PINK

Safety Assessment of PEGylated Oils as Used in Cosmetics

CIR EXPERT PANEL MEETING

SEPTEMBER 10-11, 2012

Cosmetic Ingredient Review
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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett, Scientific Writer/Analyst
Date: August 17, 2012
Subject: Draft Tentative Amended Safety Assessment of PEGylated Oils

At the March 2012 meeting, the CIR Expert Panel re-opened the safety assessment of PEG-30, -33, -35, -36, -40 castor oil and PEG-30 and -40 hydrogenated castor oil in order to expand the report to include components that have been previously reviewed and concluded to be safe for use by the CIR Panel, most notably the recent safety assessments on plant-derived fatty acid oils and PEGs with an average of 4 moles of ethylene oxide or greater. This safety assessment now contains 130 ingredients.

A search for safety data pertaining to the new ingredients was conducted and few data were found. The Personal Care Products Council provided use concentration for these ingredients. No other unpublished data were received.

The highest concentration reported was 97% in Olive Oil PEG-7 Esters. This use was in a rinse-off product. The available use concentrations for the remaining ingredients were $\leq$ 40%.

The Panel should carefully review the discussion and conclusion of this report and issue a Tentative Amended Safety Assessment.

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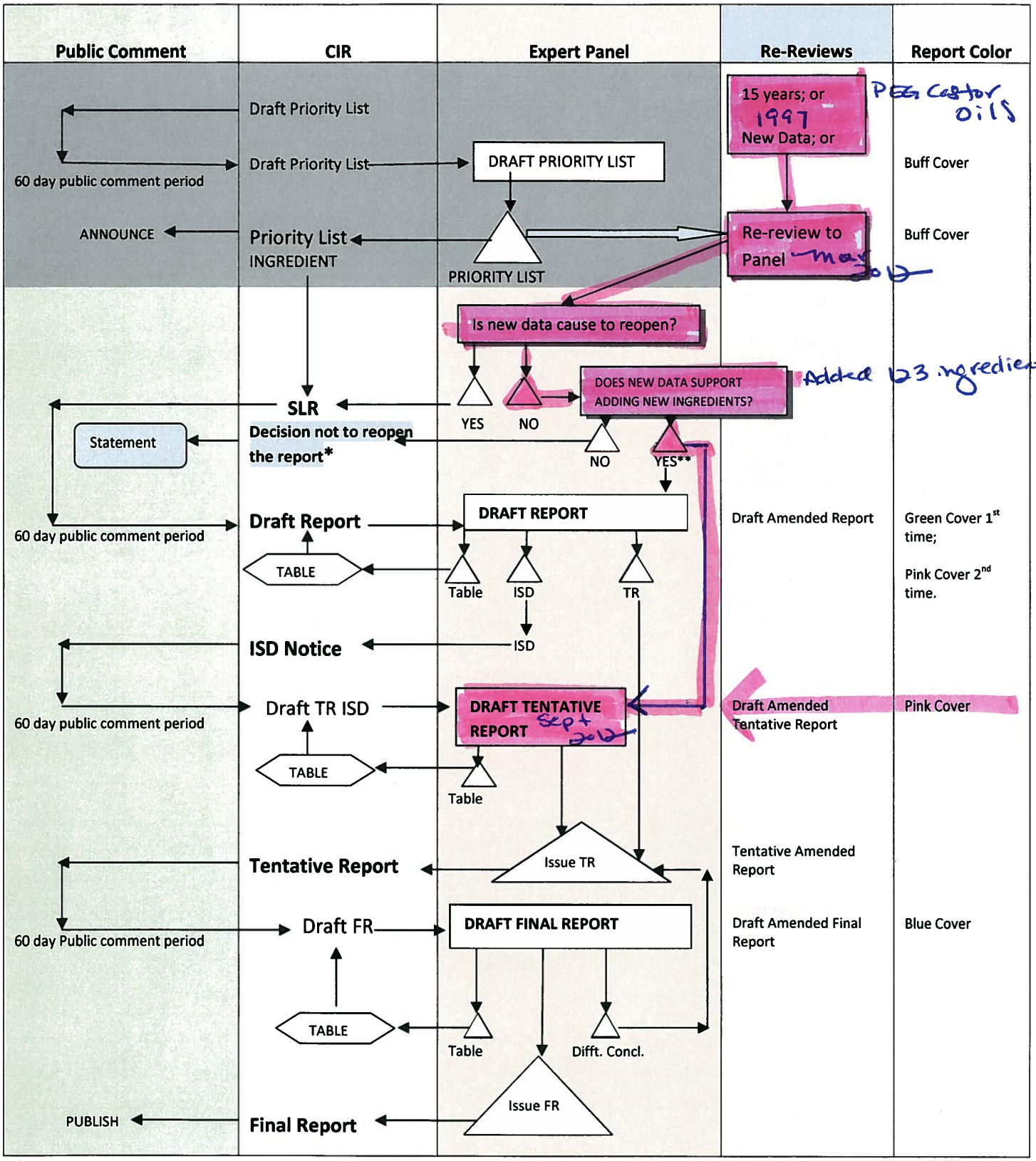
PEGylated Oils

SAFETY ASSESSMENT FLOW CHART

Sept 2012



*The CIR Staff notifies of the public of the decision not to re-open the report and prepares a draft statement for review by the Panel. After Panel review, the statement is issued to the Public.

**If Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.

Expert Panel Decision

Document for Panel Review

Option for Re-review

PEGylated Castor Oils History

Original Report: In 1997, the Expert Panel published the safety assessment for PEG Castor Oils with the conclusion that "PEG-30, -33, -35, -36, and -40 Castor Oil are safe for use in cosmetics at concentrations up to 50% and that PEG-30 and -40 Hydrogenated Castor Oil are safe for use at concentrations of up to 100%."

March 2012: The re-review of PEGylated Castor Oils was presented to the Panel. The Panel reopened this report to create a new grouping of 130 ingredients, titled **PEGylated oils**. While the conclusion reached for the original 7 ingredients was reaffirmed, the Panel considered that the available data could be used to support the safety of 123 additional PEGylated oils. Supporting the creation of this larger group were the recently completed review of PEGs and the review of vegetable oils. The Panel determined to not include PEGylated oils for which the oil moiety had not previously been reviewed.

PEGylated Oils Ingredients Data Profile* – Sept 2012 – Writer, Christina Burnett

	In-Use	Composition	Method of Mfg	Toxicokinetics	Acute Tox - Derm	Acute Tox - Oral	Acute Tox - Inhalation	Acute Tox - IV	Acute Tox - Other	Repeated Dose - Dermal	Repeated Dose - Oral	Repeated Dose - Inhalation	Repeated Dose -IV	Repeated Dose - Other	Repro/Dev Tox	Genotoxicity	Carcinogenicity/ Tumor Promoton	Dermal Irritation – Non-Human	Dermal Irritation-Human	Dermal Sens – Non-Human	Dermal Sens – Human	Ocular Irritation	Case Studies
PEGs	X	X	X	X	X	X				X	X				X	X	X	X	X	X	X	X	X
Alkyl PEG Ethers	X	X	X	X	X	X	X	X	X	X	X				X	X	X	X	X	X	X	X	X
Plant-Derived Fatty Acid Oils	X	X	X												X		X	X	X	X	X	X	X
Ricinus Communis (Castor) Oil et al.	X	X	X	X	X	X		X			X			X	X	X	X	X	X	X	X	X	X
Simmondsia Chinensis (Jojoba) Seed Oil et al.	X	X	X	X	X	X				X	X			X	X	X	X	X	X	X	X	X	X
Mink Oil	X	X	X	X	X	X									X		X	X	X	X	X		
PEGylated Castor Oils (Original Report)	X	X	X	X	X	X		X		X	X		X	X	X	X	X	X	X	X	X	X	X
PEG-9 Castor Oil	X																						
PEG-25 Castor Oil	X																						
PEG-30 Castor Oil	X																						
PEG-33Castor Oil	X																						
PEG-35 Castor Oil	X			X									X				X	X			X	X	
PEG-36 Castor Oil	X																						
PEG-40 Castor Oil	X																						
PEG-50 Castor Oil	X																						
PEG-60 Castor Oil	X																						
PEG-2 Hydrogenated Castor Oil	X					X																	
PEG-7 Hydrogenated Castor Oil	X																						X
PEG-10 Hydrogenated Castor Oil	X																						
PEG-16 Hydrogeanted Castor Oil	X																						
PEG-20 Hydrogenated Castor Oil	X																						
PEG-25 Hydrogenated Castor Oil	X																						
PEG-30 Hydrogenated Castor Oil	X																						
PEG-35 Hydrogenated Castor Oil	X																						
PEG-40 Hydrogenated Castor Oil	X			X													X						
PEG-45 Hydrogenated Castor Oil	X																						
PEG-60 Hydrogenated Castor Oil	X							X								X							X

	In-Use	Composition	Method of Mfg	Toxicokinetics	Acute Tox - Derm	Acute Tox - Oral	Acute Tox - Inhalation	Acute Tox - IV	Acute Tox - Other	Repeated Dose - Dermal	Repeated Dose - Oral	Repeated Dose - Inhalation	Repeated Dose -IV	Repeated Dose - Other	Repro/Dev Tox	Genotoxicity	Carcinogenicity/ Tumor Promoton	Dermal Irritation – Non-Human	Dermal Irritation-Human	Dermal Sens – Non-Human	Dermal Sens – Human	Ocular Irritation	Case Studies
PEG-80 Hydrogenated Castor Oil	X																						
PEG-100 Hydrogenated Castor Oil	X																						
PEG-20 Hydrogenated Castor Oil Triisosterate	X																						
PEG-40 Hydrogenated Castor Oil Triisostearate	X																						
PEG-50 Hydrogenated Castor Oil Succinate	X																		X		X	X	
PEG-40 Hydrogenated Castor Oil PCA Isostearate	X																						
Apricot Kernel Oil PEG-6 Esters	X																						
Avocado Oil PEG-11 Esters	X																						
Coconut Oil PEG-10 Esters	X																						
Grape Seed Oil PEG-8 Esters	X																						
Hydrogenated Palm/Palm Kernel Oil PEG-6 Esters	X																						
Jojoba Oil PEG-8 Esters	X																						
Olive Oil PEG-7 Esters	X																						
Olive Oil PEG-10 Esters	X																						
PEG-75 Meadowfoam Oil	X																						
NO USES OR DATA WERE AVAILABLE FOR THE REMAINING PEGYLATED OILS IN TABLE 1.																							

"X" indicates that data were available in the category for that ingredient

SEARCH STRATEGY FOR PEGylated Oils

December 2011/January 2012: SCIFINDER search for PEGylated Castor Oils- CAS NOs. 61791-12-6 and 61788-85-0 (generic), adverse effects, including toxicity

- Limited search to references published since 1995; 9 references came back.
- Limited search to books, clinical trials, journals, preprints, reports, and reviews; 9 references came back.

January 2012: SCIFINDER search for PEGylated Castor Oils – Possible expansion ingredients included, w/ generic CAS NO., adverse effects, including toxicity

- Limited search to books, clinical trials, journals, preprints, reports, and reviews; 54 references came back.

January 2012: SCIFINDER search for Cremophor, adverse effects, including toxicity

- Limited search to books, clinical trials, journals, preprints, reports, and reviews; 39 references came back.

	TOXLINE, minus PUBMED, limited to 1995-	**PUBMED, limited to 1995-**
61791-12-6	32	28
61788-85-0	23	28
Cremophor	59	822

Total references ordered: 23

Difficulty was experienced in searching for the expansion ingredients due to generic CAS No. (if one was available) and generic nature of ingredient names.

July 11, 2012: SCIFINDER search for trade names of additional ingredients

- **28 ingredients found, 64 references available, 25 ordered**

Transcript

Dr. Marks' Team Minutes – March 5, 2012

DR. MARKS: PEGylated oils.

DR. SHANK: Is that a real word?

DR. MARKS: I know. It sounds good. I like it.

DR. HELDRETH: PEGylated is a word that's used in the literature. I didn't come up with it.

DR. MARKS: So in '97 the CIR issued a safety assessment of a number of PEGs, hydrogenated castor oil, and concluded that the PEG-30, -33, -35, -36, and -40 were safe up to 50 percent and that -30 and -40 hydrogenated castor oil is safe up to 100 percent. And that conclusion was based on skin sensitization studies. We're at the point now to consider reopening this. So the first question, of course, is always are there any new evidence or data that would raise concerns to reopen it? And if there are not, then the second issue is do we want to reopen it to add ingredients? And the proposal is to go from seven to 134 ingredients, and it's a number. Ron Hill stepped out, but I'll ask for his comments when he comes back. Ron and Tom, any safety issues?

DR. SLAGA: Well, the conclusion is still the same.

DR. MARKS: Conclusion's the same.

DR. SHANK: Right. I would reopen only to add new ingredients.

DR. MARKS: Right. And do you want to reopen to add on -- this is page book 10 and 11, no I guess just 10, or the whole list. Is that correct, Christina?

DR. BURNETT: Panel Book 10 is the proposed ingredients to add. It does not include the originals.

DR. MARKS: Oh, it does not include the originals. So these would be the add-ons. These are the no-brainers.

DR. BURNETT: And the two asterisked ones do not have any crossover. They are oils or based on oils that we did not do a report on. So if you have issue with those, they've been highlighted as to not being reviewed before.

DR. MARKS: Thank you, Christina. That would seem to indicate they would not be no-brainers the way it sounds. So Ron Hill, Ron Shank, and Tom felt that we didn't need to reopen this for safety issues. But if we wanted, we could reopen it to add a number of ingredients. So Tom, Ron, do you want to reopen?

DR. SHANK: Yes.

DR. SLAGA: Yes for add-ons.

DR. SHANK: But I would eliminate the ingredients that have the asterisks in front, and I'd also eliminate PEG-2 and -3 castor oil because PEGs-2 and -3 were not in the original PEG review.

DR. MARKS: But if we reopen, we could add them. Oh, I see, but is it a no-brainer?

