel concluded that the protocol did not support any conclusions of systemic carcinogenicity.

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation

Hydrogenated Polyisobutene

CTFA (1974a) submitted results of a 72-h primary skin irritation study aimed to determine whether the following ingredients produced irritation in human skin: 100% Polysynlane (Hydrogenated Polyisobutene); 60% Polysynlane–40% petrolatum; 40% Polysynlane–60% petrolatum; 20% Polysynlane–80% petrolatum; 100% squalene (Robane); 40% squalene–60% petrolatum; 20% squalene–80% petrolatum; and 100% petrolatum (control sample). Twenty-five male and female subjects, ages 11 to 59, were used for the study. They were patched with

the eight test products under occlusive patch for 72 h. There were no reactions in any of the subjects for each of the eight samples. Therefore, the author(s) concluded that within the limits set forth in this study, none of the products produced primary skin irritation.

CTFA (1974b) submitted results of a 24-h primary skin irritation test using (a) Polysynlane (as is), (b) 50% concentration of Polysynlane in olive oil, and (c) olive oil (as is). Fifty-one male and female subjects, ages 18 to 59, participated in the study. The closed patch test was performed using the forearm's flexsure site of the subjects. The patches were removed after 24 h and the site was observed for irritation. Polysynlane, under these test conditions, produced no skin irritation in any of the subjects.

Davis (1976) reported that Polysynlane (Hydrogenated Polyisobutene), tested side by side with synthetic and natural squalene in 25 men and women, produced no dermal irritation in a 72-h primary skin irritation patch test.

A Clinical Evaluation Report submitted by CTFA (1999) summarized a 24-h single-insult patch testing procedure in humans with a lip gloss containing 66.11% Hydrogenated Polyisobutene. The control material was a lip shape and shimmer gloss and the test material was a lip polish—glaze (clear). The concentration used was considered full strength. No irritancy was observed as a result of test or control samples (Table 17).

Dermal Sensitization

CTFA (1974c) submitted a study that investigated whether the following ingredients caused any allergenic sensitization of the human skin: (a) 100% Polysynlane, (b) 20% Polysynlane–80% petrolatum, (c) 100% squalene, and (d) 20% squalene–80% petrolatum. Two-hundred seven subjects participated in the study; however seven subjects dropped from the study for unknown reasons. The subjects were patched with the 4 materials using the Draize repeat-insult patch test procedure. The materials were applied to the skin of the upper back and covered for occlusive patching. The occlusive insults were applied every Monday, Wednesday, and Friday for 3.5 weeks, for 10 insults. An 11th insult was applied following a 14-day rest period. The site was scored 48 h later. Note, a modification of the maximization test was performed on subjects 1 through 55. The outer layer of skin was stripped away before the application of each patch. Patch products were then applied to the stripped areas. Polysynlane (100%), Polysynlane (20% with 80% petrolatum), squalene (100%), and squalene (20% in 80% petrolatum) did not produce any allergic sensitizing potential.

Davis (1976) stated that Polysynlane (Hydrogenated Polyisobutene), tested side by side with natural squalene in a panel of 200 men and women, produced no dermal irritation in a modified Draize-Shelanski repeat-insult patch test.

CTFA (1996a) performed repeat-insult patch tests to evaluate the primary irritancy/sensitization of the following coded test materials: JMB-423 (containing 4% Hydrogenated Polyisobutene) and JMB-426 (containing 1.44% Hydrogenated Polyisobutene). The Hydrogenated Polyisobutene used in these coded products has an average molecular weight of 370 and contains six to seven isobutene units. Although there were initially 61 male and female volunteers, only 54 subjects, ages 18 to 69, completed this study. Seven dropped out of the study for various reasons, one being due to severe tape reactions.

All of the test samples were liquids, which, when applied to the patch with a dropper, contained approximately 0.2 to 0.3 ml of the material. Each of the participants was patched with a total of six patches on the lateral part of the upper arm (three sites per arm); the patch sites were randomized using the standard Latin square. The test period was five weeks. During weeks 1 and 2, eight induction applications were made, followed by a 2-week hiatus. A single challenge application of each formulation was made on sites adjacent to the induction sites in week 5.

Reactions were scored 24 h after each induction application (about 5 to 15 min after patch removal) and 24, 48, and 72 h following the challenge phase. Evaluation of the challenge patch was made at 96 h. Reactions were scored as 0 = no reaction; ± = questionable erythema; 1+ = slight erythema; 2+ = moderate erythema; 3+ = severe erythema; 4+ = edema and/or papules (with/without erythema); and 5+ = vesticulation (with/without edema and erythema). There were no reactions >1+ during the induction or challenge phases of this study (CTFA 1996a).

CTFA (2003a) submitted a study designed to determine the irritating and sensitizing potential of a makeup remover containing 51% Hydrogenated Polyisobutene on human skin. The study was a modified repeat-insult patch test conducted under double-blind conditions. One hundred ten subjects (35 male, 75 female), ages 18 to 76, participated in the study. The investigation consisted of nine sequential 24-h induction applications and two concurrently conducted 24-h challenge applications, one on the induction site and one on a naive site (left side of the back).

TABLE 17
Results of a single human patch test using lip gloss containing Hydrogenated Polyisobutene (CTFA 1999).

Test material concentration	Subjects	Irritation score*									
		0	±	1	1+	2	2+	3	3+	4	PII
66.11%	19	17	2	0	0	0	0	0	0	0	0.05
0% (control)	19	18	1	0	0	0	0	0	0	0	0.03

*Skin staining noted. Erythematous response were read "through" the stain.

During the initial phase, the skin sites were graded and recorded on Wednesdays, Fridays (24 h following patch removal), and Mondays (48 h following patch removal). During the challenge phase, the skin sites were graded after the patches had been removed and then again 24 and 48 h later.

No responses were seen in 109 of the 110 subjects; however, intense redness was observed in 1 of the subjects. Further exposure to this material was halted for this individual for the remainder of the induction period. During the challenge phase, there were no signs of irritation or sensitization in any of the subjects, including the one subject with intense redness in the induction phase. The author therefore concluded that the test material was found to be a nonirritant and nonsensitizer under the conditions of this study (CTFA 2003a).

Ivy Laboratories (2004a) evaluated the contact-sensitizing potential of a face powder containing 17.1% Hydrogenated Polyisobutene by means of the maximization test. Twenty-eight healthy volunteers (17 male, 11 female), ages 20 to 55, participated in this study; however, only 25 completed the study (2 dropped from study; 1 voluntarily withdrew). The study included an induction phase and a challenge phase. Patches were applied to the upper outer arm, volar forearm, or back of each subject.

During the induction phase, approximately 0.05 ml of aqueous SLS (0.25%) was applied to a specific site and the patch was left on for 24 h. After 24 h, the patch was removed and 0.05 ml of the test material (bronzer) was applied to the exact same site and covered (induction patch). The patch remained in place for 48 h (72 h when placed over a weekend). After removal, the site was examined for irritation. If there was no irritation present, a 0.25% aqueous SLS patch was reapplied to the same site for 24 h, followed by reapplication of a fresh induction patch with the test material to the same site. This procedure, 24-h SLS pretreatment followed by 48 h of test material, continued for five exposures. If at any point irritation developed during the induction phase, the 24-h SLS pretreatment patch was omitted and only the test material was reapplied to the same site after a 24-h rest period, during which no patch was applied.

After the 10-day rest period, the subjects were challenged with a single application of the test material to a new skin site on the opposite arm, forearm, or side of back in order to determine if sensitization had developed. Prior to the challenge, pretreatment with SLS was performed. Approximately 0.05 ml of a 5.0% aqueous solution was applied to a fresh skin site and covered. The SLS patch remained in place for 1 h. After removal, the test material was applied to the same site and the challenge patch remained in place for 48 h. After 48 h, the patch was removed and the site graded 1 h later and again at 24 h.

There were no adverse reactions observed in any of the subjects during the induction phase. During the challenge phase, there were no instances of contact allergy present at either 48 or 72 h. The authors concluded that under the conditions of this test, the test sample labeled bronzer did not have a contact-sensitization potential, and is therefore unlikely to cause sensitivity reactions under normal use (Ivy Laboratories 2004a).

Ivy Laboratories (2005) evaluated the contact sensitization potential of a topical coded product (eyeshadow containing 10.5% Polyisobutene) in human, by means of the maximization assay. Twenty-eight (4 male and 24 female) volunteers, ages 18 to 58 years, participated in the study. Patches were applied to the upper outer arm, volar forearm, or back of each subject. The overall test consisted of two phases—an induction phase and a challenge phase.

During the induction phase, approximately 0.05 ml of aqueous SLS (0.25%) was applied to a certain site and the patch remained in place for 24 h. After 24 h, the SLS patch was removed and 0.05 ml of the coded test material (1003213-001, Pencil) was applied to the exact same site. The induction patch remained in place for 48 h (or 72 h when placed over the weekend). Once the patch was removed, the site was examined for irritation. If there was no irritation present, a 0.25% aqueous SLS patch was reapplied to the same site for 24 h, followed by reapplication of a fresh induction patch with the test material to the same site. This sequence, 24-h SLS pretreatment followed by 48 h of test material, was continued for a total of five induction exposures.

No adverse reactions were found in any of the subjects during the induction phase.

During the challenge phase, the subjects were challenged with a single application of the test material to a new skin site on the opposite arm, forearm, or side of back in order to determine if sensitization had developed. This phase followed a 10-day rest period after the last induction patch application. Prior to the challenge, pretreatment with SLS was performed. Approximately 0.05 ml of a 5.0% aqueous solution was applied to a fresh skin site. The SLS patch remained in place for 1 h. Then, it was removed and the test material was applied to the same site. The challenge patch was covered and left in place for 48 h, followed by removal and grading 15 to 30 min later and again 24 h later for any reaction.

There were no instances of contact allergy observed at either 48 or 72 h following application of the challenge patches. According to the authors, the test sample labeled pencil does not possess a contact-sensitization potential and is therefore not likely to cause reactions under normal use conditions (Ivy Laboratories 2005).

Ivy Laboratories (2000) evaluated the contact-sensitization potential of lip gloss containing 66.11% Hydrogenated Polyisobutene in human skin by means of the maximization assay. Twenty-seven healthy male (8) and female (19) volunteers, ages 18 to 52, participated in the study. One male subject did not want to continue following the third induction exposure and voluntarily withdrew from the study. Patches were applied to the upper outer arm, volar forearm, or back of each subject. The test consisted of an induction phase and challenge phase.

During the induction phase, approximately 0.1 ml of aqueous SLS (0.25%) was applied to a designated site and the patch was

allowed to remain in place for 24 h. The patch was removed after 24 h and 0.1 ml of the test material (lip gloss) was applied to the same site and covered (induction patch). The induction patch remained in place for 48 h (or 72 h when placed over a weekend). It was then removed and examined for irritation. If there was no irritation present, a 0.25% aqueous SLS patch was reapplied to the same site for 24 h, followed by reapplication of a fresh induction patch with the test material to the same site. This procedure was continued for a total of five induction exposures. If irritation developed at any point and time during the induction phase, the 24-h SLS pretreatment patch was eliminated and only the test material was reapplied to the same site after a 24-h rest period, during which no patch was applied.

After the 10-day rest period, the subjects were challenged with a single application of the test material to a new skin site on the opposite arm, forearm, or side of back to determine if sensitization had developed. Prior to the challenge, pretreatment with SLS was performed. Approximately 0.1 ml of a 5.0% aqueous solution was applied to a fresh test site and covered with occlusive tape. The SLS patch remained in place for 1 h. When removed, the test material was applied to the same site. The challenge patch remained in place for 48 h. The patch was then removed, and the site graded 1 h and again 24 h later for any reaction.

There were no adverse or unexpected reactions observed in any of the subjects during the induction phase. Likewise, no instances of contact allergy were recorded at 48 or 72 h following application of the challenge patches. The authors concluded that under the test conditions, the test sample labeled lip gloss does not possess a detectable contact-sensitizing potential and hence is not likely to cause contact sensitivity reaction under normal use (Ivy Laboratories 2000).

Ivy Laboratories (2004b) used the same protocol as above using lip gloss containing 31.65% Hydrogenated Polyisobutene. Twenty-six healthy, adult volunteers of both sexes participated in the study; however, only 25 completed the study (1 female subject failed to return to the laboratory following the first exposure and dropped from the study). There were 23 females and 3 males, ages 18 to 59. There were no instances of contact allergy observed at either 48 or 72 h following application of the challenge patches.

The authors concluded that under the conditions of this study, the test sample labeled lip gloss does not possess a detectable contact-sensitizing potential, and is therefore unlikely to cause contact sensitivity reactions under normal use conditions (Ivy Laboratories 2004b).

Photoallergy

CTFA (1996c) reported that three products, JMB-442 (4% Hydrogenated Polyisobutene), JMB-441 (1.44% Hydrogenated Polyisobutene), and JTP-81, were evaluated to determine their ability to induce a photoallergic reaction in the skin of normal volunteer subjects under semiocclusive patch conditions. A distilled water patch served as a control. Thirty subjects, ages 18 to 69, completed the study. The experiment consisted of three phases—induction, rest, and challenge. All patch sites were located on the back in columns to the right and left of the spine (one side for irradiated sites and opposite for nonirradiated sites). For the sites designed for irradiation, ultraviolet light exposure was performed within 10 min of patch removal.

During the induction phase (weeks 1 to 3), a series of 12 applications of the test materials was made to a naive test site. The applications were made on Monday through Thursday of each of 3 consecutive weeks. The patches were removed approximately 24 h after application and site responses were evaluated and scored. After the removal of the induction patches on Tuesday and Thursday, the test sites were exposed to approximately twice the minimum erythemic dose and 6 to 8 joules of ultraviolet A (UVA).

During the rest period (weeks 4 and 5), no applications of test materials were made for 2 weeks. The challenge phase in week 6 involved a single application of duplicate contact patches of the test materials made to naive sites. One of each of the pair of patches was removed after approximately 24 h and was exposed to UVA (16 to 20 joules) within 10 min. The other duplicate patch was then removed. All sites were evaluated and scored approximately 1, 24, 48, and 72 h following the removal of patches.

Under the conditions employed in this study, no evidence of photoallergic reactions was found to JMB-441, JMB-442, and JTP-81 (CTFA 1996c).

Phototoxicity

CTFA (1996b) determined the phototoxic potential of the foundations/concealers JMB-442 (4% Hydrogenated Polyisobutene), JMB-441 (1.44% Hydrogenated Polyisobutene), and a blank patch under UVA light source (320 to 400 nm). The lamp output ranged from 3.5 to 3.9 mW/cm^2 during the study. Irradiation time was increased to 20 min on all subjects to ensure adequate UVA exposure. There were 26 fair-skinned volunteers between the ages of 18 and 69 who completed this study. One subject was dropped from the study due to an adverse reaction. This subject developed hives 5 h after the patches were applied on day 1.

Four sites on the right side of the back of each subject was selected for the phototoxic evaluation and each subject was patched with the three test materials, which were randomized by use of the Latin square. Duplicate patches (using the same randomization) were applied to the left side of the back and served as the nonirradiated controls. The test period was 4 days.

On day 1, patches were applied and subjects were instructed that the patches were to remain in place and dry for approximately 24 h (until they returned to the laboratory). On day 2, the patches on the sites designated to be irradiated were removed at the laboratory and examined for irritation. The sites were treated with approximately 0.1 g of the test sample, which were

allowed to dry for 5 to 10 min. The excess, if any, was gently removed by blotting and the sites were irradiated at a distance of 10 cm for 15 min. On the nonirradiated control sites, patches remained in place until after the light exposure. Additionally, these sites were covered with a towel to ensure complete exclusion of light. After irradiation, the exposed sites and the nonirradiated controls were evaluated for irritation. The subjects were instructed to avoid exposing the treated areas to sunlight or excessive amounts of indoor lighting for the remainder of the study.

The scoring system used was the same 0 to 5+ scale described earlier. On days 3 and 4, follow-up evaluations for irritancy were made. There were no reactions greater than ± to any of the samples tested and thus no indication of primary irritancy or phototoxicity (CTFA 1996b).

Ocular Toxicity

CTFA (1996d) evaluated the ocular irritation potential of three shades of concealer (JMB-428, JMB-429, and JMB-442) when used for 29 days. JMB-442 consisted of 4% Hydrogenated Polyisobutene. Fifty-nine subjects, ages 18 to 55 years, completed the study. Thirty-two wore contact lenses. On day 1, all of the prospective candidates underwent screening of the eyes and skin, as well as vision exams. Eye area skin and the eyes were graded on a scale of 0 to 3 (0 being no reaction and 3 the most extreme reaction).

After cleansing and prior to applying foundation, the subjects were instructed to apply the concealers sparingly under the eyes to cover dark circles at least once daily. Contact lens wearers were required to insert contact lenses prior to applying the concealer and no other concealers were to be worn throughout the study. After 1, 2, and 3 weeks (days 8, 15, and 22) of use, all of the subjects were evaluated for irritation. For the three formulations, there were no adverse reactions during this study. All subjects had 0's on all ophthalmologist gradings. Slight irritation was noted on day 8 for one of the subjects, and there were three reports of itching and eye irritation during the final examination. Overall, there was no observed ocular irritation and visions stayed the same or within normal limits throughout the course of the study (CTFA 1996d).