DR. SHANK: But we didn't add them because we didn't have data, and those are different from the real PEGs.

DR. MARKS: So you would eliminate PEG-2 castor oil and PEG-3 castor oil?

DR. SHANK: Yes.

DR. MARKS: And then everything that's asterisked? Thanks, Christina, again. Ron Hill, you weren't here when Christina had asterisked those oils as you can see by the footnote down there that we had never reviewed before. So we don't have anything that we could easily refer to, and it wouldn't be a no-brainer.

DR. HILL: Well, I looked at it, believe it or not, the other way, which was that these aren't oils either. And if they were small PEGs, if we were talking -- these are what? All -6 and above? I think maybe they're all -8 and above. I thought there was one small one. Yeah, I think they're all -8 and above. And my way of looking at it was if we can get -- the way we did vegetable oils pretty much was we looked at the fatty acid compositions and did read-across based on a huge matrix of data. If these fit, if fatty acid compositions -- and we have information that there are no other significant components in these oils -- then I don't see any reason why because they're not the oils anyway. They're not being metabolized to the oils, so we're reviewing the PEG oils, not the oils. And if we have the composition data on the oils to indicate safety, then to me there's no reason to exclude them.

DR. MARKS: Huh, I'm not sure that quite qualifies as a no-brainer. Now you're going back and looking at original, looking for data to support why this oil, this new ingredient, is safe whereas our rules of engagement were that we didn't have to go back and look at any data. It just was there, and we could no brain and say it's going to be safe.

DR. HILL: But not all of these PEGs have been reviewed before, right? So we're reviewing PEG oils, PEGylated oils, and so --

DR. MARKS: Can we read across with the PEGs?

DR. HILL: So knowing -- the oil toxicology does nothing for me in this. I mean, it's totally irrelevant. The only thing that's relevant from the oils is the composition data and what gets PEGylated other than if we have some minor impurities that are non-phosphate glyceride, non-glyceride ester components. So for me we're not reviewing the vegetable oils and so brain or no-brainer has no bearing here. If we're going to read across to other PEGylated oils, we have no reason to exclude these others from where I sit.

Of course, if we can't get the composition data telling us these are the fatty acids that are in there, 2 percent and above or whatever, and we can't get data indicating there's not much else in these oils, then we still can't. We'll have to say insufficient information. But to me, we're not reviewing vegetable oils here. We're reviewing PEGylated oils. So if there are any that haven't been reviewed before for safety that we're adding on, whether or not we have the vegetable oil pre-review, to me then there's no

reason to exclude them. But that's just my logic. And I'm looking at it from the other point of view, which is if we have some unique oil that some little village in Ecuador grows this stuff and they can market the oil, it might help them to know that it's safe.

DR. MARKS: So I guess I would ask you if we have PEG-30 and PEG-40 hydrogenated castor oil. That was felt to be safe. Is it a no-brainer that we would say -35 is safe? Safe? Ron Hill? I mean, to me there is the read-across it whereas if I look at what's been asterisked, bitter cherry seed oil, I'm not -- I assume it is, it's probably GRAS -- but we have to do a lot more digging. Just like you said Ron, we now have to go out, create a chart, find out what the ingredients of bitter cherry seed oil is. So that's not a no- brainer whereas perhaps PEG-35 hydrogenated castor oil is a no-brainer since we've done -35 castor oil and we've done -30 and -40 hyrdrogenated. But that's my reasoning. Ron Shank and Tom, what are your feelings?

DR. HILL: Before they answer that, have we done PEGylated almond oil before? Have we done PEGylated apricot kernel oil? I know we've done the oils themselves, but have we done those PEGylated oils? I mean, I get it on the castor oil where we're just changing the number of PEGs because if we're going to take that approach, then it should only be castor oils only.

DR. MARKS: I assume we did almond oil.

DR. BURNETT: Correct. We did not PEGylated oil. We did the oil --

DR. HILL: That doesn't matter. My point is that's irrelevant other than the fatty acid composition. And we're going to have to look at that again anyway to do the read- across. Now if we just stick to castor oils and add the number of PEG groups, then that's a no-brainer.

DR. MARKS: Ron Shank? So what you would suggest then, Ron Hill, is that anything that doesn't have castor oil would be eliminated.

DR. HILL: No, I think we should do them all, but I'm just saying --

DR. MARKS: Now this is a re-review.

DR. HILL: A re-review?

DR. MARKS: Yes, so that's what the rules are somewhat different in terms of we aren't opening to do these add-ons. The intent was to get more ingredients reviewed in a reasonable way, but as a no-brainer.

DR. HILL: Okay, I think as soon as you go apart from castor oil, then if you went to apply the no-brainer rule that way, then yes we should exclude all those.

DR. MARKS: Ron Shank? Tom?

DR. SLAGA: I felt what Ron stated with -2 and -3 and the ones with asterisks since we haven't previously reviewed those. The rest of them were fine.

DR. MARKS: Well, the good thing is tomorrow I'm not making a move other than reopening, and then we can have the discussion on ingredients. And Ron Hill, I think probably what I will do is we'll see how the Belsito Team -- and then I'll ask you to react to it in terms of whether we limit it to just eliminating besides PEG-2 and -3 castor oil, these other asterisks or getting into the group. What I hear from Tom and Ron Shank is that we just eliminate PEG-2 and -3 castor oil and then those asterisked components. And we'll see what the team tomorrow -- and Ron, you can express your concerns. Be sure and remind me if I --

The one thing I had, question a couple of things. One in the back you had previous words were mink and jojoba. Were they relevant to this, some of the background data? There was mink oil and --

DR. BURNETT: One of the proposed ingredients is mink oil PEG-13 esters.

DR. MARKS: Safe, okay.

DR. BURNETT: And jojoba oil PEG-18 and -150 esters.

DR. MARKS: And then how are we going to reconcile with when we reopen it if we add all these other ingredients where in the original report we limited the concentration to 50 percent? And now we're going to read across. Do we read across 50 percent or do we read across 100 percent when it comes to sensitization with these?

DR. SHANK: It has to be 50 percent; otherwise we'd need more data and then it's not a no-brainer.

DR. MARKS: Then it's a no, okay. So we would have to have HRIPT or max to indicate that it's safe at greater than 50 percent. Good, thanks Ron. I was struggling on how we would read across and do that. Any other comments?

MS. WEINTRAUB: There are a few uses in baby products, not that many. And there's been a big increase percentage wise for PEG-40s. For hydrogenated castor oil, there was one reported use in '97 and 18 in 2011.

DR. HILL: I have one other question and maybe Bart could answer this.

DR. MARKS: Thanks, Rachel.

DR. HILL: Just had made a note of it and then forgot about it. Where it says something like rapeseed oil PEG-3 esters, what are we actually talking about because we don't have any --

DR. HELDRETH: Where's that at?

DR. HILL: In the second -- if you look at the master ingredient list where we were just looking with the asterisks and so forth. When it says rapeseed oil PEG-3 esters --

DR. HELDRETH: Okay, so if you think about an oil as a triglyceride, you could have --

DR. HILL: Never mind; I just answered my own question. Missed a little transesterification tidbit. I got it.

DR. MARKS: Okay, I'll summarize here tomorrow. Presumably I'm going to second a motion to reopen this report, and the purpose to do a number of add-ons on page 10. We'll have some discussion as to which ones they actually will be and then concerning what the limit concentration from sensitivity. We're going to put it at 50 percent based on the original assessment. Any other comments?

Dr. Belsito's Team Minutes – March 5, 2012

DR. BELSITO: Okay, so, same question. Re-review based upon new data and you need to reopen, no, add-ons, yes, but I guess I had a question on PEG-2 and PEG-3 because the PEGs, we only went down to four.

DR. ANDERSEN: We actually went down to three, triethylene glycol.

DR. BELSITO: Okay. But we haven't gotten down to two.

MR. HELDRETH: Yes, that's with the PEG.

DR. BELSITO: Right.

MR. HELDRETH: As PEG, no.

DR. BELSITO: Right. So, can we do PEG-3?

DR. ANDERSEN: Well, the ingredient that you would name PEG-3 is actually called triethylene glycol in the dictionary.

DR. BELSITO: PEG-2, I'm sorry. Because PEG-2 castor oil is one of the suggested add-ons. As is PEG-3 castor oil. Page 12 of the Panel Book.

DR. ANDERSEN: Yes, yes, I'm just trying to remember what we said in the PEG report itself.

DR. BELSITO: I don't know. I looked up the PEG report and the information I got was that it went down to PEG-4.

DR. ANDERSEN: Yes. Yes, PEG-4, for PEGs, that's the lowest as described.

DR. BELSITO: Right.

DR. ANDERSEN: PEG-3 uses different terminology and there is no PEG-2 as a cosmetic ingredient. No, I'm sorry, there is. Diethylene --

DR. BELSITO: Glycol.

DR. ANDERSEN: And that's been separately reviewed.

DR. BELSITO: Has it been?

MR. HELDRETH: Not by us.

DR. ANDERSEN: Not by us. Oh, I thought I was, okay.

MR. HELDRETH: But we didn't do triethylene glycol, which would be PEG-3.

DR. ANDERSEN: We can add that to the table then.

DR. BELSITO: So, do we need to put this on hold and do diethylene glycol first?

DR. ANDERSEN: Not on a PEG. (Laughter)

DR. BELSITO: Not on a PEG. Is PEG-2 castor oil used at all?

MS. BURNETT: The hydrogenated oils (inaudible) uses.

SPEAKER: It's the hydrogenated.

DR. BELSITO: It would be a shame to leave that little PEG-gy out in the cold, wouldn't it?

DR. SNYDER: This little PEG-gy.

DR. BELSITO: It's been a long day.

DR. SNYDER: Yes.

SPEAKER: This little PEG-gy had none.

DR. BELSITO: I mean, our concern with cutting off at PEG-4 was what, ethylene glycol, monomer residual? Is that it?

DR. ANDERSEN: No, that's all that's described in the dictionary.

MR. HELDRETH: The nomenclatures are different (inaudible).

DR. ANDERSEN: Yes. For some reason.

MR. HELDRETH: If it's 3, it's called triethylene glycol and I think diethylene glycol.

DR. ANDERSEN: Correct.

DR. BELSITO: So, but why did we when we did the PEGs and said if it's PEG number N, it's okay and we don't care anymore, why did we do diethylene and triethylene glycol with the PEGs?

DR. LIEBLER: We weren't thinking.

DR. ANDERSEN: It's probably closer into the radar as where the diethylene and the triethylene nomenclature typical.

DR. BELSITO: I mean, are we concerned about greater absorption in diethylene versus triethylene or more ethylene glycol and diethylene?

DR. LIEBLER: It's really a moot point with these because the dominating feature is this big triglyceride. So, these PEGs are ornaments on the ends of the carboxylic acids. And, so, in that context, I mean, PEG-2 versus PEG-3 or PEG-2 versus like PEG-5, for example, significant difference, but PEG-2 castor oil versus PEG-5 castor oil, I would think a very significant difference because I think neither of those can be triple absorbed, but basically triglycerides with the addition of the PEG on the --

DR. BELSITO: End.

DR. LIEBLER: On the end of the carboxyl, right, and (inaudible).

DR. BELSITO: So, are you saying, Dan, that the absence of a review on PEG-2 does not stop you from adding PEG-2 castor oil to this report?

DR. LIEBLER: Right.

DR. BELSITO: So, you don't want to throw out any of them?

DR. LIEBLER: Oh, no, I had a couple others I wanted to throw out.

DR. BELSITO: Oh, okay.

DR. LIEBLER: But we hadn't gotten there yet.

DR. BELSITO: Okay.

DR. LIEBLER: I wanted to throw out the PEG-2 --

DR. BELSITO: Hold on, hold on.

DR. LIEBLER: Yes.

DR. BELSITO: Page.

DR. LIEBLER: So --

DR. BELSITO: The list starts on page 7, Panel Book 12.

DR. LIEBLER: Yes, Panel Book page 10 --

MS. BURNETT: That's the (inaudible).

DR. LIEBLER: Yes, table 1, right-hand column, the fifth line down, PEG-200 hydrogenated --

DR. BELSITO: Wait a minute, where are you?

MS. BURNETT: Panel book --

DR. LIEBLER: Panel book page 10, table 1.

MS. BURNETT: The first table, table 1.

DR. LIEBLER: Panel book page 10, okay.

DR. BELSITO: Okay, first table, yes, okay.

DR. LIEBLER: Okay, right-hand column, fifth line down, PEG-200 hydrogenated castor oil IPDI copolymer. That's an isophorone diisocyanate copolymer, and it seemed like it didn't belong on this list.

DR. BELSITO: Okay.

DR. LIEBLER: And then the other one I flagged was the reaction to the others, but of the oils that had not been previously reviewed. So, the esters from the oils that had not been previously reviewed. And I guess my question is: Should we remove those if those oils had not been previously reviewed? I don't have chemical reasons to throw them out, but I'm just wondering.

DR. BELSITO: So, when we reviewed the vegetable oils, these didn't come up because they weren't used as pure vegetable oils? Is that it?

MS. BURNETT: Or in the case of cannabis, you could say not going to touch it with a 10-foot pole.

DR. BELSITO: In the case of what?

MS. BURNETT: Cannabis, we didn't want to touch it. We were looking at it at the original point in time, they were edible oils when we first made the list because edible and that they are GRAS and that's how we were able to make the list.

SPEAKER: Well, isn't that a (inaudible)?

(Laughter)

SPEAKER: It's GRAS.

MS. BURNETT: It is GRAS.

SPEAKER: It's edible.

MS. BRESLAWEC: We would not object if oils that -- if the ones without the oil component being reviewed would be removed.

DR. EISENMANN: Because you made such an effort in that report to find a composition of each one, but now you don't necessarily have a record of the composition of those.

MS. BRESLAWEC: Right.

MS. BURNETT: And there was a motion in the other group that if you want to do that, then you need to have the fatty acid profiles and then it went back and forth as well, then that wouldn't be a no-brainer if we don't have that stuff already.