CTFA (2003b) assessed the eye irritancy of a product containing 10% Hydrogenated Polyisobutene (Permethyl 104). The subjects were five healthy, adult females who experienced strong stinging to 10% lactic acid and/or who had a history of self-assessed sensitive skin or sensitive eyes. The author noted that lactic acid stingers have more reactive skin and are more likely to respond to mild irritants. The product was applied to the exterior skin around both eyes on the morning and afternoons of 5 weekdays. As a result, no subject experienced signs of irritation during the 5 days of treatment. Therefore, this product was concluded by the authors to be nontoxic to the external eye area when applied twice a day for 5 days to lactic acid stingers and/or those with sensitive skin or eyes.

Case Report

Parslew et al. (1996) reported on the case of a 48-year-old woman who was diagnosed as having Crohn's disease. The patient underwent a total colectomy and ileostomy following numerous fistulae. Briefly after wearing her stoma bag, she developed an eroded eczematous area around the stoma. A skin biopsy indicated dermatitis and excluded Crohn's disease.

When the patient discontinued use of the stoma bag, symptoms would disappear within 10 to 14 days. However, when she began reusing the stoma bag, symptoms would consistently reappear within 2 days. The initial patch testing showed reactions (++ at day 4) to colophony, benzoyl peroxide, and the adhesive ring of the bag. Concerns involving the constituents of the ring revealed that colophony and benzoyl peroxide were absent. The ring itself consisted of a hydrocolloid laminated with a polyethylene film. The hydrocolloid component was made up of a citrus-derived pectin of edible food grade, sodium carboxymethylcellulose, gelatine BP, and Polyisobutene.

The patch test carried out with Polyisobutene brought forth a contact urticaria after 10 min and a ++ eczematous reaction at day 4. Polyisobutene (diluted to 0.1%, 0.5%, 1.0%, and 5% solutions in ether) was tested on the patient and five control subjects. There was a positive reaction to 5% Polyisobutene in ether with the patient, but negative reactions in the five control subjects. The authors note that irritant reactions to stoma appliances and drainage fluid are common, but allergic reactions are rare (Parslew et al. 1996).

SUMMARY

Polyisobutene and Hydrogenated Polyisobutene are both homopolymers of isobutene. Polyisobutene has a double bond in its end unit, whereas the final carbon is fully hydrogenated in Hydrogenated Polyisobutene. These ingredients are produced in a wide range of molecular weights. Polybutene is a chemically related cosmetic ingredient previously determined to be safe as used in cosmetic products.

Polyisobutene is used in cosmetic products as a binder, film former, and nonaqueous viscosity-increasing agent. In addition to its cosmetic uses, Polyisobutene is also used in a number of noncosmetic applications such as adhesives, sealants, coatings, lubricants, and plasticizers. Hydrogenated Polyisobutene has an additive function, which improves the feel of and generally upgrade the spreading and penetrating properties of lotions based on mineral oil and petrolatum. It functions as a skin-conditioning agent—emollient and nonaqueous viscosity-increasing agent, with a wide range of uses in cosmetic formulations. Furthermore, Polybutene functions as a binder, epilating agent, and nonaqueous viscosity-increasing agent in a variety of cosmetic products.

The water solubility was estimated at 5.6×10^{-3} ng/L (0.0056 parts per trillion) for the Indopol® (trade name Polybutene) and the Panalane® (trade name Hydrogenated Polyisobutene).

Acute oral toxicity testing with mice caused no deaths with a maximum of 89.608 g/kg of Polysynlane (trade name Hydrogenated Polyisobutene mixture).

Oral toxicity using a single dose of 5 g/kg Permethyl 104A/105A Blend Aliphatic Hydrocarbon (trade name Polyisobutene) caused no deaths in rats; however, all of the animals appeared lethargic after dosing.

Single-dose oral toxicity studies in rats dosed with two Hydrogenated Polyisobutenes (Poly Iso 6-50-DN and Poly Iso 4-50-EN) at 5.0 g/kg body weight caused wetness in the anogenital area on the day of dosing. All animals survived the 5.0 g/kg oral dose and both Hydrogenated Polyisobutenes were found to be nontoxic. The authors of these studies also concluded that the LD_{50} is greater than 5.0 g/kg body weight.

A 2-year chronic oral toxicity study of Polybutene H-100 (75% concentrate) in Charles River albino rats given up to 20,000 ppm Polybutene blended into their regular diets revealed no gross or microscopic pathological changes that could be correlated with Polybutene ingestion. No significant differences were found after 24 months of feeding in the body weights or weight of food consumption, hematological results, urology, or tumor formation between the animals fed Polybutene and those that were not. In the 20,000 ppm group, three out of six males that died between weeks 17 and 24 exhibited hematuria.

In a 2-year chronic oral toxicity study of Polybutene H-100 (75% concentrate) in Beagle dogs, it was found by the authors that daily oral administration of Polybutene H-100 to pure-bred Beagle dogs over a period of 2 years at doses up to 1000 mg/kg/day caused no abnormalities in body weight, food consumption, survival, behavioral patterns, hematology, blood chemistry, urinalysis, liver function, gross and histopathologic examinations, or organ weights and ratios.

A three-generation reproductive study in Charles River albino rats that ingested Polybutene H-100 up to 20,000 ppm demonstrated that, except for the test (F_2) male parental animals that were fed 20,000 ppm Polybutene, none of the animals in successive generations differed from controls with regard to weight gains. The F_2 male parental animals showed slight weight depression, although their growth patterns were still within the normal range. In all three generations, there were no significant differences between test and control animals with regard to litter size, the number of stillborn, and the number of viable pups during lactation. The survival, body weights, and reactions of test animals were comparable to those of controls.

A 7-day eye irritation study on rabbits using 0.1 ml Polysynlane (trade name Hydrogenated Polyisobutene) produced no eye irritation in any of the washed or unwashed rabbit eyes.

Irritant and corrosive effects were examined using a single instillation of Permethyl 104A/105A Blend Aliphatic Hydrocarbon (trade name Polyisobutene) into rabbit eyes. No corneal or iridial damage was recorded in the study. One eye had irritation to the conjunctivae by 72 h, which was present as slight hyperemia.

An unknown concentration of Prisorine 3758 (trade name Hydrogenated Polyisobutene) instilled into the right eyes of six rabbits produced a score of 1 on the Draize scale. No other effects were observed.

When 0.1 ml Poly Iso 6-50-DN (trade name Hydrogenated Polyisobutene) was instilled into the conjunctival sac of rabbit eyes, the test material caused slight conjunctival irritation in 33% of eyes which cleared up by day 2. The authors determined that Poly Iso 6-50-DN is not an eye irritant. Poly Iso 4-50-EN, (another trade name Hydrogenated Polyisobutene), under similar test conditions, produced the same results.

A Draize eye irritation study in the right eyes of three rabbits using a facial lotion containing 3% Hydrogenated Polyisobutene caused no signs of irritation.

A skin irritation study in six rabbits using four patches each containing 0.5 g/patch of Polysynlane (trade name Hydrogenated Polyisobutene mixture) caused no reactions in any of the animals on intact or abraded skin. The primary irritation index was 0.0. There was a primary irritation index score of 1.8 for rabbits treated with Permethyl 104A/105A Blend Aliphatic Hydrocarbon (trade name Polyisobutene) on the intact or abraded skin. Rabbits dosed dermally with 0.5 ml Poly Iso 6-50-DN (trade name Hydrogenated Polyisobutene) on intact and abraded skin exhibited a primary irritation index of 0.38; not a dermal irritant. In a similar study, Poly Iso 4-50-EN (another trade name Hydrogenated Polyisobutene) produced a primary irritation index of 0.96; also not a dermal irritant. Polysynlane (trade name Hydrogenated Polyisobutene) was intradermally injected in an area of the skin on the back and flanks of guinea pigs. Erythema and edema were observed after most inoculations, but no sensitization reactions.

Hydrogenated Polyisobutene injections (5%) in guinea pigs using a maximization procedure resulted in no observed reactions and an irritation index of 0.0 in both challenge phases I and II.

The comedogenic potential of Permethyl 104A/105A Aliphatic Hydrocarbon (trade name Polyisobutene) was studied using adult New Zealand white rabbits. The test material was applied to the right ear of each animal daily on 5 consecutive days per week for 3 weeks. There were no signs of hyperkeratosis or comedone formation during weeks 1 and 2. By the third week, two treated ears exhibited signs of hyperkeratosis. The ear of the third rabbit, however, remained clear. Histological examination showed no signs of follicular hyperkeratosis on the treated, untreated, or control ears of any rabbits.