DR. BELSITO: Right, so, it wouldn't be. So, okay, all the asterisked ones go away. Although, I don't know, I liked rosa rubiginosa seed oil. Sort of reminded me of Rosa Mae (inaudible).

DR. EISENMANN: What about did you vote Passiflora one? I guess so.

DR. BELSITO: What?

DR. EISENMANN: There's a mixture of agula and Passiflora and Granada.

MS. BURNETT: I know we did the agula. I don't know. I can't remember. I guess it's in here.

DR. EISENMANN: We may have. Yes, it's edible.

MS. BURNETT: The report (inaudible).

DR. BELSITO: Okay. So, all the asterisked ones go away and the IPDI copolymer goes away.

SPEAKER: Right.

DR. LIEBLER: So, are we okay with PEG-2 castor oil?

DR. BELSITO: If you tell me you're okay with it, Dan. You're the man.

DR. LIEBLER: Okay. If it's nothing more than an ornament, I agree. I mean, I think that since it's on the big structures, it's not as much of an issue as it would be in particle smaller structures. It might be like absorbed and metabolized.

DR. BELSITO: I mean, I'm concerned about cleavage and the surface of the skin or --

DR. LIEBLER: (inaudible) really will come out.

DR. BELSITO: Okay.

DR. LIEBLER: But if we have to duke it out tomorrow, we'll do it (inaudible).

DR. BELSITO: So, the deletions are from page 5, Panel Book 10. Okie-doke I think that's it. Reopen is going to be safe as used.

SPEAKER: Yes.

FULL PANEL – March 6, 2012

DR. BELSITO: In 1997 we issued a final report on five PEGs, castor oil, safe up to 50 percent and two PEGs hydrogenated, castor oil, safe up to 100 percent. The question is are there any new data that would cause us to reopen the report and the answer was no. Are there ingredients that we could put into a PEGylated oil family and the answer is yes. The potential add-ons were listed on Panel Book page 10, the actual report, page 5. Jim, I think this is where you were talking about the lower molecular weight PEGs because the other ones only went down to 5. I'm told that we have reviewed triethylene glycol. I wasn't thinking of that as PEG 3, but we have not reviewed diethylene glycol. One of the questions that I had is whether PEG 2 castor oil should be included in this list and I'll let Dan comment on it. Then as part of the no-brainer approach, we deleted all of the oils where we didn't have the components so that all of the asterisked ingredients on that table were removed. Then Dan felt that PEG 200 hydrogenated castor oil IPDI copolymer should be removed as well and then reopen with probably a safe-as-used conclusion. I think the biggest question we had is whether to include PEG 2 castor oil or not.

DR. BERGFELD: Dan, do you wish to comment?

DR. LIEBLER: I'm of a mixed opinion on this. On the one hand, first of all these things, the PEG 2 castor oil for example is dominated by the chemistry of the triacyl lipid compound as opposed to the very small PEG tag and I don't think we have any evidence that the PEG 2 presents a hazard. I confused myself so I put delete here on this, but I don't necessarily think this has to be deleted.

DR. BELSITO: You said they were adornments.

DR. LIEBLER: They are adornments. They are mere adornments on the lipid core of these molecules, these big triglycerides. I don't see any reason that we would need to remove PEG 2 castor oil if we're keeping PEG 3, for example.

DR. BERGFELD: Ron Hill, to clarify this and hear from both sides?

DR. HILL: I concur on that, but I guess we're on their team's view of it. I concur on that.

DR. BELSITO: I'm fine with PEG 2 castor oil being in there and then just delete the ones where we don't have components of the oil and delete the IPDI copolymer and go with safe as used.

DR. BERGFELD: That's a tentative safe?

DR. BELSITO: Yes.

DR. BERGFELD: Do we have a second to that motion?

DR. MARKS: Yes. We'd reopen it. I'd second it.

DR. BERGFELD: I'll call for the vote then. All those in favor? Do you want discussion?

DR. HILL: I had a different view about the added components in that we're not reviewing the oils, we're reviewing the PEGylated oils and in all those ones that are starred the lowest PEGylation was PEG 8. So my way of looking at it was assuming we could get the component information about those oils, there is no reason to exclude them. The only one I would agree that we definitely exclude is that IPDI copolymer. But I don't see why we need to exclude any of these starred oils as long as we can get the fatty acid composition. If we can't then we go insufficient on those.

DR. BERGFELD: This is a motion to reopen.

DR. HILL: It's a motion to reopen.

DR. BERGFELD: Your comments are well taken.

DR. HILL: But if we're going to reopen and follow the recommendation to remove all of those ingredients then I'm not good with that. I don't see any reason to do that because none of these are no-brainers, quite frankly, because knowing the components of an oil doesn't necessarily relate when we're reviewing the PEGylated oils.

DR. BERGFELD: The issue is to reopen and then let's go back and discuss the components.

DR. HILL: Okay.

DR. BERGFELD: I call for the vote to reopen. All those in favor? Unanimous. Coming back to the ingredients that might be included, there are two sides to this at least as I see it. The recommendations have been made by Dr. Belsito and then by Dr. Hill's comments and the comments seem to ride on the fact that structures are not present in the component parts of some of these ingredients or are not well known. Can that be resolved internally?

DR. ANDERSEN: No. I think the best guidance at this point would be that Don's description of how the group would be created, that the one ingredient because it is so chemically different with that extra alphabet soup at the end of it, but all of the plant-derived fatty acids that have yet to be reviewed that are on the list are not no-brainers because we're missing the key information about their fatty acid composition so that that would be a basis for deleting them from the list. As we move forward and as we ask the Council for use concentration data, those would not be on the list. The opportunity would exist if industry had an interest and I'm going to assume that the only interested party that's going to care would be industry. If those were to be added back to the list then both use concentration and fatty acid composition would be provided. If they're not, they would stay off the list.

DR. BRESLAWEC: We ask that they be removed from the list.

DR. BERGFELD: That resolves that. How about the PEG 2 and the PEG 3 castor oil?

DR. BELSITO: As Dan said, first of all, we have looked at triethylene glycol so PEG 3 doesn't pose an issue. We have not looked at diethylene glycol, but Dan describes it as an ornament on the end of the castor oil and it's dominated by the castor oil.

DR. BERGFELD: Keep that one in?

DR. BELSITO: Yes.

DR. BERGFELD: We always have an opportunity at a later date to move it. Go ahead, Ron Hill.

DR. HILL: Again I concur with what Dan said because reviewing the PEGylated oils and those small glycols unless they're present as impurities which I highly doubt, not relevant.

DR. BERGFELD: Thank you. You have your marching orders then Alan?

DR. ANDERSEN: Yes.

DR. BERGFELD: Thank you very much.

DR. MARKS: I'd like to bring up one issue that will come up as we discuss these. There was a limit placed on the PEG 30, 33, 35, 36 and 40 castor oil of 50 percent and that was based on skin sensitization and irritation data. So as we reopen and do all these add-ons, are we going to put a limit of 50 percent? The other half of the previous report, the PEG 30 and 40 hydrogenated castor oil was at 100 percent so I had some difficulty in how to reconcile that with all these add- ons because I'm sure we're not going to have irritation or sensitization for a number of those and Ron Shank had suggested we put a limit of 50 percent to over all these add- ons so put that in your thinking. Don, I don't know whether your team discussed this. I had difficulty reconciling. If we reopen then do we continue forward with a limit at least for the old ones and then these add-ons no limit or how do we deal with that?

DR. BELSITO: I think we need to relook at the data. I think that the panel has evolved in its thinking about the issues of irritation and how to resolve them and carefully look at why those limits were set and see what other data comes in. I looked at this report several weeks ago so I don't specifically remember, but I did go back and check and I think it was an issue where there was some irritation seen and we didn't have good concentrations of use and it was when the panel was setting limits based on the weakest link in the chain which happened to be irritation. I think we need to see what concentration these are used at and look at new irritation and sensitization data.

DR. BERGFELD: Thank you. Rachel wanted to make a comment.

MS. WEINTRAUB: In look at this list of potential ingredient, some of these seem like they can go into different buckets. For example, we're reviewed jojoba oil 4. We've reviewed avocado oil. So that for all the non-castor-oil ingredients does the panel think it would make more sense for these to go in here or for them to go with the other corn oils and the other jojoba oils?

DR. HILL: They definitely should go here because they're not oils anymore, the PEGylated oils, so they're different. If they were PEG 2 I might ask that question because then we might have some free oil. But I think partly by what we saw yesterday and partly by what we already know, when at PEG 6, PEG 7, especially above PEG 8, there are no free oils anymore so we're dealing with PEGylated oils. At least that's my view on that particular issue.

DR. LIEBLER: These oils are all triglycerides and the thing that made the castor oil a group unto itself is because castor oil has a characteristic fatty acid that's part of the triglyceride, ricinoleic acid, but the other compounds are chemically analogous enough or analogous enough in terms of their usage that it makes certainly logical sense to group them all together in this report.

DR. BERGFELD: Thank you. Alan needed to clarify.

DR. ANDERSEN: I think by reopening this, the document that will be prepared for your review is a draft tentative amended safety assessment and amended opens the door to both amending the list of ingredients and the language of the conclusion so that it's perfectly appropriate to make those changes with the next version.

DR. BERGFELD: Halyna, would you be calling then for information on these ingredients if that is the mode that we're going to take?

DR. BRESLAWEC: Yes, we would be.

DR. BERGFELD: Ron Hill, thank you.

DR. HILL: Just a question about the irritation issue that you were discussing. Can't you just put in the conclusion when formulated to be nonirritating and that way if somebody discovered that PEG 2 castor oil was 5 percent instead of 50 that it would still be all right?

DR. BELSITO: I think that's what we're going to end up doing. Again the panel had a different mindset back in the mid-1990s.

DR. EISENMANN: Dr. Bergfeld?

DR. BERGFELD: Yes?

DR. EISENMANN: For clarification, for re-reviews I usually do not go to suppliers and ask for information.

DR. BERGFELD: I know that.

DR. EISENMANN: For this one as I go out for concentration of use information which I haven't done yet because I wanted to have you clarify what ingredients, I will say if you use more than 50 percent of an ingredient please provide some data on that product.

DR. BRESLAWEC: Would that be adequate then?

DR. BERGFELD: Yes. Thank you. I think we have voted on this.

DR. MARKS: We reopened.

DR. BRESLAWEC: We reopened it.

DR. MARKS: Would you also in the next booklet that we receive for the next time we consider this put in that original review again so that we can go back and look at the source document as to how the 50 percent was derived?

DR. BERGFELD: Are there any other comments that need to be made on any of the ingredients we've reviewed, these 12 today? We are still sort of hazy about the reopening and the add-ons and the merging so I hope that this continues to work itself out. We're going to move on to some discussant items. The first one up is the aerosols that Dr. Marks is going to speak on.

DR. MARKS: I thought I could put my hands on it easily, on Panel Book page 54 I'm back again to the castor oil, it says, "Under the discussion the highest concentration tested yielding negative results for the PEG castor oil family was 50 percent PEG 35 castor oil in a sensitization study with guinea pigs." It would imply in that that it was based on a sensitization study so I'm still not quite sure about the irritation.

DR. BELSITO: What page are you on?

DR. MARKS: Page 54 under the discussion.

DR. BELSITO: What Panel Book page?

DR. MARKS: Panel Book page 54, or 299. I'm sorry.

DR. BERGFELD: 54.

DR. MARKS: At the bottom. It's under the discussion and it's the second sentence from the bottom of the page. That would imply they're talking about sensitization rather than irritation so that I think we've never issued a report formulated to be nonsensitizing.

DR. ANDERSEN: We have.

DR. MARKS: Have we?

DR. BELSITO: I'm sorry. It's Panel Book page 54. Is that correct?

DR. BERGFELD: Under discussion.

DR. MARKS: Under the discussion at the bottom there. It seems to be relevant to sensitization, but we'll clarify that as long as, again, Christina, you include this report with the next panel book. Are you in the right book? PEGylated oils.

DR. BELSITO: Castor oil.

DR. MARKS: I just wanted to point that out.

DR. BELSITO: It's on the other page, but that's a summary.

DR. MARKS: Yes.

DR. BELSITO: I'm actually looking for the data.

DR. MARKS: We'll get that clarified the next time we evaluate these PEGylated oils.

Report

Amended Safety Assessment of PEGylated Oils as Used in Cosmetics

Status: Draft Tentative Amended Report for CIR Expert Panel Review
Release Date: August 17, 2012
Panel Meeting Date: September 10-11, 2012

The 2012 Cosmetic Ingredient Review Expert Panel members are: Chairman, 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 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 F. Alan Andersen, Ph.D.
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TABLE OF CONTENTS

INTRODUCTION

In 1997, the Cosmetic Ingredient Review (CIR) published the safety assessment on PEG-30, -33, -35, -36, -40 castor oil and PEG-30 and -40 hydrogenated castor oil with the conclusion "PEG-30, -33, -35, -36, and -40 castor oil are safe for use in cosmetics at concentrations up to 50% and that PEG-30 and -40 hydrogenated castor oil are safe for use at concentrations of up to 100%."[1] These PEGylated castor oils function primarily as surfactants in cosmetic products.

Since the original review, numerous additional studies were published related to the noncosmetic use of PEG-35 castor oil and PEG-40 hydrogenated castor oil (trade name Cremophor EL and Cremophor RH, respectively) in drug delivery systems. A few of these studies that appear relevant to assessing the safety of PEGylated oils in cosmetics are summarized in this safety assessment. Overall, single-dose and repeated-dose toxicity, reproductive and developmental toxicity, genotoxicity, carcinogenicity, dermal and ocular irritation, and sensitization and photsensitization data were available.

Because of similarities in chemical properties and cosmetic function, the PEGylated oils listed in Table 1 have been added to the safety assessment on PEG-30 castor oil, et al. These cosmetic ingredients include components that have been previously reviewed and concluded to be safe for use by the CIR Expert Panel, most notably the recent safety assessments on plant-derived fatty acid oils and polyethylene glycols (PEGs) with an average of 4 moles of ethylene oxide or greater. The ingredients, their conclusions, a summary of the findings, and published citations are found in Table 2.