In a study to determine the ability of various insulating fluids to induce transformation in the SHE cell transformation assay and to enhance MCA–induced transformation of C3H/10T1/2 cells, it was found by the authors to be not active and low cytotoxicity was found for a low-viscosity Polyisobutene-based oil. In the two-stage transformation assay of C3H/10T1/2 cells, the Polyisobutene oil had promoter activity.

In a carcinogenicity study conducted to determine the skin tumorigenicity effects of certain oils used for impregnation of paper-insulated power cables and their synthetic alternatives, including Polyisobutene oil, no evidence of a direct tumorigenic or carcinogenic effect was reported and Polyisobutene oil appeared to reduce the number of DMBA-induced tumors.

Repeat-insult patch tests performed to evaluate the primary irritancy/sensitization potential of coded cosmetic foundations/concealer products JMB-423 (containing 4% Hydrogenated Polyisobutene) and JMB-426 (containing 1.44% Hydrogenated Polyisobutene) in 54 male and female subjects found no reactions greater than slight erythema.

No primary skin irritation was produced in a 72-h primary skin irritation patch test study with 100% Polysynlane (Hydrogenated Polyisobutene) in 25 male and female participants.

There was no irritancy observed in humans during a 24-h single-insult patch test with a lip gloss containing 66.11% Hydrogenated Polyisobutene. In a modified repeat-insult patch test under double-blind conditions, no irritation or sensitization was found in human skin patched with a makeup remover containing 51% Hydrogenated Polyisobutene.

The phototoxic potential of coded cosmetic foundations/concealer products JMB-442 (containing 4% Hydrogenated Polyisobutene), JMB-441 (containing 1.44% Hydrogenated Polyisobutene), and a blank patch under UVA light source (320 to 400 nm) was studied in 26 fair-skinned volunteers. No significant reactions were reported.

JMB-442 (containing 4% Hydrogenated Polyisobutene) and JMB-441 (containing 1.44% Hydrogenated Polyisobutene) were evaluated to determine their potential to induce a photoallergic reaction in the skin of 30 subjects. No response was reported at induction, rest, or challenge.

Three shades of coded cosmetic foundations/concealer products, JMB-428 (containing an unspecified concentration of Hydrogenated Polyisobutene), JMB-429 (containing an unspecified concentration of Hydrogenated Polyisobutene), and JMB-442 (containing 4% Hydrogenated Polyisobutene), were examined for signs of ocular irritation when used at least once a day for 29 days by 59 subjects. There were no adverse reactions reported.

DISCUSSION

The available acute, short-term, and subchronic toxicity studies do not suggest that any toxicity would be associated with the use of these ingredients in cosmetic products of a type and at the concentrations reported.

The CIR Expert Panel recognizes that there are data gaps regarding use and concentration of these ingredients. However, the overall information available on the types of products in which these ingredients are used and at what concentrations indicate a pattern of use, which was considered by the Expert Panel in assessing safety.

Although one study did suggest possible systemic carcinogenic potential of Polyisobutene and Hydrogenated Polyisobutene, the CIR Expert Panel noted that there was no evidence of tumorigenicity in the study. On review of the study experimental design, it was not possible to make any implications regarding systemic carcinogenicity. Other chronic toxicity studies on the related material Polybutene using rats and dogs, including a 2-year chronic oral toxicity study and a three-generation reproductive and developmental toxicity study, did not result in any carcinogenic effect or reproductive/developmental toxicity, respectively.

The Panel acknowledged the absence of UV absorption data for these ingredients. Clinical tests of phototoxicity and photoallergenicity in which formulations containing Hydrogenated Polyisobutene were used, however, empirically demonstrated the absence of effects.

The Panel also noted the absence of dermal absorption data for Polyisobutene and Hydrogenated Polyisobutene. The available log K_{ow} data and the low solubility in water suggest very slow absorption, so additional data are not needed. Gastrointestinal absorption is also not a major concern due to the low solubility of these chemicals.

CONCLUSION

The CIR Expert Panel concluded that Polyisobutene and Hydrogenated Polyisobutene are safe as cosmetic ingredients in the practices of use and concentration as described in this safety assessment.

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2015 FDA VCRP Raw Data

07E - Lipstick	BUTYLENE/ETHYLENE COPOLYMER	1
03F - Mascara	BUTYLENE/ETHYLENE/PROPYLENE COPOLYMER	1
03G - Other Eye Makeup Preparations	BUTYLENE/ETHYLENE/PROPYLENE COPOLYMER	1
07C - Foundations	BUTYLENE/ETHYLENE/PROPYLENE COPOLYMER	1
07E - Lipstick	BUTYLENE/ETHYLENE/PROPYLENE COPOLYMER	8
07I - Other Makeup Preparations	BUTYLENE/ETHYLENE/PROPYLENE COPOLYMER	1
12F - Moisturizing	BUTYLENE/ETHYLENE/PROPYLENE COPOLYMER	1
12J - Other Skin Care Preps	BUTYLENE/ETHYLENE/PROPYLENE COPOLYMER	1
03F - Mascara	DECENE/BUTENE COPOLYMER	1
07E - Lipstick	DECENE/BUTENE COPOLYMER	2
03A - Eyebrow Pencil	ETHYLENE/PROPYLENE COPOLYMER	5
03B - Eyeliner	ETHYLENE/PROPYLENE COPOLYMER	4
03C - Eye Shadow	ETHYLENE/PROPYLENE COPOLYMER	2
04E - Other Fragrance Preparation	ETHYLENE/PROPYLENE COPOLYMER	4
05G - Tonics, Dressings, and Other Hair Grooming Aids	ETHYLENE/PROPYLENE COPOLYMER	3
07A - Blushers (all types)	ETHYLENE/PROPYLENE COPOLYMER	1
07B - Face Powders	ETHYLENE/PROPYLENE COPOLYMER	1
07C - Foundations	ETHYLENE/PROPYLENE COPOLYMER	3
07E - Lipstick	ETHYLENE/PROPYLENE COPOLYMER	72
07G - Rouges	ETHYLENE/PROPYLENE COPOLYMER	4
07I - Other Makeup Preparations	ETHYLENE/PROPYLENE COPOLYMER	4
12C - Face and Neck (exc shave)	ETHYLENE/PROPYLENE COPOLYMER	1
12F - Moisturizing	ETHYLENE/PROPYLENE COPOLYMER	3
07B - Face Powders	HYDROGENATED POLY(C6-14 OLEFIN)	2
07C - Foundations	HYDROGENATED POLY(C6-14 OLEFIN)	1
07E - Lipstick	HYDROGENATED POLY(C6-14 OLEFIN)	10
12C - Face and Neck (exc shave)	HYDROGENATED POLY(C6-14 OLEFIN)	3
12F - Moisturizing	HYDROGENATED POLY(C6-14 OLEFIN)	3
12J - Other Skin Care Preps	HYDROGENATED POLY(C6-14 OLEFIN)	1
03A - Eyebrow Pencil	HYDROGENATED C6-14 OLEFIN POLYMERS	1
03C - Eye Shadow	HYDROGENATED C6-14 OLEFIN POLYMERS	5
03D - Eye Lotion	HYDROGENATED C6-14 OLEFIN POLYMERS	3
07A - Blushers (all types)	HYDROGENATED C6-14 OLEFIN POLYMERS	1
07C - Foundations	HYDROGENATED C6-14 OLEFIN POLYMERS	5
07E - Lipstick	HYDROGENATED C6-14 OLEFIN POLYMERS	6

07G - Rouges	HYDROGENATED C6-14 OLEFIN POLYMERS	6
07I - Other Makeup Preparations	HYDROGENATED C6-14 OLEFIN POLYMERS	10
12A - Cleansing	HYDROGENATED C6-14 OLEFIN POLYMERS	3
12C - Face and Neck (exc shave)	HYDROGENATED C6-14 OLEFIN POLYMERS	7
12D - Body and Hand (exc shave)	HYDROGENATED C6-14 OLEFIN POLYMERS	4
12F - Moisturizing	HYDROGENATED C6-14 OLEFIN POLYMERS	6
12G - Night	HYDROGENATED C6-14 OLEFIN POLYMERS	1
12J - Other Skin Care Preps	HYDROGENATED C6-14 OLEFIN POLYMERS	4

03B - Eyeliner	HYDROGENATED POLYBUTENE	6
03C - Eye Shadow	HYDROGENATED POLYBUTENE	4
03E - Eye Makeup Remover	HYDROGENATED POLYBUTENE	2
03F - Mascara	HYDROGENATED POLYBUTENE	1
03G - Other Eye Makeup Preparations	HYDROGENATED POLYBUTENE	1
07E - Lipstick	HYDROGENATED POLYBUTENE	26
07I - Other Makeup Preparations	HYDROGENATED POLYBUTENE	8
10E - Other Personal Cleanliness Products	HYDROGENATED POLYBUTENE	2
12J - Other Skin Care Preps	HYDROGENATED POLYBUTENE	1

03A - Eyebrow Pencil	HYDROGENATED POLYDECENE	1
03B - Eyeliner	HYDROGENATED POLYDECENE	1
03C - Eye Shadow	HYDROGENATED POLYDECENE	53
03D - Eye Lotion	HYDROGENATED POLYDECENE	11
03F - Mascara	HYDROGENATED POLYDECENE	2
03G - Other Eye Makeup Preparations	HYDROGENATED POLYDECENE	9
04B - Perfumes	HYDROGENATED POLYDECENE	8
04E - Other Fragrance Preparation	HYDROGENATED POLYDECENE	9
05A - Hair Conditioner	HYDROGENATED POLYDECENE	9
05F - Shampoos (non-coloring)	HYDROGENATED POLYDECENE	10
05G - Tonics, Dressings, and Other Hair Grooming Aids	HYDROGENATED POLYDECENE	14
05I - Other Hair Preparations	HYDROGENATED POLYDECENE	5
06G - Hair Bleaches	HYDROGENATED POLYDECENE	2
07A - Blushers (all types)	HYDROGENATED POLYDECENE	6
07B - Face Powders	HYDROGENATED POLYDECENE	5
07C - Foundations	HYDROGENATED POLYDECENE	1
07D - Leg and Body Paints	HYDROGENATED POLYDECENE	11
07E - Lipstick	HYDROGENATED POLYDECENE	188
07G - Rouges	HYDROGENATED POLYDECENE	3
07H - Makeup Fixatives	HYDROGENATED POLYDECENE	1

07I - Other Makeup Preparations	HYDROGENATED POLYDECENE	11
08G - Other Manicuring Preparations	HYDROGENATED POLYDECENE	1
10E - Other Personal Cleanliness Products	HYDROGENATED POLYDECENE	3
11A - Aftershave Lotion	HYDROGENATED POLYDECENE	1
12A - Cleansing	HYDROGENATED POLYDECENE	7
12C - Face and Neck (exc shave)	HYDROGENATED POLYDECENE	40
12D - Body and Hand (exc shave)	HYDROGENATED POLYDECENE	75
12F - Moisturizing	HYDROGENATED POLYDECENE	186
12G - Night	HYDROGENATED POLYDECENE	15
12H - Paste Masks (mud packs)	HYDROGENATED POLYDECENE	1
12I - Skin Fresheners	HYDROGENATED POLYDECENE	1
12J - Other Skin Care Preps	HYDROGENATED POLYDECENE	15
13B - Indoor Tanning Preparations	HYDROGENATED POLYDECENE	8

03A - Eyebrow Pencil	HYDROGENATED POLYISOBUTENE	5
03B - Eyeliner	HYDROGENATED POLYISOBUTENE	51
03C - Eye Shadow	HYDROGENATED POLYISOBUTENE	55
03D - Eye Lotion	HYDROGENATED POLYISOBUTENE	43
03E - Eye Makeup Remover	HYDROGENATED POLYISOBUTENE	2
03F - Mascara	HYDROGENATED POLYISOBUTENE	15
03G - Other Eye Makeup Preparations	HYDROGENATED POLYISOBUTENE	56
04B - Perfumes	HYDROGENATED POLYISOBUTENE	3
04C - Powders (dusting and talcum, excluding aftershave talc)	HYDROGENATED POLYISOBUTENE	3
04E - Other Fragrance Preparation	HYDROGENATED POLYISOBUTENE	5
05A - Hair Conditioner	HYDROGENATED POLYISOBUTENE	4
05F - Shampoos (non-coloring)	HYDROGENATED POLYISOBUTENE	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	HYDROGENATED POLYISOBUTENE	6
05I - Other Hair Preparations	HYDROGENATED POLYISOBUTENE	4
06E - Hair Color Sprays (aerosol)	HYDROGENATED POLYISOBUTENE	2
06H - Other Hair Coloring Preparation	HYDROGENATED POLYISOBUTENE	1
07A - Blushers (all types)	HYDROGENATED POLYISOBUTENE	31
07B - Face Powders	HYDROGENATED POLYISOBUTENE	39
07C - Foundations	HYDROGENATED POLYISOBUTENE	41
07E - Lipstick	HYDROGENATED POLYISOBUTENE	865
07F - Makeup Bases	HYDROGENATED POLYISOBUTENE	6

07G - Rouges	HYDROGENATED POLYISOBUTENE	54
07H - Makeup Fixatives	HYDROGENATED POLYISOBUTENE	4
07I - Other Makeup Preparations	HYDROGENATED POLYISOBUTENE	132
08B - Cuticle Softeners	HYDROGENATED POLYISOBUTENE	1
08E - Nail Polish and Enamel	HYDROGENATED POLYISOBUTENE	3
08G - Other Manicuring Preparations	HYDROGENATED POLYISOBUTENE	3
10A - Bath Soaps and Detergents	HYDROGENATED POLYISOBUTENE	6
10B - Deodorants (underarm)	HYDROGENATED POLYISOBUTENE	4
11A - Aftershave Lotion	HYDROGENATED POLYISOBUTENE	9
11E - Shaving Cream	HYDROGENATED POLYISOBUTENE	7
11G - Other Shaving Preparation Products	HYDROGENATED POLYISOBUTENE	1
12A - Cleansing	HYDROGENATED POLYISOBUTENE	20
12C - Face and Neck (exc shave)	HYDROGENATED POLYISOBUTENE	111
12D - Body and Hand (exc shave)	HYDROGENATED POLYISOBUTENE	107
12E - Foot Powders and Sprays	HYDROGENATED POLYISOBUTENE	1
12F - Moisturizing	HYDROGENATED POLYISOBUTENE	136
12G - Night	HYDROGENATED POLYISOBUTENE	44
12H - Paste Masks (mud packs)	HYDROGENATED POLYISOBUTENE	5
12I - Skin Fresheners	HYDROGENATED POLYISOBUTENE	2
12J - Other Skin Care Preps	HYDROGENATED POLYISOBUTENE	67
13A - Suntan Gels, Creams, and Liquids	HYDROGENATED POLYISOBUTENE	1
13B - Indoor Tanning Preparations	HYDROGENATED POLYISOBUTENE	4
13C - Other Suntan Preparations	HYDROGENATED POLYISOBUTENE	3
03A - Eyebrow Pencil	POLYBUTENE	9
03B - Eyeliner	POLYBUTENE	78
03C - Eye Shadow	POLYBUTENE	27
03D - Eye Lotion	POLYBUTENE	22
03E - Eye Makeup Remover	POLYBUTENE	2
03F - Mascara	POLYBUTENE	72
03G - Other Eye Makeup Preparations	POLYBUTENE	29
04B - Perfumes	POLYBUTENE	1
04C - Powders (dusting and talcum, excluding aftershave talc)	POLYBUTENE	1
04E - Other Fragrance Preparation	POLYBUTENE	1
05A - Hair Conditioner	POLYBUTENE	2

05G - Tonics, Dressings, and Other Hair Grooming Aids	POLYBUTENE	1
05I - Other Hair Preparations	POLYBUTENE	1
07A - Blushers (all types)	POLYBUTENE	12
07B - Face Powders	POLYBUTENE	10
07C - Foundations	POLYBUTENE	11
07D - Leg and Body Paints	POLYBUTENE	2
07E - Lipstick	POLYBUTENE	1322
07F - Makeup Bases	POLYBUTENE	4
07G - Rouges	POLYBUTENE	4
07H - Makeup Fixatives	POLYBUTENE	1
07I - Other Makeup Preparations	POLYBUTENE	172
10E - Other Personal Cleanliness Products	POLYBUTENE	4
11A - Aftershave Lotion	POLYBUTENE	3
11F - Shaving Soap	POLYBUTENE	5
12C - Face and Neck (exc shave)	POLYBUTENE	2
12D - Body and Hand (exc shave)	POLYBUTENE	6
12F - Moisturizing	POLYBUTENE	9
12G - Night	POLYBUTENE	1
12H - Paste Masks (mud packs)	POLYBUTENE	1
12J - Other Skin Care Preps	POLYBUTENE	6
13C - Other Suntan Preparations	POLYBUTENE	1
03C - Eye Shadow	POLY(C30-45 OLEFIN)	1
07C - Foundations	POLY(C30-45 OLEFIN)	1
03C - Eye Shadow	POLYDECENE	4
03D - Eye Lotion	POLYDECENE	2
03E - Eye Makeup Remover	POLYDECENE	1
03G - Other Eye Makeup Preparations	POLYDECENE	1
04E - Other Fragrance Preparation	POLYDECENE	1
05A - Hair Conditioner	POLYDECENE	1
05I - Other Hair Preparations	POLYDECENE	1
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	POLYDECENE	2
06F - Hair Lighteners with Color	POLYDECENE	1
06G - Hair Bleaches	POLYDECENE	12
06H - Other Hair Coloring Preparation	POLYDECENE	1