CHEMISTRY

The definitions of the PEGylated oils can be found in Table 3.

Just as oils and other PEGylated materials are mixtures, PEGylated oils are mixtures. As most natural source oils are primarily triglycerides (and mono- and diglycerides) and fatty acids, PEGylated oils are primarily PEGylated glycerides, along with some PEGylated fatty acids. PEGylation of glycerides occurs not only as an etherification of the free alcohol groups of the glycerides with ethylene oxide groups, but also as a transesterification which results in net insertion of PEG groups between the glyceryl and fatty acid components of the glyceride.[2,3] For example, the primary component of castor oil, the ricinoleate triglyceride, is ethoxylated as shown in Figure 1, wherein n is equal to the number of ethylene oxide repeat units and need not be the same at all places of the molecule. It should be noted that n is not equal to X. In other words, wherein the value of X in PEG-X is equal to 2 (e.g., PEG-2 Castor Oil), n is not equal to 2. Instead, X represents the number of stoichiometric equivalents of ethylene oxide that were added to one stoichiometric equivalent of castor oil. Therefore, the sum of all of the different n values in the mixture may be no more than X. Indeed, when one mole of ethylene oxide is reacted with one mole of fatty alcohol, adducts having ***no*** added ethylene oxide are the predominate material in the mixture.[2] Furthermore, when ethylene oxide reacts with castor oil it is approximately twice as likely that it will react at an ester site versus an alcohol site. Moreover, a percentage (13% in one specific case) of the ethylene oxide simply reacts with other molecules of ethylene oxide, resulting in some polyethylene glycols unattached to glycerides or acid groups.

While castor oil triglycerides are primarily (approximately 87%) composed of ricinoleic acid residues, approximately 7% are oleic acid, 3% are linoleic acid, 2% are palmitic acid, 1% are stearic acid, and a trace are dihydroxysteric acid.[1] Thus, these PEGylated castor oil ingredients, and all of the PEGylated oil ingredients, are rather complex mixtures of structurally related molecules.

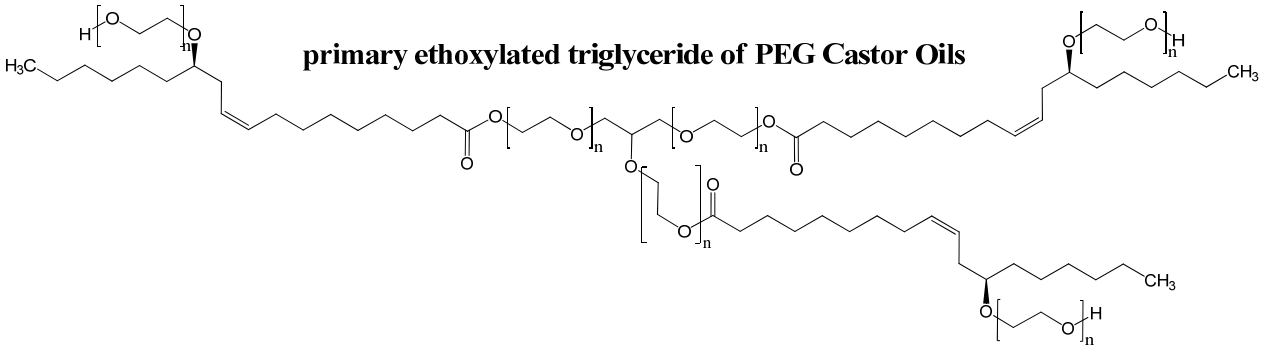

Figure 1. Glyceryl triricinoleyl polyethylene glycol

The available free fatty acids found in castor oil, and the other oils, may also be esterified by the ethoxylation process, as seen in Figure 2 (and etherified with ethylene oxide groups if there are any reactive alcohol functionalities on the fatty acids).

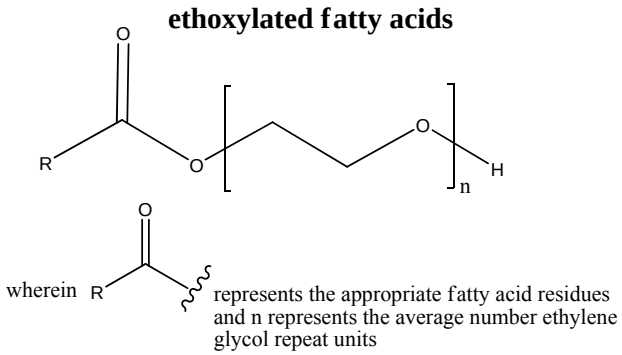

Figure 2. Fatty acid esterification

Some of the castor oil derived ingredients in this report have been hydrogenated. Hydrogenation of castor oil primarily results in the reduction of the Ω-9 unsaturation of ricinoleate triglycerides (and the Ω-9 unsaturation of any free ricinoleic fatty acids).[2] Accordingly, hydrogenated castor oil is principally 12-hydroxystearic triglyceride. The resultant ethoxylated triglyceride, therefore, differs from that of PEGylated non-hydrogenated castor oil only in the loss of these double bonds, as seen in Figure 3.

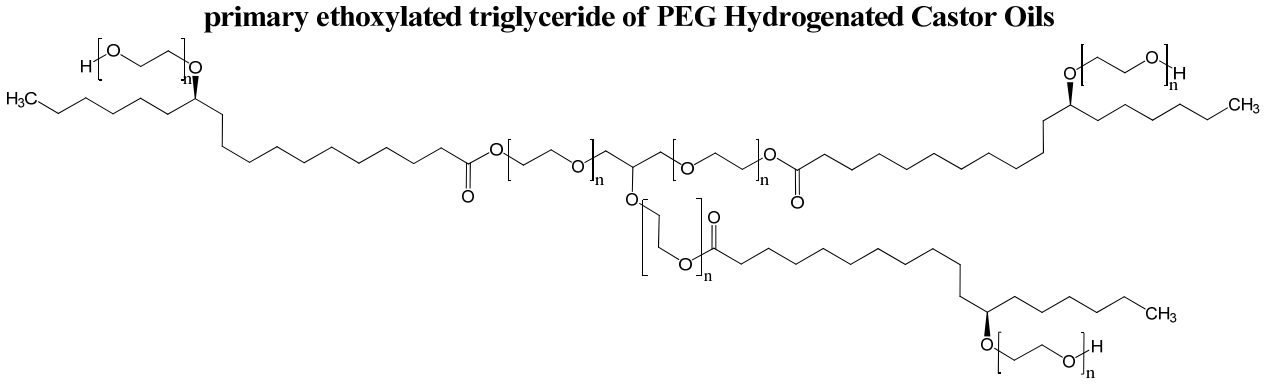

Figure 3. Glyceryl 12-hydroxystearyl polyethylene glycol

Physical and Chemical Properties

Physical and chemical properties of PEG-30, -33, -35, -36, -40 castor oil and PEG-30 and -40 hydrogenated castor oil can be found in the original safety assessment.[1] A supplier reports that PEG-30,-35, and-40 are pale yellow viscous liquids at 30° C and have a maximum water content of 0.2%.[4] PEG-40 hydrogenated castor oil is reported to be a waxy liquid at 30° C and also has a maximum water content of 0.2%.

Impurities

PEGs are the condensation products of ethylene oxide and water, with the chain length controlled by number of moles of ethylene oxide that are polymerized. PEGs may contain trace amounts of 1,4-dioxane, a by-product of ethoxylation. 1,4-Dioxane is a known animal carcinogen.[5] The cosmetic industry reported that it is aware that 1,4-dioxane may be an impurity in PEGs and, thus, uses additional purification steps to remove it from the ingredient before blending into cosmetic formulations.[6]

USE

Cosmetic

Table 4a presents the historical and current product formulation data for PEG-30, -33, -35, -36, -40 castor oil and PEG-30 and -40 hydrogenated castor oil. These PEGylated castor oils function primarily as surfactants (emulsifying or solubilizing agents) in cosmetic formulations.[7] According to information supplied to the Food and Drug Administration's (FDA) Voluntary Cosmetic Registration Program (VCRP) database by industry in 1997, PEG-40 hydrogenated castor oil had the most uses at 268, with the majority of the uses reported in leave-on products with a dermal exposure route.[1] The ingredient with the second most uses was PEG-40 castor oil with 170 uses, most in leave-on products with a dermal exposure route. An industry survey reported use concentrations for PEG-40 hydrogenated castor oil and PEG-40 castor oil of ≤ 10% and ≤ 5%, respectively. Currently, the FDA's VCRP database indicates that uses have decreased for PEG-30 castor oil, PEG-40 castor oil, and PEG-30 hydrogenated castor oil, with the most significant decrease occurring with PEG-40 castor oil

which now has 95 reported uses.[8] Increases in use are reported in the remaining PEGylated castor oils from the original report, with the most significant occurring in PEG-40 hydrogenated castor oil, which now has 2107 reported uses. In a recent survey of use concentrations, PEG-40 hydrogenated castor oil had a maximum use concentration range of 7.0×10^{-5} to 22%, with the 22% reported in leave-on non-coloring hair products.[9] PEG-30 castor oil had a maximum use concentration of 0.1% in a rinse-off non-coloring hair product.

Table 4b presents the current product formulation data for the cosmetic ingredients that were added to the PEGylated oil safety assessment. Currently, the VCRP database indicate that of the additional ingredients, PEG-60 hydrogenated castor oil has the most uses of 349 with the majority in leave-on products with a dermal exposure route.[8] The maximum use concentration range for PEG-60 hydrogenated castor oil was 4.0×10^{-5} to 18%, with the 18% reported in leave-on non-coloring hair products.[10] Olive oil PEG-7 esters had the second most reported uses of 97. The maximum use concentration range for olive oil PEG-7 esters was 0.05 to 97%, with the 97% reported in a rinse-off product.

In some cases, reports of uses were received in the VCRP, but no concentration of use data are available. For example, PEG-33 castor oil is reported to be used in 41 formulations, but no use concentration data were available. In other cases, no reported uses were received in the VCRP, but a use concentration was provided in the industry survey. For example, PEG-25 castor oil was not reported in the VCRP to be in use, but the industry survey indicated that it is used in leave-on formulations at maximum concentrations ranging from 3-17%. It should be presumed that PEG-25 castor oil is used in at least one cosmetic formulation.

PEGylated oils were reported to be used in fragrance products, hair sprays, deodorants, and indoor tanning preparations and could possibly be inhaled. These ingredients are reportedly used at concentrations up to 16%. 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.[11-14] 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.[12,13] 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.[13] 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 PEGylated oils are not restricted from use in any way under the rules governing cosmetic products in the European Union.[16]

Non-Cosmetic

PEG-30 castor oil and PEG-40 hydrogenated castor oil may be used as nonionic surfactants in oral, topical, and parenteral drug delivery systems.[3,4,17-23] PEGylated castor oil derivatives may also be used in animal feeds and textiles.[4]

PEG-30, -33, -35. -36, and -40 castor oil have been approved by the FDA as indirect food additives in adhesives and components of coatings (21 CFR § 175.105 and §175.300) and packaging and food contact surfaces (21 CFR §176.210, §177.2800). PEG-30 and -40 hydrogenated castor oil are approved as direct food additives (21 CFR §73.1) as well as in indirect food additives in packaging and food contact surfaces (21 CFR §177.2800).

TOXICOKINETICS

Toxicokinetics data were available supporting the safety of alkyl PEG ethers and castor oil as summarized in Table 2.

Absorption, Distribution, Metabolism, Excretion

The disposition of PEG-35 castor oil was determined in 31 cancer patients treated with a 1-h infusion of paclitaxel (87.8 mg PEG-35 castor oil per mg drug).[25] Dose levels of PEG-35 castor oil ranged from 70 to 100 mg/m^2. Plasma concentrations were measured. Clearance of PEG-35 castor oil appeared to be independent of infusion duration and the administered dose in the range studied (P =.797). Exposure measures increased in near proportion to an increase in dose. PEG-35 castor oil had a half-life and clearance of 35.7 $\pm$ 18.9 h and 0.216 $\pm$ 0.075 L/h, respectively (P < .00001). The volume of distribution at steady state was 9.48 $\pm$ 2.59 L and indicated limited distribution of the excipient outside of the central compartment. These results were compared to those of the excipient Tween 80, which had a shorter terminal half-life (0.607 $\pm$ 0.245 h) and total plasma clearance (7.70 $\pm$ 2.90 L/h). The other values were similar. The study concluded that use of PEG-35 castor oil as a formulation vehicle could result in drug interaction and excipient-related toxic side effects due to its rates of elimination.

Penetration Enhancement

A study of the development of a topical gel for treatment of acne vulgaris reports that various types of PEGS are hydrophilic penetration enhancers and are used in topical dermatological preparations.[17] The authors selected PEG-40 hydrogenated castor oil because of its properties as a very hydrophilic, non-ionic solubilizer for fat-soluble vitamins A, D, E, and K, and for its stability and clarity in alcohol solution.

In a study evaluating vehicle effects on in vitro skin permeation of model drugs caffeine and testosterone, PEG fatty acid ester facilitated the flux and diffusivity of caffeine across the stratum corneum, when compared to propylene glycol.[26]

TOXICOLOGICAL STUDIES

Acute Toxicity

Dermal and oral acute toxicity data were available supporting the safety of alkyl PEG ethers as summarized in Table 2.

Intravenous – Non-Human

PEG-X CASTOR OIL

Castor oil with an unspecified number of stoichiometric equivalents of ethylene oxide (just generically listed as Cremophor) that was mixed with dimethyl acetamide (DMA) was evaluated as a vehicle in a diabetes drug.[27] The mixture was composed of 23-45% DMA/10-12% Cremophor in water and the dose volume was 1.67 to 3 ml/kg. Groups of 3 New Zealand White rabbits received intravenously the test material, saline, insulin, or N-methyl-2-pyrrolidone (NMP) into the marginal ear vein. Blood was drawn just before injection and again at 0.25, 0.5, 1, 2, 4, and 24 h after injection to determine glycemia values. Glycemia after injection with the DMA/Cremophor mixture remained stable and within the normal range of 3.6 to 5.0 mmol/l. These results were comparable to the rabbits that received saline. In addition to these results, the test material did not elicit irritation at the site of injection.