07A - Blushers (all types)	POLYDECENE	3
07B - Face Powders	POLYDECENE	7
07C - Foundations	POLYDECENE	4
07E - Lipstick	POLYDECENE	75
07F - Makeup Bases	POLYDECENE	4
07I - Other Makeup Preparations	POLYDECENE	2
11G - Other Shaving Preparation Products	POLYDECENE	1
12A - Cleansing	POLYDECENE	5
12C - Face and Neck (exc shave)	POLYDECENE	2
12D - Body and Hand (exc shave)	POLYDECENE	6
12F - Moisturizing	POLYDECENE	12
12H - Paste Masks (mud packs)	POLYDECENE	3
12J - Other Skin Care Preps	POLYDECENE	5
02D - Other Bath Preparations	POLYETHYLENE	1
03A - Eyebrow Pencil	POLYETHYLENE	31
03B - Eyeliner	POLYETHYLENE	365
03C - Eye Shadow	POLYETHYLENE	181
03D - Eye Lotion	POLYETHYLENE	38
03E - Eye Makeup Remover	POLYETHYLENE	6
03F - Mascara	POLYETHYLENE	70
03G - Other Eye Makeup Preparations	POLYETHYLENE	43
04B - Perfumes	POLYETHYLENE	3
04C - Powders (dusting and talcum, excluding aftershave talc)	POLYETHYLENE	6
04E - Other Fragrance Preparation	POLYETHYLENE	14
05F - Shampoos (non-coloring)	POLYETHYLENE	5
05G - Tonics, Dressings, and Other Hair Grooming Aids	POLYETHYLENE	12
05I - Other Hair Preparations	POLYETHYLENE	2
06G - Hair Bleaches	POLYETHYLENE	1
06H - Other Hair Coloring Preparation	POLYETHYLENE	1
07A - Blushers (all types)	POLYETHYLENE	57
07B - Face Powders	POLYETHYLENE	76
07C - Foundations	POLYETHYLENE	55
07D - Leg and Body Paints	POLYETHYLENE	1
07E - Lipstick	POLYETHYLENE	885
07F - Makeup Bases	POLYETHYLENE	17
07G - Rouges	POLYETHYLENE	42

07H - Makeup Fixatives	POLYETHYLENE	1
07I - Other Makeup Preparations	POLYETHYLENE	103
08B - Cuticle Softeners	POLYETHYLENE	2
08E - Nail Polish and Enamel	POLYETHYLENE	30
10A - Bath Soaps and Detergents	POLYETHYLENE	174
10B - Deodorants (underarm)	POLYETHYLENE	8
10E - Other Personal Cleanliness Products	POLYETHYLENE	125
11A - Aftershave Lotion	POLYETHYLENE	1
11F - Shaving Soap	POLYETHYLENE	4
11G - Other Shaving Preparation Products	POLYETHYLENE	2
12A - Cleansing	POLYETHYLENE	163
12B - Depilatories	POLYETHYLENE	5
12C - Face and Neck (exc shave)	POLYETHYLENE	47
12D - Body and Hand (exc shave)	POLYETHYLENE	23
12F - Moisturizing	POLYETHYLENE	80
12G - Night	POLYETHYLENE	20
12H - Paste Masks (mud packs)	POLYETHYLENE	15
12J - Other Skin Care Preps	POLYETHYLENE	50
13A - Suntan Gels, Creams, and Liquids	POLYETHYLENE	2
13B - Indoor Tanning Preparations	POLYETHYLENE	3
13C - Other Suntan Preparations	POLYETHYLENE	3
03A - Eyebrow Pencil	POLYISOBUTENE	5
03B - Eyeliner	POLYISOBUTENE	3
03C - Eye Shadow	POLYISOBUTENE	11
03D - Eye Lotion	POLYISOBUTENE	10
03F - Mascara	POLYISOBUTENE	65
03G - Other Eye Makeup Preparations	POLYISOBUTENE	14
04B - Perfumes	POLYISOBUTENE	2
04E - Other Fragrance Preparation	POLYISOBUTENE	4
05G - Tonics, Dressings, and Other Hair Grooming Aids	POLYISOBUTENE	4
05I - Other Hair Preparations	POLYISOBUTENE	1
07A - Blushers (all types)	POLYISOBUTENE	4
07B - Face Powders	POLYISOBUTENE	4
07C - Foundations	POLYISOBUTENE	11

07E - Lipstick	POLYISOBUTENE	54
07F - Makeup Bases	POLYISOBUTENE	1
07I - Other Makeup Preparations	POLYISOBUTENE	19
11E - Shaving Cream	POLYISOBUTENE	7
12C - Face and Neck (exc shave)	POLYISOBUTENE	22
12D - Body and Hand (exc shave)	POLYISOBUTENE	8
12F - Moisturizing	POLYISOBUTENE	26
12G - Night	POLYISOBUTENE	8
12H - Paste Masks (mud packs)	POLYISOBUTENE	8
12J - Other Skin Care Preps	POLYISOBUTENE	15
13A - Suntan Gels, Creams, and Liquids	POLYISOBUTENE	2
13B - Indoor Tanning Preparations	POLYISOBUTENE	2
03B - Eyeliner	POLYISOPRENE	1
03C - Eye Shadow	POLYISOPRENE	1
07A - Blushers (all types)	POLYISOPRENE	1
07B - Face Powders	POLYISOPRENE	3
07E - Lipstick	POLYISOPRENE	3
07I - Other Makeup Preparations	POLYISOPRENE	2
12C - Face and Neck (exc shave)	POLYISOPRENE	5
12D - Body and Hand (exc shave)	POLYISOPRENE	1
12F - Moisturizing	POLYISOPRENE	9
12H - Paste Masks (mud packs)	POLYISOPRENE	2
03B - Eyeliner	POLYPROPYLENE	1
03C - Eye Shadow	POLYPROPYLENE	1
03F - Mascara	POLYPROPYLENE	4
07A - Blushers (all types)	POLYPROPYLENE	1
07C - Foundations	POLYPROPYLENE	1
08E - Nail Polish and Enamel	POLYPROPYLENE	1
10E - Other Personal Cleanliness Products	POLYPROPYLENE	1
12A - Cleansing	POLYPROPYLENE	3
12C - Face and Neck (exc shave)	POLYPROPYLENE	7
12F - Moisturizing	POLYPROPYLENE	2
12J - Other Skin Care Preps	POLYPROPYLENE	2

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: February 10, 2015

SUBJECT: Ethylene/Propylene Copolymer

As an estimate of remaining ethylene and propylene monomers, a supplier completed a potassium permanganate consumption test on their Ethylene/Propylene Copolymer as indicated in the attachment.

Japan Natural Products, Inc. 2015. Potassium permanganate consumption test on Ethylene/Propylene Copolymer.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

JNP JAPAN NATURAL PRODUCTS, INC.

To intend the determination of monomer value at .(Ethylene Propylene copolymer) , we conduct the measurement of Potassium permanganate consumption value at extract condition mentioned below.

Test material· (Ethylene Propylene copolymer)
Extraction vehicle: water (temp 60℃ , period : 30 mim)
Vehicle volume / test material surface area = 2mL / cm^2

Testing organization: Japan Food Research Laboratories
Test No.15003168001-01

Extraction test result (Potassium permanganate consumption value)

0.8ppm

JAPAN NATURAL PRODUCTS, INC.
539-9,SHIMOMIZO SAGAMIHARA CITY KANAGAWA

NAOKAZU KOGA
President

Date of issue: February 10, 2015

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: March 23, 2015

SUBJECT: HRIPT of a Product Containing Polyisoprene

Consumer Product Testing Co. 2004. Repeated insult patch test: Lip gloss containing 12.33% Polyisoprene.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

Consumer Product Testing Co.

EST. 1975

FINAL REPORT

CLIENT: [redacted]

ATTENTION: [redacted]

TEST: Repeated Insult Patch Test
Protocol No.: 1.01

TEST MATERIAL: [redacted]

Lip gloss contains 12.33% Polyisoprene

EXPERIMENT REFERENCE NUMBER: C04-0323.01

Richard R. Eisenberg, M.D.
Board Certified Dermatologist

Michael Traudt, Ph.D.
Director, Clinical Evaluations

Joy Frank, R.N.
Executive Vice President, Clinical Evaluations

Report Date: 6/11/04

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

Consumer Product Testing Co.
EST. 1975

QUALITY ASSURANCE UNIT STATEMENT

Study No.: C04-0323.01

The objective of the Quality Assurance Unit (QAU) is to monitor the conduct and reporting of clinical laboratory studies. These studies have been performed with adherence to the applicable ICH Guideline E6 for Good Clinical Practice and requirements provided for in 21 CFR parts 50 and 56 and in accordance to standard operating procedures and applicable protocols. The QAU maintains copies of study protocols and standard operating procedures and has inspected this study. All data pertinent to this study will be stored in the Consumer Product Testing Company archive, unless specified otherwise, in writing by the Sponsor.

Quality Assurance personnel involved:

6/11/04

Richard Hettenbach, M.A. Date
Senior Director of Regulatory Affairs & Quality Assurance

The representative signature of the Quality Assurance Unit signifies that this study has been performed in accordance with standard operating procedures and the applicable study protocol as well as any government regulations regarding such procedures and protocols.

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

Objective: To determine by repetitive epidermal contact the potential of a test material to induce primary or cumulative irritation and/or allergic contact sensitization.

Participants: One hundred and twelve (112) qualified subjects, male and female, ranging in age from 17 to 79 years, were selected for this evaluation. One hundred and three (103) subjects completed this study. The remaining subjects discontinued their participation for various reasons, none of which were related to the application of the test material.

Inclusion Criteria:

a. Male and female subjects, age 16[a] and over.
b. Absence of any visible skin disease which might be confused with a skin reaction from the test material.
c. Prohibition of use of topical or systemic steroids and/or antihistamines for at least seven days prior to study initiation.
d. Completion of a Medical History form and the understanding and signing of an Informed Consent form.
e. Considered reliable and capable of following directions.

Exclusion Criteria:

a. Ill health.
b. Under a doctor's care or taking medication(s) which could influence the outcome of the study.
c. Females who are pregnant or nursing.
d. A history of adverse reactions to cosmetics or other personal care products.

Test Material: [redacted]

Lip gloss containing 12.33% Polyisoprene

Study Schedule:

Panel #	Initiation Date	Completion Date
20040195	April 12, 2004	May 20, 2004
20040210	April 19, 2004	May 27, 2004

[a]With parental or guardian consent

Methodology:

The upper back between the scapulae served as the treatment area. Approximately 0.2 g of the test material, or an amount sufficient to cover the contact surface, was applied to the 1" x 1" absorbent pad portion of a clear adhesive dressing* and allowed to dry for approximately 30 minutes. This was then applied to the appropriate treatment site to form a semi-occluded patch.

Induction Phase:

Patches were applied three (3) times per week (e.g., Monday, Wednesday, and Friday) for a total of nine (9) applications. The site was marked to ensure the continuity of patch application. Following supervised removal and scoring of the first Induction patch, participants were instructed to remove all subsequent Induction patches at home, twenty-four hours after application. The evaluation of this site was made again just prior to re-application. If a participant was unable to report for an assigned test day, one (1) makeup day was permitted. This day was added to the Induction period.

With the exception of the first supervised Induction Patch reading, if any test site exhibited a moderate (2-level) reaction during the Induction Phase, application was moved to an adjacent area. Applications are discontinued for the remainder of this test phase, if a moderate (2-level) reaction was observed on this new test site. Applications would also be discontinued if marked (3-level) or severe (4-level) reactivity was noted.

Rest periods consisted of twenty-four hours following each Tuesday and Thursday removal, and forty-eight hours following each Saturday removal.

Challenge Phase:

Approximately two (2) weeks after the final Induction patch application, a Challenge patch was applied to a virgin test site adjacent to the original Induction patch site, following the same procedure described for Induction. The patch was removed and the site scored at the clinic twenty-four and seventy-two hours post-application.

*Manufactured by TruMed Technologies, Inc., Burnsville, MN

Evaluation Key:

0 = No visible skin reaction
+ = Barely perceptible or spotty erythema
1 = Mild erythema covering most of the test site
2 = Moderate erythema, possible presence of mild edema
3 = Marked erythema, possible edema
4 = Severe erythema, possible edema, vesiculation, bullae and/or ulceration

Results:

The results of each participant are appended (Table 1).

Observations remained within normal limits throughout the test interval.

Summary:

Under the conditions of this study, test material, [redacted] did not indicate a potential for dermal irritation or allergic contact sensitization.

Table I
Panel #20040195

Individual Results

[redacted]

Subject Number	24*hr	Induction Phase 1	2	3	4	5	6	7	8	9	Virgin Challenge Site 24*hr	72 hr
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	-----	DID NOT COMPLETE STUDY										
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	1	0	0	0	0
23	-----	DID NOT COMPLETE STUDY										
24	0	0	0	0	0	0	0	---DID NOT COMPLETE STUDY---				
25	0	0	0	0	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0

24* = Supervised removal of 1st Induction and Challenge Patch

Table I
(continued)
Panel #20040195

Individual Results

[redacted]

Subject Number	24*hr	Induction Phase 1	2	3	4	5	6	7	8	9	Virgin Challenge Site 24*hr	72 hr
29	0	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0
48	-	0	0	DID NOT COMPLETE STUDY								
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0
51	0	0	DID NOT COMPLETE STUDY									
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0[m]	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0

24* = Supervised removal of 1st Induction and Challenge Patch
m = Additional makeup day granted at the discretion of the clinic supervisor
- = Subject not present for supervised patch removal

Table 1
(continued)
Panel #20040210

Individual Results

[redacted]

Subject Number	24*hr	Induction Phase 1	2	3	4	5	6	7	8	9	Virgin Challenge Site 24*hr	72 hr
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	2[A]	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0
16	-	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	--------DID NOT COMPLETE STUDY--------					
21	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	+	0	0	0	0	0	0	0

24* = Supervised removal of 1st Induction and Challenge Patch
- = Subject not present for supervised removal
A = Changed to adjacent site

Table 1
(continued)
Panel #20040210

Individual Results

[redacted]

Subject Number	24*hr	Induction Phase 1	2	3	4	5	6	7	8	9	Virgin Challenge Site 24*hr	72 hr
29	0	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	DID NOT COMPLETE STUDY										
51	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	DID NOT COMPLETE STUDY							
54	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	DID NOT COMPLETE STUDY									

24* = Supervised removal of 1st Induction and Challenge Patch

Table 2
Panel #20040195

Subject Data

Subject Number	Initials	Age	Sex
1	CP	46	F
2	DP	45	M
3	MS	52	F
4	JV	37	F
5	WB	62	M
6	WQ	30	M
7	AL	44	F
8	CL	25	F
9	MD	51	F
10	MD	54	M
11	LD	19	M
12	IZ	45	F
13	KQ	45	F
14	LM	62	F
15	JS	65	F
16	MR	17	F
17	JS	42	F
18	RB	51	F
19	TS	25	M
20	GS	44	F
21	SV	26	F
22	MG	33	M
23	SP	37	F
24	SS	35	F
25	EB	59	F
26	MH	48	F
27	JW	50	F
28	BC	78	F

Table 2
(continued)
Panel #20040195

Subject Data

Subject Number	Initials	Age	Sex
29	LR	42	F
30	RE	23	F
31	PA	58	F
32	LT	38	F
33	LR	70	F
34	SM	68	F
35	DM	69	M
36	JC	37	F
37	CC	57	F
38	MD	79	F
39	PD	64	F
40	PL	74	F
41	JB	56	F
42	JM	35	M
43	MR	41	F
44	AM	30	F
45	IB	27	F
46	ES	44	F
47	MP	68	F
48	GV	24	M
49	SD	58	F
50	RA	45	F
51	BH	41	M
52	LR	44	F
53	MR	46	M
54	KT	31	F
55	JT	45	M
56	FH	18	F

Table 2
(continued)
Panel #20040210

Subject Data

Subject Number	Initials	Age	Sex
1	BT	64	F
2	LF	42	F
3	BR	72	F
4	CG	41	F
5	ML	37	F
6	MB	73	F
7	JB	73	M
8	DW	64	F
9	RW	67	M
10	JS	65	F
11	FR	75	F
12	SK	37	F
13	KM	46	F
14	EA	64	F
15	CG	59	F
16	MB	78	F
17	BC	42	F
18	AK	61	F
19	VB	65	F
20	MB	38	F
21	AS	37	F
22	DG	33	F
23	AU	60	F
24	RS	50	M
25	JC	48	F
26	GC	50	M
27	KS	48	F
28	MS	70	F

Table 2
(continued)
Panel #20040210

Subject Data

Subject Number	Initials	Age	Sex
29	KF	33	F
30	CM	52	F
31	LW	55	M
32	FP	64	F
33	HV	72	F
34	GV	77	M
35	LS	37	F
36	DT	46	F
37	CW	55	F
38	DT	32	F
39	ST	47	M
40	JO	17	M
41	AS	75	M
42	AS	70	F
43	SH	36	F
44	DG	40	F
45	RF	47	F
46	MC	22	F
47	KG	39	F
48	LG	18	M
49	RN	55	F
50	WS	44	M
51	DF	70	F
52	NS	76	F
53	RS	37	M
54	ER	40	F
55	DP	47	F
56	WR	22	M

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: March 12, 2015

SUBJECT: Comments on the Draft Report Prepared for the March 16-17, 2015 CIR Expert Panel Meeting: Safety Assessment of Polyene Group as Used in Cosmetics

Key Issues

Although ChemID may be incorrect reporting a molecular weight of 140.26 with CAS No. 68037-01-4, suppliers reported molecular weight ranges of 954-2168 for Polyisobutene, 187-468 for Hydrogenated Polyisobutene and 367-596 for Hydrogenated Polydecene (this information is currently in the Impurities section of the report). Therefore, in the Introduction and Chemical and Physical Properties section, rather than saying that "These polyenes are high molecular weigh moieties", it would be more appropriate to state that the reviewed polyenes cover a wide range of molecular weights.