PEG-60 HYDROGENATED CASTOR OIL

The toxicity of PEG-60 hydrogenated castor oil was evaluated in male and female beagle dogs, male and female cynomolgus monkeys, male New Zealand White rabbits, male Hartley guinea pigs, and male Sprague Dawley rats.[28] The test material was injected intravenously to groups of 3 dogs at 0.625, 1.25. 2.5. or 10 mg/kg; in groups of 3 monkeys or 5 rabbits at 50 or 100 mg/5 ml/kg; and in groups of 5 guinea pigs, and 5 rats at 10 or 100 mg/5 ml/kg. Blood pressure was monitored in the dogs before the injection and 10, 30, and 60 min after injection. Blood was taken in all animals to measure plasma histamine levels. In dogs, further histopathological examinations were performed on mast cells in the liver and skin. Clinical signs of toxicity were observed until 60 min after injection in all animals.

In dogs injected with 1.25, 2.5 or 10 mg/kg of the test material, blood pressure decreased and flush, swelling and itching were observed. Additionally in the 10 mg/kg dose group, a decrease in spontaneous motility was observed. An increase in histamine levels was observed in the 2.5 and 10 mg/kg dose groups. Degranulation was observed after injection in the mast cells of the skin, but not in the liver cells. No signs of toxicity were observed in monkeys, rabbits, guinea pigs or rats and there was no change in plasma histamine levels. The toxicity of PEG-60 hydrogenated castor oil may be species specific.[28]

Repeated Dose Toxicity

Dermal and oral repeated dose toxicity data were available supporting the safety of castor oil and alkyl PEG ethers as summarized in Table 2.

PEG-35 CASTOR OIL

Several rat studies investigated the effects of the use of Cremophor EL (PEG-35 castor oil) as a vehicle in intravenous drugs.[29-32] Effects on cardiac and skeletal function have been observed.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Reproductive and developmental toxicity data were available supporting the safety of PEGS, castor oil, and alkyl PEG ethers, as summarized in Table 2.

GENOTOXICITY

Genotoxicity data were available supporting the safety of castor oil, PEGs, and alkyl PEG ethers, as summarized in Table 2.

PEG-60 HYDROGENATED CASTOR OIL

The genotoxic potential of PEG-60 hydrogenated castor oil was studied in a reverse mutation test in *Salmonella typhimurium* strains TA100, TA98, TA1535, and TA1537 and in *Escherichia coli* strain WP2uvrA, with and without metabolic activation.[33] The test concentrations ranged from 313-5000 μg/plate. The positive controls were 9-aminoacridine, sodium azide, 2-(2-furyl)-3-(5-nitro-2-furyl)-acrylamide, and 2-aminoanthracene. No biologically relevant increases in revertant colony numbers were observed in any test strain at any dose level, with or without metabolic activation. Controls yielded expected results. The study concluded that PEG-60 hydrogenated castor oil was not genotoxic.

The research study above also investigated the genotoxic potential of PEG-60 hydrogenated castor oil in a chromosome aberration study with Chinese hamster V79 cells, with and without metabolic activation.[33] The test concentrations ranged from 313-5000 μg/ml. The positive controls were mitomycin C and dimethylnitrosamine. The test material without metabolic activation had dose-related inhibition of cell proliferation after 24 and 48 h treatments. With metabolic activation, the test material induced only slight inhibition of cell proliferation even at the highest concentration

after 6 h treatment. PEG-60 hydrogenated castor oil did not induce chromosome aberrations at any dose, with or without metabolic activation. The controls yielded expected results. The study concluded that PEG-60 hydrogenated castor oil was not genotoxic.

The same study also researched the genotoxic potential of PEG-60 hydrogenated castor oil in a mouse micronucleus test using BDF1 male and female mice.[33] A dose range finding experiment preceded the main study. In the main study, groups of 5 mice of each sex received single intraperitoneal injections of 2000 mg/kg body weight PEG-60 hydrogenated castor oil. Control groups received physicological saline or mitomycin C. Bone marrow cells were collected at 24, 48, or 72 h. The number of micronucleated erythrocytes in 1000 polychromatic erythrocytes and the number of polychromatic erythrocytes in 1000 erythrocytes were recorded for each mouse. In the dose range finding study, no deaths occurred. In the main study, no treatment-related mortalities or clinical signs of toxicity were observed. No significant increase of micronucleated polychromatic erythrocytes or significant decrease of the ratio of polychromatic to normochromatic erythrocytes were observed in male or female mice that received the test material. The controls yielded expected results. The study concluded that PEG-60 hydrogenated castor oil was not genotoxic.

CARCINOGENICITY

Carcinogenicity data were available supporting the safety of PEGs and alkyl PEG ethers, as summarized in Table 2.

IRRITATION AND SENSITIZATION

Irritation

Irritation data were available supporting the safety of PEGs, mink oil, and plant-derived fatty acid oils, as summarized in Table 2.

Dermal – Non-Human

PEG-35 CASTOR OIL

A skin irritation study of a pharmaceutical microemulsion that contained 20% w/w PEG-35 castor oil was performed in male guinea pigs (strain not specified).[34] The hair on the backs of the guinea pigs was removed 24 h before treatment, and the animals were divided into a group with intact skin and a group with skin injury due to scarifying. These groups were again subdivided into single and multiple applications. There were a total of 5 guinea pigs in each subgroup. All guinea pigs received the test material and a control cream. Single application animals were treated for 24 h and the test sites were inspected for erythema and edema 1, 24, 48, and 72 h after material removal. Multiple application animals were treated for 24 h, followed by assessment for skin irritation 1 h after material removal, in a total of 7 applications. The test sites were observed for an additional 3 days after the last application. While very slight irritation was observed on average at the 1 h observation in guinea pigs treated with multiple applications with damaged skin, the average scores were still in the range that was considered to be "no irritation". No irritation was observed in any of the single application animals or in the intact skin of the multiple application animals. It was concluded that single and multiple applications of the microemulsion that contained 20% w/w PEG-35 castor oil did not cause irritation effects in guinea pigs.

PEG-40 HYDROGENTATED CASTOR OIL

A dermal irritation test was performed in mice (species and number not described) to investigate the potential irritancy of a microemulsion that contains 20% PEG-40 hydrogenated castor oil.[23] A single dose of 10 µl of the test microemulsion was applied to the left ear of the mouse. The right ear served as a control. The mice were observed for development of erthyma for 6 days. No signs of irritation were observed in the mice. The authors concluded that the formulation containing 20% PEG-40 hydrogenated castor oil would probably not irritate human skin.

The dermal irritancy potential of a microemulsion gel system that contained 20.66% PEG-40 hydrogenated castor oil as a surfactant was studied in male albino rats using the Draize method.[35] Animals were divided into 3 groups of 6: a negative control (no treatment), a positive control (0.8% aq. formalin), and the test formulation. The rats received a dose of 0.5 g of the formulation on a 5 cm^2 area on the shaved dorsal side daily for 3 consecutive days. Signs of erythema and edema were monitored daily for 3 days. After 3 days, the rats were killed and skin samples were taken for histopathological examination. No signs of irritation were observed in the test formulation. The controls yielded expected results. Histopathological examination found no apparent signs of skin irritation. The study concluded that the test formulation that contained 20.66% PEG-40 hydrogenated castor oil was not a skin irritant.

Ocular

PEG-35 CASTOR OIL

Several different formulations of a potential glaucoma drug in form of a nanoemulsion were tested for ocular irritation potential.[36] A few of these formulations contained PEG-35 castor oil as a surfactant. Groups of 6 New Zealand albino rabbits received test formulations that contained 0-13% PEG-35 castor oil. In each rabbit, the right eye received 50 µl of the tested formulation, while the left eye was used as a control. The rabbits received the test formulation every 2.5 h

through a period of 7.5 h per day for 3 successive days and once on the fourth day. Eyes were examined according to the Draize method 1 and 24 h after the last instillation. The eyelids, cornea, iris, conjunctiva, and anterior chamber were inspected for inflammation or other toxic reactions. The eyes were then stained with fluorescein and examined under UV light to verify possible corneal lesion. A few nanoemulsion formulations that contained up to 13.5% PEG-35 castor oil were found to be non-irritating and tolerated well by the rabbit eye. Cross sections from the corneas of rabbits' eye after application of the tested formulations together with a control section showed that both corneal structure and integrity were unaffected by treatment.

Sensitization

Sensitization data were available support the safety of PEGs, mink oil, plant-derived fatty acid oils, and alkyl PEG ethers, as summarized in Table 2.

CLINICAL USE

Case Studies

PEG-35 CASTOR OIL

A 40-year-old female undergoing chemotherapy treatment for breast cancer had a cutaneous lupus erythematosus-like reaction within 24 h of intravenous administration of the drug paclitaxel that contained the diluent, PEG-35 castor oil.[44] When treatment was switched to a paclitaxel that was bound with albumin, no lupus-like reactions were observed. The case study concluded that PEG-35 castor oil induced the lupus-like reaction and suggested that previously reported incidences of lupus-like reaction in chemotherapy patients was from this diluent and not from the chemotherapeutic agent.

PEG-7 HYDROGENATED CASTOR OIL

A 73-year-old male was reported to have an eczematous rash on the face and neck after use of a sunscreen lotion.[45] The patient was patch tested with an extended British Contact Dermatitis Society standard series, medicament series, facial series, photoallergic series, and the sunscreen. A positive reaction was elicited only with the patient's sunscreen, both on nonirradiated and irradiated skin. When tested with the individual ingredients of the sunscreen, a positive reaction occurred to 10% PEG-7 hydrogenated castor oil in petrolatum (+ on days 2 and 4). Negative reactions were observed to the remaining sunscreen ingredients.

PEG-60 HYDROGENATED CASTOR OIL

A 27-year-old male undergoing maintenance chemotherapy for acute myeloblastic leukemia developed a high-grade fever and erythroblastopenia within 6 h of after intravenous administration of the chemotherapy drugs that included enocitabine.[46] The enocitabine product contained PEG-60 hydrogenated castor oil. When enocitabine was administered alone, the same symptoms reoccurred. Co-culturing the patient's bone marrow with enocitabine or PEG-60 hydrogenated castor oil found significant growth inhibition of late erythroid progenitors in the presence of the patient's IgG. The researchers of the study believe that PEG-60 hydrogenated castor oil acted as a hapten and caused the immunological suppression of the growth of erythroid progenitors through a hypersensitive reaction mediated by IgG.

SUMMARY

Just as oils and other PEGylated materials are mixtures, PEGylated oils are mixtures. As most natural source oils are primarily triglycerides (and mono- and diglycerides) and fatty acids, PEGylated oils are primarily PEGylated glycerides, along with some PEGylated fatty acids.

PEGs are the condensation products of ethylene oxide and water, with the chain length controlled by number of moles of ethylene oxide that are polymerized. PEGs may contain trace amounts of 1,4-dioxane, a by-product of ethoxylation.

The PEGylated castor oils function primarily as surfactants that function as emulsifying or solubilizing agents in cosmetic formulations. Current FDA data indicates that PEG-40 hydrogenated castor oil has 2107 reported uses, with a maximum use concentration range of 7.0×10^{-5} to 22%, with the 22% reported in leave-on non-coloring hair products.

PEG-30 castor oil and PEG-40 hydrogenated castor oil may be used as nonionic surfactants in oral, topical, and parenteral drug delivery systems. PEGylated castor oil derivatives may also be used in animal feeds and textiles. PEG-30, -33, -35. -36, and -40 castor oil have been approved by the FDA as indirect food additives in adhesives and PEG-30 and -40 hydrogenated castor oil are approved as direct and indirect food additives.

Various types of PEGS are hydrophilic penetration enhancers and are used in topical dermatological preparations.

Unspecified PEG castor oil did not elicit irritation in rabbits when evaluated as a vehicle in an intravenous drug.

The toxicity of PEG-60 hydrogenated castor oil was evaluated in male and female beagle dogs, male and female cynomolgus monkeys, male New Zealand White rabbits, male Hartley guinea pigs, and male Sprague Dawley rats. Toxicity, including decreased blood pressure, flush, swelling, itching, and increase histamine levels, was observed in dogs injected with 1.25, 2.5 or 10 mg/kg of the test material. No signs of toxicity were observed in monkeys, rabbits, guinea pigs or rats.

Several rat studies investigated the effects of the use of Cremophor EL (PEG-35 castor oil) as a vehicle in intravenous drugs. Effects on cardiac and skeletal function have been observed.

The genotoxic potential of PEG-60 hydrogenated castor oil was studied in a reverse mutation test, in a chromosome aberration study, and in a mouse micronucleus test: the studies concluded that PEG-60 hydrogenated castor oil was not genotoxic.

A study of single and multiple applications of a microemulsion that contained 20% w/w PEG-35 castor oil did not cause irritation effects in guinea pigs. A dermal irritation test performed in mice concluded that a formulation containing 20% PEG-40 hydrogenated castor oil would probably not irritate human skin. A study of the dermal irritancy potential of a microemulsion gel system in rats concluded that the test formulation containing 20.66% PEG-40 hydrogenated castor oil was not a skin irritant. Nanoemulsions containing up to 13.5% PEG-35 castor oil were non-irritating in rabbit eyes.

Case studies of adverse events occurring in cancer patients were reported following use of chemothrapty drugs that contained PEG-35 castor oil and PEG-60 hydrogenated castor oil. Another case report reported an adverse dermatological event following use of a sunscreen.

DISCUSSION

Although there are data gaps, the similar chemical structures, physicochemical properties, and functions and concentrations in cosmetics allow grouping these ingredients and extending the available toxicological data on any of the ingredients to support the safety of the entire group. Overall, single-dose and repeated-dose toxicity, reproductive and developmental toxicity, genotoxicity, carcinogenicity, dermal and ocular irritation, and sensitization and photsensitization data were available.