Impurities - It is not clear what is meant by the word "formulations" in the Impurities section. The word "formulations" should be used for finished cosmetic products. If "formulations" in the impurities section represents mixtures of ingredients sold to the cosmetics industry, please change "formulations" to "tradename mixtures".

Additional Comments

Chemistry - It would be helpful if somewhere in the Chemistry section it could be clearly stated that many of these ingredients are sold to the cosmetic industry as components of mixtures.

Impurities - If composition information in addition to impurities is left in this section, the heading of the section should be revised to Composition/Impurities.
The molecular weight information from suppliers should not be presented in the Impurities section.

Cosmetic Use - Please use INCI names ("hydrogenated C6-14 olefin polymers" should be Hydrogenated Poly(C6-14 Olefin).

Noncosmetic Use - Table 5 indicates that use in chewing gum base is the only approval as a direct food additive. Therefore, the text of the Noncosmetic Use section should be

revised to indicate this single use as a direct food additive and indicate that these ingredients have many approved uses as indirect food additives.

Single Dose Exposure - The single dose studies should be summarized in a table rather than presented as text.

Single Dose Exposure, Inhalation - Please include the duration of exposure for the Polybutene study summarized from the original CIR report.

Single Dose Exposure, Dermal - Rather than stating "average molecular weight not specified" for the dimer of Hydrogenated Decene, please estimate a molecular weight.

Repeated Dose Exposure, Oral - Please delete the statement from a supplier indicating that "repeated exposures to Ethylene/Octene Copolymer are not anticipated to cause significant adverse effects" as this is not a study.

Repeated Dose Exposure, Dermal - In the description of the 4-week dermal study of rats to Hydrogenated Polyisobutene (references 39-42), it is not clear if the effects were observed only in treated rats, or if they were also observed in the control rats (it states that effects were limited to the application site).

Reproductive and Developmental Toxicity - In the summary of the developmental toxicity study of Polybutene from the original CIR report, did the male rats really loose weight, or was there a "slight weight gain depression"?

Genotoxicity, Hydrogenated Polydecene, reference 6 - Units of μg/ml should be described as concentration rather than dose.

Carcinogenicity - Please provide some indication of what data IARC reviewed in coming to their conclusions for Polyethylene and Polypropylene.

Irritation, Polybutene - It is not clear if "formulations" in this paragraph means finished cosmetic products or a tradename mixture.

Irritation, Dermal - Human - If they studied skin sensitization in the study of Ethylene/Octene Copolymer (reference 12), this study should be in the sensitization section. If it was as study of dermal irritation "skin sensitization" needs to be revised to "skin irritation".

Ocular - Non-Human, Mucous Membrane - Non-Human - What concentration/dose was used in the rabbit studies of Polybutene?

Table 1 - Please note that the CAS No. 68037-01-4 has been deleted from the Dictionary database for Hydrogenated Poly(C6-12 Olefin) and Hydrogenated Poly(C6-14 Olefin), as this CAS number appears to be specific for Hydrogenated Polydecene.

Table 2 - Please use primary references rather than the original CIR reports.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: April 9, 2015

SUBJECT: Comments on the Tentative Report: Safety Assessment of Polyene Group as Used in Cosmetics

Key Issues

The following sentence found in the Abstract and Discussion is not appropriate for this report. "The available data on many of the ingredients are sufficient, however, and similarity between structural activity relationships and biologic functions in cosmetic concentrations of use can be extrapolated to support the safety of the entire group." What are the "biologic functions" of these ingredients? What activity do these ingredient have that is related to structure? The Discussion also notes that these ingredients have "apparent biological inertness." This sentence also implies that these polymers have biological activity at cosmetic use concentrations which is not correct. It would be sufficient to state that ingredients are similar in structure and that data available on a number of the ingredients supports the safety of all the ingredients in the report.

Introduction, Summary - As some of these ingredients are liquids and some are solids (even under the same INCI name the ingredient can be a liquid or a solid), it is not appropriate to state that the ingredients in the report have "very similar" properties. The ingredients do have similar structures and reaction starting materials.

Cosmetic Use, Summary, Discussion - This report should include a discussion of the use concentrations included in the original reports. For example, the use of Hydrogenated Polyisobutene in lip products at a concentration of 95% is not new as the 2008 report included a use concentration of 96% for Hydrogenated Polyisobutene in "lipstick". Although the official FDA product category is "lipstick", the high concentration Hydrogenated Polyisobutene products are liquid lip glosses.

Additional Comments

Chemical and Physical Properties - The last paragraph of this section should be revised as it implies that a molecular weight is stated in the Dictionary. The definitions of

Hydrogenated Poly(C6-12 Olefin) and Hydrogenated Poly(C6-14 Olefin) state that they are "a series of low molecular weigh polymers" without providing a molecular weight. These ingredients are used as Squalane replacements, e.g., see https://www.chemical-navi.com/english/product_search/detail344.html, and are liquids. The last sentence of this paragraph should be deleted as it implies that these ingredients have 8 or more monomeric units - the number of monomers in these polymers is not known.

Cosmetic Use - Because deodorant spray products may result in higher inhalation exposure than other product types, please state the ingredient and concentration reported to be used in spray deodorants (Polyethylene 1.6% in an aerosol deodorant).

Genotoxicity - Although the amount of Ethylene/Octene Copolymer in the trade name mixture tested in the genotoxicity assays (reference 12) is not known precisely, it would be helpful to state what is known (contains 30-50% Ethylene/Octene Copolymer and Ethylene/sodium Acrylate Copolymer).

Carcinogenicity, Polypropylene - What studies did IARC review to reach the conclusion of "not classifiable"?

Sensitization, Polybutene - It is not clear why it states in the same paragraph that formulations containing Polybutene produce minimal irritation and no irritation. In addition, irritation should be discussed in the irritation section not in the sensitization section.

Sensitization, Hydrogenated Polyisobutene - "Hydrolyzed polyisobutene" should be corrected to "Hydrogenated polyisobutene"

Table 7 - Throughout this table, please give some indication of the amount of polymer in the trade name mixtures containing Ethylene/Octene Copolymer (reference 11 the mixture contained 14-16% Ethylene/Octene Copolymer; reference 12 the mixture contained 30-50% Ethylene/Octene Copolymer and Sodium Acrylate Copolymer).

Oral, Hydrogenated Polyisobutene, reference 39-42 - Why are the results written out in this row when they are presented as LD_{50} > in the other rows?

Dermal, Hydrogenated Polydodecene, reference 5 - The concentration is described as "undiluted"; 2000 mg/kg should be called a dose not a concentration.

Inhalation, hydrogenated decene dimer - Please state the percentage for the confidence interval (generally 95% CI).

Table 8, first row - ppm is a concentration not a dose; please indicate that this was a dietary study

third and ninth rows - Please state how the rats were treated (gavage, dietary, water).

sixth row, method column - "90-day oral toxicity study, groups of 20 male and 20 female Sprague-Dawley rats received" is not complete.

seventh row - ppm is a concentration not a dose

Table 9, Table 10, reference 12 - Please state the amount of polymer in the trade name mixture (30-50% Ethylene/Octene Copolymer and Sodium Acrylate Copolymer)

Table 11, references 11 and 12 - Please state the amount of polymer in the trade name mixtures containing Ethylene/Octene Copolymer (reference 11 the mixture contained 14-16% Ethylene/Octene Copolymer; reference 12 the mixture contained 30-50% Ethylene/Octene Copolymer and Sodium Acrylate Copolymer).

Hydrogenated Polydecene, Results, reference 5 - Please correct: “body were comparable to vehicle controls through the study period”