The CIR Expert Panel expressed concern regarding the possible presence of ethylene oxide and trace amounts of 1,4-dioxane as impurities in any cosmetic ingredient containing a PEG moiety. They stressed that the cosmetic industry should continue to use the necessary purification procedures to remove these impurities from the ingredient before blending it into cosmetic formulations.

The Expert Panel also expressed concern regarding pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities in the ingredient before blending into cosmetic formulation.

While a safety assessment of diethylene glycol (aka PEG-2) has not been completed, the safety assessment of the PEGs group of ingredients includes PEG-4, which is a mixture that would include PEG-2, which suggested that PEG-2 would be safe for use in cosmetics.

The Panel noted that adverse reactions have been reported on PEG-35 castor oil when used as a vehicle in intravenous drugs. Because this route of exposure does not occur from cosmetic use, the Panel considered that such data were not relevant to assessing the use of the ingredient in cosmetics.

Because some of these ingredients were reported to be used in products that may be sprayed, the Panel discussed the issue of incidental inhalation exposure. In the absence of inhalation data, the Panel considered other pertinent data indicating that incidental inhalation exposures to some of these ingredients in aerosolized cosmetic products would not cause adverse health effects, including dermal irritation and sensitization. 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. 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 that may be aerosolized is available at http://www.cir-safety.org/cir-findings.

CONCLUSION

The CIR Expert Panel concluded that the PEGylated oil ingredients listed below are safe when formulated to be non-irritating. This conclusion supersedes the earlier conclusion issued by the Expert Panel in 1997.

PEG-2 Castor Oil*
PEG-3 Castor Oil*
PEG-4 Castor Oil*
PEG-5 Castor Oil*
PEG-8 Castor Oil*
PEG-9 Castor Oil
PEG-10 Castor Oil*
PEG-11 Castor Oil*
PEG-15 Castor Oil*
PEG-16 Castor Oil*
PEG-20 Castor Oil*
PEG-25 Castor Oil
PEG-26 Castor Oil*
PEG-29 Castor Oil*
PEG-30 Castor Oil
PEG-33 Castor Oil
PEG-35 Castor Oil
PEG-36 Castor Oil
PEG-40 Castor Oil
PEG-44 Castor Oil*
PEG-50 Castor Oil
PEG-54 Castor Oil*
PEG-55 Castor Oil*
PEG-60 Castor Oil

PEG-75 Castor Oil*
PEG-80 Castor Oil*
PEG-100 Castor Oil*
PEG-200 Castor Oil*
PEG-18 Castor Oil Dioleate*
PEG-60 Castor Oil Isostearate*
PEG-2 Hydrogenated Castor Oil
PEG-5 Hydrogenated Castor Oil*
PEG-6 Hydrogenated Castor Oil*
PEG-7 Hydrogenated Castor Oil
PEG-8 Hydrogenated Castor Oil*
Hydrogenated Castor Oil PEG-8 Esters*
PEG-10 Hydrogenated Castor Oil
PEG-16 Hydrogenated Castor Oil
PEG-20 Hydrogenated Castor Oil
PEG-25 Hydrogenated Castor Oil
PEG-30 Hydrogenated Castor Oil
PEG-35 Hydrogenated Castor Oil
PEG-40 Hydrogenated Castor Oil
PEG-45 Hydrogenated Castor Oil
PEG-50 Hydrogenated Castor Oil
PEG-54 Hydrogenated Castor Oil*
PEG-55 Hydrogenated Castor Oil*
PEG-60 Hydrogenated Castor Oil
PEG-65 Hydrogenated Castor Oil*
PEG-80 Hydrogenated Castor Oil
PEG-100 Hydrogenated Castor Oil
PEG-200 Hydrogenated Castor Oil*
PEG-5 Hydrogenated Castor Oil Isostearate*
PEG-10 Hydrogenated Castor Oil Isostearate*
PEG-15 Hydrogenated Castor Oil Isostearate*
PEG-20 Hydrogenated Castor Oil Isostearate*
PEG-30 Hydrogenated Castor Oil Isostearate*
PEG-40 Hydrogenated Castor Oil Isostearate*
PEG-50 Hydrogenated Castor Oil Isostearate*
PEG-58 Hydrogenated Castor Oil Isostearate*
PEG-20 Hydrogenated Castor Oil Laurate*
PEG-30 Hydrogenated Castor Oil Laurate*
PEG-40 Hydrogenated Castor Oil Laurate*
PEG-50 Hydrogenated Castor Oil Laurate*
PEG-60 Hydrogenated Castor Oil Laurate*
PEG-20 Hydrogenated Castor Oil PCA Isostearate*
PEG-30 Hydrogenated Castor Oil PCA Isostearate*
PEG-40 Hydrogenated Castor Oil PCA Isostearate
PEG-60 Hydrogenated Castor Oil PCA Isostearate*
PEG-50 Hydrogenated Castor Oil Succinate
Potassium PEG-50 Hydrogenated Castor Oil Succinate*
Sodium PEG-50 Hydrogenated Castor Oil Succinate*
PEG-5 Hydrogenated Castor Oil Triisostearate*
PEG-10 Hydrogenated Castor Oil Triisostearate*
PEG-15 Hydrogenated Castor Oil Triisostearate*
PEG-20 Hydrogenated Castor Oil Triisostearate
PEG-30 Hydrogenated Castor Oil Triisostearate*
PEG-40 Hydrogenated Castor Oil Triisostearate
PEG-50 Hydrogenated Castor Oil Triisostearate*
PEG-60 Hydrogenated Castor Oil Triisostearate*
Adansonia Digitata Seed Oil PEG-8 Esters*
Almond Oil PEG-6 Esters*
Almond Oil PEG-8 Esters *
Apricot Kernel Oil PEG-6 Esters
Apricot Kernel Oil PEG-8 Esters*
Apricot Kernel Oil PEG-40 Esters*
Argan Oil PEG-8 Esters*
Avocado Oil PEG-8 Esters*
Avocado Oil PEG-11 Esters
Bertholletia Excelsa Seed Oil PEG-8 Esters*
Borage Seed Oil PEG-8 Esters*
Coconut Oil PEG-10 Esters
Corn Oil PEG-6 Esters*
Corn Oil PEG-8 Esters*
Grape Seed Oil PEG-8 Esters
Hazel Seed Oil PEG-8 Esters*
Hydrogenated Palm/Palm Kernel Oil PEG-6 Esters
Jojoba Oil PEG-8 Esters
Jojoba Oil PEG-150 Esters*
Linseed Oil PEG-8 Esters*
Macadamia Ternifolia Seed Oil PEG-8 Esters*
Mango Seed Oil PEG-70 Esters*
Mink Oil PEG-13 Esters*
Olive Oil PEG-6 Esters*
Olive Oil PEG-7 Esters
Olive Oil PEG-8 Esters*
Olive Oil PEG-10 Esters
Orbignya Oleifera Seed Oil PEG-8 Esters*
Palm Oil PEG-8 Esters*
Passiflora Edulis/Passiflora Incarnata Seed Oils PEG-8 Esters*
Peanut Oil PEG-6 Esters*
PEG-75 Crambe Abyssinica Seed Oil*
PEG-75 Meadowfoam Oil
Pumpkin Seed Oil PEG-8 Esters*
Rapeseed Oil PEG-3 Esters*
Rapeseed Oil PEG-20 Esters*
Raspberry Seed Oil PEG-8 Esters*
Safflower Seed Oil PEG-8 Esters*
Schinziophyton Rautanenii Kernel Oil PEG-8 Esters*
Sclerocarya Birrea Seed Oil PEG-8 Esters*
Sesame Seed Oil PEG-8 Esters*
Soybean Oil PEG-8 Esters*
Soybean Oil PEG-20 Esters*
Soybean Oil PEG-36 Esters*
Sunflower Seed Oil PEG-8 Esters*
Sunflower Seed Oil PEG-32 Esters*
Sweet Almond Oil PEG-8 Esters*
Watermelon Seed Oil PEG-8 Esters*
Wheat Germ Oil PEG-40 Butyloctanol Esters*
Wheat Germ Oil PEG-8 Esters*

*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.

Table 1. PEGylated Oils

PEG-2 Castor Oil
PEG-3 Castor Oil
PEG-4 Castor Oil
PEG-5 Castor Oil
PEG-8 Castor Oil
PEG-9 Castor Oil
PEG-10 Castor Oil
PEG-11 Castor Oil
PEG-15 Castor Oil
PEG-16 Castor Oil
PEG-20 Castor Oil
PEG-25 Castor Oil
PEG-26 Castor Oil
PEG-29 Castor Oil
PEG-30 Castor Oil
PEG-33 Castor Oil
PEG-35 Castor Oil
PEG-36 Castor Oil
PEG-40 Castor Oil
PEG-44 Castor Oil
PEG-50 Castor Oil
PEG-54 Castor Oil
PEG-55 Castor Oil
PEG-60 Castor Oil
PEG-75 Castor Oil
PEG-80 Castor Oil
PEG-100 Castor Oil
PEG-200 Castor Oil
PEG-18 Castor Oil Dioleate
PEG-60 Castor Oil Isostearate
PEG-2 Hydrogenated Castor Oil
PEG-5 Hydrogenated Castor Oil
PEG-6 Hydrogenated Castor Oil
PEG-7 Hydrogenated Castor Oil
PEG-8 Hydrogenated Castor Oil
Hydrogenated Castor Oil PEG-8 Esters
PEG-10 Hydrogenated Castor Oil
PEG-16 Hydrogenated Castor Oil
PEG-20 Hydrogenated Castor Oil
PEG-25 Hydrogenated Castor Oil
PEG-30 Hydrogenated Castor Oil
PEG-35 Hydrogenated Castor Oil
PEG-40 Hydrogenated Castor Oil
PEG-45 Hydrogenated Castor Oil
PEG-50 Hydrogenated Castor Oil
PEG-54 Hydrogenated Castor Oil
PEG-55 Hydrogenated Castor Oil
PEG-60 Hydrogenated Castor Oil
PEG-65 Hydrogenated Castor Oil
PEG-80 Hydrogenated Castor Oil
PEG-100 Hydrogenated Castor Oil
PEG-200 Hydrogenated Castor Oil
PEG-5 Hydrogenated Castor Oil Isostearate
PEG-10 Hydrogenated Castor Oil Isostearate
PEG-15 Hydrogenated Castor Oil Isostearate
PEG-20 Hydrogenated Castor Oil Isostearate
PEG-30 Hydrogenated Castor Oil Isostearate
PEG-40 Hydrogenated Castor Oil Isostearate
PEG-50 Hydrogenated Castor Oil Isostearate
PEG-58 Hydrogenated Castor Oil Isostearate
PEG-20 Hydrogenated Castor Oil Laurate
PEG-30 Hydrogenated Castor Oil Laurate
PEG-40 Hydrogenated Castor Oil Laurate
PEG-50 Hydrogenated Castor Oil Laurate
PEG-60 Hydrogenated Castor Oil Laurate
PEG-20 Hydrogenated Castor Oil PCA Isostearate
PEG-30 Hydrogenated Castor Oil PCA Isostearate
PEG-40 Hydrogenated Castor Oil PCA Isostearate
PEG-60 Hydrogenated Castor Oil PCA Isostearate
PEG-50 Hydrogenated Castor Oil Succinate
Potassium PEG-50 Hydrogenated Castor Oil Succinate
Sodium PEG-50 Hydrogenated Castor Oil Succinate
PEG-5 Hydrogenated Castor Oil Triisostearate
PEG-10 Hydrogenated Castor Oil Triisostearate
PEG-15 Hydrogenated Castor Oil Triisostearate
PEG-20 Hydrogenated Castor Oil Triisostearate
PEG-30 Hydrogenated Castor Oil Triisostearate
PEG-40 Hydrogenated Castor Oil Triisostearate
PEG-50 Hydrogenated Castor Oil Triisostearate
PEG-60 Hydrogenated Castor Oil Triisostearate
Adansonia Digitata Seed Oil PEG-8 Esters
Almond Oil PEG-6 Esters
Almond Oil PEG-8 Esters
Apricot Kernel Oil PEG-6 Esters
Apricot Kernel Oil PEG-8 Esters
Apricot Kernel Oil PEG-40 Esters
Argan Oil PEG-8 Esters
Avocado Oil PEG-8 Esters
Avocado Oil PEG-11 Esters
Bertholletia Excelsa Seed Oil PEG-8 Esters
Borage Seed Oil PEG-8 Esters
Coconut Oil PEG-10 Esters
Corn Oil PEG-6 Esters
Corn Oil PEG-8 Esters
Grape Seed Oil PEG-8 Esters
Hazel Seed Oil PEG-8 Esters
Hydrogenated Palm/Palm Kernel Oil PEG-6 Esters
Jojoba Oil PEG-8 Esters
Jojoba Oil PEG-150 Esters
Linseed Oil PEG-8 Esters
Macadamia Ternifolia Seed Oil PEG-8 Esters
Mango Seed Oil PEG-70 Esters
Mink Oil PEG-13 Esters
Olive Oil PEG-6 Esters
Olive Oil PEG-7 Esters
Olive Oil PEG-8 Esters
Olive Oil PEG-10 Esters
Orbignya Oleifera Seed Oil PEG-8 Esters
Palm Oil PEG-8 Esters
Passiflora Edulis/Passiflora Incarnata Seed Oils PEG-8 Esters
Peanut Oil PEG-6 Esters
PEG-75 Crambe Abyssinica Seed Oil
PEG-75 Meadowfoam Oil
Pumpkin Seed Oil PEG-8 Esters
Rapeseed Oil PEG-3 Esters
Rapeseed Oil PEG-20 Esters
Raspberry Seed Oil PEG-8 Esters
Safflower Seed Oil PEG-8 Esters
Schinziophyton Rautanenii Kernel Oil PEG-8 Esters
Sclerocarya Birrea Seed Oil PEG-8 Esters
Sesame Seed Oil PEG-8 Esters
Soybean Oil PEG-8 Esters
Soybean Oil PEG-20 Esters
Soybean Oil PEG-36 Esters
Sunflower Seed Oil PEG-8 Esters
Sunflower Seed Oil PEG-32 Esters
Sweet Almond Oil PEG-8 Esters
Watermelon Seed Oil PEG-8 Esters
Wheat Germ Oil PEG-40 Butyloctanol Esters
Wheat Germ Oil PEG-8 Esters

Table 2. Previous CIR safety assessments related to proposed expansion ingredients.

Ingredient(s)	Conclusion	Summary	Reference
PEGylated Castor Oils	PEG-30, -33, -35, -36, and -40 castor oil are safe for use in cosmetics at concentrations up to 50% and PEG-30 and -40 hydrogenated castor oil are safe for use at concentrations up to 100%	PEG Castor Oils and PEG Hydrogenated Castor Oils are used as skin conditioning agents and as surfactants (emulsifying and/or solubilizing agents). Results from animal studies indicate very high LD_{50} values. Repeated exposure studies with intravenous exposure produced some evidence of toxicity in dogs, but intramuscular injection and oral studies were negative. No ocular irritation was observed in studies in rabbits. Some irritation was observed in animals, but no sensitization was found on challenge in guinea-pig studies using up to 50% PEG-35 Castor Oil. No evidence of developmental toxicity was seen in mice and rat feeding studies. These ingredients, tested as vehicle controls, produced no mutagenic or carcinogenic effect. Clinical data were generally negative for irritation and sensitization.	IJT 16(3):269-306, 1997
Ricinus Communis (Castor) Oil and Hydrogenated Castor Oil	Safe for use in cosmetics in the present practices of use and concentration	Castor oil, its salts and esters function primarily as skin-conditioning agents, emulsion stabilizers, and surfactants in cosmetics. These ingredients are not acute or repeated dose toxicants. Undiluted castor oil was an irritant in several animal studies. Castor oil was not genotoxic in bacterial or mammalian test systems. No dose-related reproductive toxicity was found in mice fed up to 10% castor oil for 13 weeks. Castor oil is not a significant skin irritant, sensitizer, or photosensitizer in human clinical tests, but it was a mild ocular irritant.	IJT 16 (Suppl. 3):31-77, 2007
Plant-Derived Fatty Acid Oils	Safe for use in cosmetics in the present practices of use and concentration	Oils are used in a wide variety of cosmetic products for their skin conditioning, occlusive, emollient, and moisturizing properties. Undiluted, technical grade, Arachis Hypogaea (Peanut) Oil was moderately irritating to rabbits and guinea pig skin, and 5% aq. solutions of a bar soap containing 13% sodium cocoate had irritation scores of 1.6-4.0/8 in animal studies. However, the remaining animal and clinical irritation and/or sensitization studies conducted on a large number of the oils included in this report, primarily in formulation, did not report any significant irritation or sensitization reactions, indicating that refined oils derived from plants are not ocular or dermal irritants or sensitizers.	CIR 2011
Triethylene Glycol and Polyethylene Glycols (PEGs) $\geq$ 4	Safe for use in cosmetics in the present practices of use and concentration	PEGS function primarily as binders, humectants, and solvents in cosmetic ingredients. In general, PEGs are not oral toxicants, exhibit little ocular irritation, and have minimal dermal irritation and sensitization. PEGs are not genotoxic or carcinogenic. PEGs are not reproductive or developmental toxicants. Use of antimicrobial creams with a PEG vehicle was associated with renal toxicity when applied to burned skin, but studies of extensively tape stripped skin demonstrated that the levels of PEGs that could penetrate in a worst case analysis are >100 times less than the renal toxicity no observable effect level, providing a margin of safety.	CIR 2010
Simmondsia Chinensis (Jojoba) Seed Oil	Safe for use in cosmetics in the present practices of use and concentration	Simmondsia Chinensis (Jojoba) Seed Oil and the hydrogenated oil function primarily as hair and skin conditioning agents. The oil was not an acute oral toxicant to mice or rats. Neither the wax nor the oil were toxic when applied dermally to the shaved backs of guinea pigs in short-term tests. Simmondsia Chinensis (Jojoba) Seed Oil may be a slight ocular irritant. None of the tested ingredients were genotoxic and there were no structural alerts for carcinogenicity. No carcinogenicity, reproductive or developmental toxicity data were available. In clinical tests, Simmondsia Chinensis (Jojoba) Seed Oil was neither a significant dermal irritant, nor a sensitizer. Simmondsia Chinensis (Jojoba) Seed Oil and Jojoba Alcohol were not phototoxic.	CIR 2008

Mink Oil	Safe for use in cosmetics in the present practices of use and concentration	Mink oil functions primarily as a hair-conditioning agent, skin-conditioning agent, and surfactant. This ingredient does not absorb significant UVA or UVB radiation. Mink oil is not an acute oral toxicant. Non-human test data indicate that mink oil is not a dermal or ocular irritant or a dermal sensitizer. No irritation was observed in clinical studies of mink oil up to 28%, although some transient irritation was noted in exaggerated-use studies. Because mink oil is a mixture of glycerides, namely triglycerides, it may enhance the penetration of other chemicals.	IJT 24 (Suppl.3):57-64, 2005
Akyl PEG Ethers	Safe for use in cosmetics in the present practices of use and concentration when formulated to be non-irritating	These ingredients primarily function in cosmetics as surfactants, and some have additional functions as skin conditioning agents, fragrance ingredients, and emulsion stabilizers. Alkyl PEG ethers are readily absorbed through the skin of guinea pigs and rats and through the intestinal mucosa of rats, and they are quickly eliminated from the body through the urine, feces, and expired air. Some alkyl PEG ethers, such as ceteareths and oleths, have been reported to enhance the penetration of certain compounds through the skin. Acute oral toxicity data were available for with the LD_{50} ranging from 1 mg/kg to >10,000 mg/kg, while dermally, the data available indicated the LD_{50} values were mostly >2000 mg/kg for these families of ingredients. Multiple repeated dose feeding studies have been performed. These ingredients were not carcinogenic. Most of the alkyl PEG ethers produced ocular and dermal irritation in studies with animals; however they were not sensitizers in guinea pigs. These ingredients were not reproductive or developmental toxicants and were not genotoxic in in vivo or in vitro assays. In clinical studies, many of the alkyl PEG ethers were irritants but not sensitizers.	CIR 2010

Table 3. Names, CAS registry numbers, and definitions of the PEGylated Oil ingredients

Ingredient CAS No.	Definition[7](*italicized text has been generated by CIR*)
PEGylated Castor Oils & PEGylated Hydrogenated Castor Oils	
PEG-2 Castor Oil 61791-12-6 (generic to any number PEG Castor Oil, i.e. PEG-X Castor Oil)	PEG-2 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil, with an average of 2 moles of ethylene oxide. *PEG-2 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with two equivalents of ethylene oxide.*
PEG-3 Castor Oil 61791-12-6 (generic)	PEG-3 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 3 moles of ethylene oxide. *PEG-3 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with three equivalents of ethylene oxide.*
PEG-4 Castor Oil 61791-12-6 (generic)	PEG-4 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 4 moles of ethylene oxide. *PEG-4 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with four equivalents of ethylene oxide.*
PEG-5 Castor Oil 61791-12-6 (generic)	PEG-5 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 5 moles of ethylene oxide. *PEG-5 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with five equivalents of ethylene oxide.*
PEG-8 Castor Oil 61791-12-6 (generic)	PEG-8 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 8 moles of ethylene oxide. *PEG-8 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with eight equivalents of ethylene oxide.*
PEG-9 Castor Oil 61791-12-6 (generic)	PEG-9 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 9 moles of ethylene oxide. *PEG-9 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with nine equivalents of ethylene oxide.*
PEG-10 Castor Oil 61791-12-6 (generic)	PEG-10 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 10 moles of ethylene oxide. *PEG-10 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with ten equivalents of ethylene oxide.*
PEG-11 Castor Oil 61791-12-6 (generic)	PEG-11 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 11 moles of ethylene oxide. *PEG-11 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with eleven equivalents of ethylene oxide.*
PEG-15 Castor Oil 61791-12-6 (generic)	PEG-15 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 15 moles of ethylene oxide. *PEG-15 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with fifteen equivalents of ethylene oxide.*
PEG-16 Castor Oil 61791-12-6 (generic)	PEG-16 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 16 moles of ethylene oxide. *PEG-16 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with sixteen equivalents of ethylene oxide.*
PEG-20 Castor Oil 61791-12-6 (generic)	PEG-20 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 20 moles of ethylene oxide. *PEG-20 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with twenty equivalents of ethylene oxide.*
PEG-25 Castor Oil 61791-12-6 (generic)	PEG-25 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 25 moles of ethylene oxide. *PEG-25 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with twenty-five equivalents of ethylene oxide.*
PEG-26 Castor Oil 61791-12-6 (generic)	PEG-26 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 26 moles of ethylene oxide. *PEG-26 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with twenty-six equivalents of ethylene oxide.*
PEG-29 Castor Oil 61791-12-6 (generic)	PEG-29 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 29 moles of ethylene oxide. *PEG-29 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with twenty-nine equivalents of ethylene oxide.*
PEG-30 Castor Oil 61791-12-6 (generic)	PEG-30 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 30 moles of ethylene oxide. *PEG-30 Castor Oil is a mixture of the etherification product of castor oil glycerides and the esterification product of the fatty acids from castor oil, with one end of a polyethylene glycol chain, averaging thirty ethylene glycol repeat units in length.*
PEG-33 Castor Oil 61791-12-6 (generic)	PEG-33 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 33 moles of ethylene oxide. *PEG-33 Castor Oil is a mixture of the etherification product of castor oil glycerides and the esterification product of the fatty acids from castor oil, with one end of a polyethylene glycol chain, averaging thirty-three ethylene glycol repeat units in length.*
PEG-35 Castor Oil 61791-12-6 (generic)	PEG-35 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 35 moles of ethylene oxide. *PEG-35 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with thirty-five equivalents of ethylene oxide.*
PEG-36 Castor Oil 61791-12-6 (generic)	PEG-36 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 36 moles of ethylene oxide. *PEG-36 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with thirty-six equivalents of ethylene oxide.*
PEG-40 Castor Oil 61791-12-6 (generic)	PEG-40 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 40 moles of ethylene oxide. *PEG-40 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with forty equivalents of ethylene oxide.*
PEG-44 Castor Oil 61791-12-6 (generic)	PEG-44 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 44 moles of ethylene oxide. *PEG-44 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with forty-four equivalents of ethylene oxide.*
PEG-50 Castor Oil 61791-12-6 (generic)	PEG-50 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 50 moles of ethylene oxide. *PEG-50 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with fifty equivalents of ethylene oxide.*
PEG-54 Castor Oil 61791-12-6 (generic)	PEG-54 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 54 moles of ethylene oxide. *PEG-54 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with fifty-four equivalents of ethylene oxide.*

Table 3. Names, CAS registry numbers, and definitions of the PEGylated Oil ingredients

Ingredient CAS No.	Definition[7](*italicized text has been generated by CIR*)
PEG-55 Castor Oil 61791-12-6 (generic)	PEG-55 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 55 moles of ethylene oxide. *PEG-55 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with fifty-five equivalents of ethylene oxide.*
PEG-60 Castor Oil 61791-12-6 (generic)	PEG-60 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 60 moles of ethylene oxide. *PEG-60 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with sixty equivalents of ethylene oxide.*
PEG-75 Castor Oil 61791-12-6 (generic)	PEG-75 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 75 moles of ethylene oxide. *PEG-75 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with seventy-five equivalents of ethylene oxide.*
PEG-80 Castor Oil 61791-12-6 (generic)	PEG-80 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 80 moles of ethylene oxide. *PEG-80 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with eighty equivalents of ethylene oxide.*
PEG-100 Castor Oil 61791-12-6 (generic)	PEG-100 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 100 moles of ethylene oxide. *PEG-100 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with one-hundred equivalents of ethylene oxide.*
PEG-200 Castor Oil 61791-12-6 (generic)	PEG-200 Castor Oil is a polyethylene glycol derivative of Ricinus Communis (Castor) Oil with an average of 200 moles of ethylene oxide. *PEG-200 Castor Oil is a mixture of the etherification and esterification products of castor oil glycerides and fatty acids from castor oil, with two hundred equivalents of ethylene oxide.*
Diesters	
PEG-18 Castor Oil Dioleate	PEG-18 Castor Oil Dioleate is the oleic acid diester of ethoxylated castor oil in which the average ethoxylation value is 18.
PEG-60 Castor Oil Isostearate	PEG-60 Castor Oil Isostearate is the ester of Isostearic Acid and PEG-60 Castor Oil.
Hydrogenated	
PEG-2 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-2 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 2 moles of ethylene oxide. *PEG-2 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with two equivalents of ethylene oxide.*
PEG-5 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-5 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 5 moles of ethylene oxide. *PEG-5 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with five equivalents of ethylene oxide.*
PEG-6 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-6 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 6 moles of ethylene oxide. *PEG-6 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with six equivalents of ethylene oxide.*
PEG-7 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-7 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 7 moles of ethylene oxide. *PEG-7 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with seven equivalents of ethylene oxide.*
PEG-8 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-8 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 8 moles of ethylene oxide. *PEG-8 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with eight equivalents of ethylene oxide.*
PEG-10 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-10 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 10 moles of ethylene oxide. *PEG-10 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with ten equivalents of ethylene oxide.*
PEG-16 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-16 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 16 moles of ethylene oxide. *PEG-16 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with sixteen equivalents of ethylene oxide.*
PEG-20 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-20 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 20 moles of ethylene oxide. *PEG-20 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with twenty equivalents of ethylene oxide.*
PEG-25 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-25 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 25 moles of ethylene oxide. *PEG-25 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with twenty-five equivalents of ethylene oxide.*
PEG-30 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-30 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 30 moles of ethylene oxide. *PEG-30 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with thirty equivalents of ethylene oxide.*
PEG-35 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-35 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 35 moles of ethylene oxide. *PEG-35 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with thirty-five equivalents of ethylene oxide.*

Table 3. Names, CAS registry numbers, and definitions of the PEGylated Oil ingredients

Ingredient CAS No.	Definition[7](*italicized text has been generated by CIR*)
PEG-40 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-40 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 40 moles of ethylene oxide. *PEG-40 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with forty equivalents of ethylene oxide.*
PEG-45 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-45 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 45 moles of ethylene oxide. *PEG-45 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with forty-five equivalents of ethylene oxide.*
PEG-50 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-50 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 50 moles of ethylene oxide. *PEG-50 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with fifty equivalents of ethylene oxide.*
PEG-54 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-54 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 54 moles of ethylene oxide. *PEG-54 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with fifty-four equivalents of ethylene oxide.*
PEG-55 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-55 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 55 moles of ethylene oxide. *PEG-55 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with fifty-five equivalents of ethylene oxide.*
PEG-60 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-60 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 60 moles of ethylene oxide. *PEG-60 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with sixty equivalents of ethylene oxide.*
PEG-65 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-65 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 65 moles of ethylene oxide. *PEG-65 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with sixty-five equivalents of ethylene oxide.*
PEG-80 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-80 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 80 moles of ethylene oxide. *PEG-80 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with eighty equivalents of ethylene oxide.*
PEG-100 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-100 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 100 moles of ethylene oxide. *PEG-100 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with one hundred equivalents of ethylene oxide.*
PEG-200 Hydrogenated Castor Oil 61788-85-0 (generic)	PEG-200 Hydrogenated Castor Oil is a polyethylene glycol derivative of Hydrogenated Castor Oil with an average of 200 moles of ethylene oxide. *PEG-200 Hydrogenated Castor Oil is a mixture of the etherification and esterification products of hydrogenated castor oil glycerides and fatty acids from hydrogenated castor oil, with two hundred equivalents of ethylene oxide.*
PEG-8 block added transester	
Hydrogenated Castor Oil PEG-8 Esters	Hydrogenated Castor Oil PEG-8 Esters is a product obtained by the transesterification of Hydrogenated Castor Oil and PEG-8.
PEGylated Hydrogenated Castor Oil Diesters	
PEG-5 Hydrogenated Castor Oil Isostearate	PEG-5 Hydrogenated Castor Oil Isostearate is a polyethylene glycol derivative of the isostearic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 5.
PEG-10 Hydrogenated Castor Oil Isostearate	PEG-10 Hydrogenated Castor Oil Isostearate is a polyethylene glycol derivative of the isostearic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 10.
PEG-15 Hydrogenated Castor Oil Isostearate	PEG-15 Hydrogenated Castor Oil Isostearate is a polyethylene glycol derivative of the isostearic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 15.
PEG-20 Hydrogenated Castor Oil Isostearate	PEG-20 Hydrogenated Castor Oil Isostearate is a polyethylene glycol derivative of the isostearic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 20.
PEG-30 Hydrogenated Castor Oil Isostearate	PEG-30 Hydrogenated Castor Oil Isostearate is a polyethylene glycol derivative of the isostearic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 30.
PEG-40 Hydrogenated Castor Oil Isostearate	PEG-40 Hydrogenated Castor Oil Isostearate is a polyethylene glycol derivative of the isostearic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 40.
PEG-50 Hydrogenated Castor Oil Isostearate	PEG-50 Hydrogenated Castor Oil Isostearate is a polyethylene glycol derivative of the isostearic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 50.
PEG-58 Hydrogenated Castor Oil Isostearate	PEG-58 Hydrogenated Castor Oil Isostearate is a polyethylene glycol derivative of the isostearic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 58.
PEG-20 Hydrogenated Castor Oil Laurate [868047-47-6, generic to all PEG-X Hydrogenated Castor Oil]	PEG-20 Hydrogenated Castor Oil Laurate is a polyethylene glycol derivative of the ester of Lauric Acid and Hydrogenated Castor Oil, with an average ethoxylation value of 20
PEG-30 Hydrogenated Castor Oil Laurate [868047-47-6 (generic)]	PEG-30 Hydrogenated Castor Oil Laurate is a polyethylene glycol derivative of the ester of Lauric Acid and Hydrogenated Castor Oil, with an average ethoxylation value of 30.

Table 3. Names, CAS registry numbers, and definitions of the PEGylated Oil ingredients

Ingredient CAS No.	Definition[7](*italicized text has been generated by CIR*)
PEG-40 Hydrogenated Castor Oil Laurate [868047-47-6 (generic)]	PEG-40 Hydrogenated Castor Oil Laurate is a polyethylene glycol derivative of the ester of Lauric Acid and Hydrogenated Castor Oil, with an average ethoxylation value of 40.
PEG-50 Hydrogenated Castor Oil Laurate [868047-47-6 (generic)]	PEG-50 Hydrogenated Castor Oil Laurate is a polyethylene glycol derivative of the ester of Lauric Acid and Hydrogenated Castor Oil, with an average ethoxylation value of 50.
PEG-60 Hydrogenated Castor Oil Laurate [868047-47-6 (generic)]	PEG-60 Hydrogenated Castor Oil Laurate is a polyethylene glycol derivative of the ester of Lauric Acid and Hydrogenated Castor Oil, with an average ethoxylation value of 60.
PEG-20 Hydrogenated Castor Oil PCA Isostearate	PEG-20 Hydrogenated Castor Oil PCA Isostearate is the diester of PEG-20 Hydrogenated Castor Oil and a mixture of PCA and Isostearic Acid.
PEG-30 Hydrogenated Castor Oil PCA Isostearate	PEG-30 Hydrogenated Castor Oil PCA Isostearate is the diester of PEG-30 Hydrogenated Castor Oil and a mixture of PCA and Isostearic Acid.
PEG-40 Hydrogenated Castor Oil PCA Isostearate	PEG-40 Hydrogenated Castor Oil PCA Isostearate is the diester of PEG-40 Hydrogenated Castor Oil and a mixture of PCA and Isostearic Acid.
PEG-60 Hydrogenated Castor Oil PCA Isostearate	PEG-60 Hydrogenated Castor Oil PCA Isostearate is the diester of PEG-60 Hydrogenated Castor Oil and a mixture of PCA and Isostearic Acid.
PEG-50 Hydrogenated Castor Oil Succinate	PEG-50 Hydrogenated Castor Oil Succinate is a polyethylene glycol derivative of the succinic acid ester of Hydrogenated Castor Oil with an average ethoxylation value of 50.
PEG-5 Hydrogenated Castor Oil Triisostearate [188734-82-9, generic to all PEG-X Hydrogenated Castor Oil Triisostearate]	PEG-5 Hydrogenated Castor Oil Triisostearate is the triester of isostearic acid and Hydrogenated Castor Oil with an average of 5 moles of ethylene oxide.
PEG-10 Hydrogenated Castor Oil Triisostearate [188734-82-9 (generic)]	PEG-10 Hydrogenated Castor Oil Triisostearate is the triester of isostearic acid and Hydrogenated Castor Oil with an average of 10 moles of ethylene oxide.
PEG-15 Hydrogenated Castor Oil Triisostearate	PEG-15 Hydrogenated Castor Oil Triisostearate is the triester of isostearic acid and Hydrogenated Castor Oil with an average of 15 moles of ethylene oxide.
PEG-20 Hydrogenated Castor Oil Triisostearate [188734-82-9 (generic)]	PEG-20 Hydrogenated Castor Oil Triisostearate is the isostearic acid triester of Hydrogenated Castor Oil with an average ethoxylation value of 20.
PEG-30 Hydrogenated Castor Oil Triisostearate [188734-82-9 (generic)]	PEG-30 Hydrogenated Castor Oil Triisostearate is the triester of isostearic acid and Hydrogenated Castor Oil with an average of 30 moles of ethylene oxide.
PEG-40 Hydrogenated Castor Oil Triisostearate [188734-82-9 (generic)]	PEG-40 Hydrogenated Castor Oil Triisostearate is the triester of isostearic acid and Hydrogenated Castor Oil with an average of 40 moles of ethylene oxide.
PEG-50 Hydrogenated Castor Oil Triisostearate [188734-82-9 (generic)]	PEG-50 Hydrogenated Castor Oil Triisostearate is the isostearic acid triester of Hydrogenated Castor Oil with an average of 50 moles of ethylene oxide.
PEG-60 Hydrogenated Castor Oil Triisostearate [188734-82-9 (generic)]	PEG-60 Hydrogenated Castor Oil Triisostearate is the isostearic acid triester of Hydrogenated Castor Oil with an average of 60 moles of ethylene oxide.
Potassium PEG-50 Hydrogenated Castor Oil Succinate	Potassium PEG-50 Hydrogenated Castor Oil Succinate is the potassium salt of PEG-50 Hydrogenated Castor Oil Succinate.
Sodium PEG-50 Hydrogenated Castor Oil Succinate	Sodium PEG-50 Hydrogenated Castor Oil Succinate is the sodium salt of PEG-50 Hydrogenated Castor Oil Succinate.
Other PEG-X block added Oils	
Adansonia Digitata Seed Oil PEG-8 Esters	Adansonia Digitata Seed Oil PEG-8 Esters is the product obtained by the transesterification of Adansonia Digitata Seed Oil and PEG-8.
Almond Oil PEG-6 Esters	Almond Oil PEG-6 Esters is the product obtained by the transesterification of Prunus Amygdalus Dulcis (Almond) Oil and PEG-6.
Almond Oil PEG-8 Esters	Almond Oil PEG-8 Esters is the product obtained by the transesterification of Prunus Amygdalus Dulcis (Almond) Oil and PEG-8.
Apricot Kernel Oil PEG-6 Esters	Apricot Kernel Oil PEG-6 Esters is the product obtained by the transesterification of Prunus Armeniaca (Apricot) Kernel Oil and PEG-6.
Apricot Kernel Oil PEG-8 Esters	Apricot Kernel Oil PEG-8 Esters is the product obtained by the transesterification of Prunus Armeniaca (Apricot) Kernel Oil and PEG-8.
Apricot Kernel Oil PEG-40 Esters	Apricot Kernel Oil PEG-40 Esters is the product obtained by the transesterification of Prunus Armeniaca (Apricot) Kernel Oil and PEG-40.
Argan Oil PEG-8 Esters	Argan Oil PEG-8 Esters is the product obtained by the transesterification of Argania Spinosa Kernel Oil and PEG-8.
Avocado Oil PEG-8 Esters	Avocado Oil PEG-8 Esters is the product obtained by the transesterification of Persea Gratissima (Avocado) Oil and PEG-8.
Avocado Oil PEG-11 Esters	Avocado Oil PEG-11 Esters is the product obtained from the transesterification of Persea Gratissima (Avocado) Oil and PEG-11.
Bertholletia Excelsa Seed Oil PEG-8 Esters	Bertholletia Excelsa Seed Oil PEG-8 Esters is the product obtained from the transesterificaton of Bertholletia Excelsa Seed Oil and PEG-8.

Table 3. Names, CAS registry numbers, and definitions of the PEGylated Oil ingredients

Ingredient CAS No.	Definition[7] (*italicized text has been generated by CIR*)
Bitter Cherry Seed Oil PEG-8 Esters	Bitter Cherry Seed Oil PEG-8 Esters is a product obtained by the transesterification of Prunus Cerasus (Bitter Cherry) Seed Oil and PEG-8.
Borage Seed Oil PEG-8 Esters	Borage Seed Oil PEG-8 Esters is the product obtained by the transesterification of Borago Officinalis (Borage) Seed Oil and PEG-8.
Coconut Oil PEG-10 Esters	Coconut Oil PEG-10 Esters is a polyethylene glycol derivative of Cocos Nucifera (Coconut) Oil with an average of 10 moles of ethylene oxide.
Corn Oil PEG-6 Esters	Corn Oil PEG-6 Esters is a product obtained by the transesterification of Zea Mays (Corn) Oil and PEG-6.
Corn Oil PEG-8 Esters	Corn Oil PEG-8 Esters is a product obtained by the transesterification of Zea Mays (Corn) Oil and PEG-8.
Grape Seed Oil PEG-8 Esters	Grape Seed Oil PEG-8 Esters is the product obtained by the transesterification of Vitis Vinifera (Grape) Seed Oil and PEG-8.
Hazel Seed Oil PEG-8 Esters	Hazel Seed Oil PEG-8 Esters is the product obtained by the transesterification of Corylus Avellana (Hazel) Seed Oil and PEG-8.
Hydrogenated Palm/Palm Kernel Oil PEG-6 Esters	Hydrogenated Palm/Palm Kernel Oil PEG-6 Esters is the product obtained by the transesterification of Hydrogenated Palm Kernel Oil, Hydrogenated Palm Oil and PEG-6.
Jojoba Oil PEG-8 Esters	Jojoba Oil PEG-8 Esters is the polyethylene glycol derivative of the acids and alcohols derived from Simmondsia Chinensis (Jojoba) Oil containing an average of 8 moles of ethylene oxide.
Jojoba Oil PEG-150 Esters	Jojoba Oil PEG-150 Esters is the polyethylene glycol derivative of the acids and alcohols derived from Simmondsia Chinensis (Jojoba) Oil containing an average of 150 moles of ethylene oxide.
Linseed Oil PEG-8 Esters	Linseed Oil PEG-8 Esters is the product obtained by the transesterification of Linum Usitatissimum (Linseed) Oil and PEG-8.
Macadamia Ternifolia Seed Oil PEG-8 Esters	Macadamia Ternifolia Seed Oil PEG-8 Esters is the product obtained by the transesterification of Macadamia Ternifolia Seed Oil and PEG-8.
Mango Seed Oil PEG-70 Esters	Mango Seed Oil PEG-70 Esters is the product obtained by the transesterification of Mangifera Indica (Mango) Seed Oil and PEG-70.
Mink Oil PEG-13 Esters	Mink Oil PEG-13 Esters is the product obtained by the transesterification of Mink Oil and PEG-13.
Olive Oil PEG-6 Esters	Olive Oil PEG-6 Esters is a product obtained by the transesterification of Olea Europaea (Olive) Oil and PEG-6.
Olive Oil PEG-7 Esters	Olive Oil PEG-7 Esters is a product obtained by the transesterification of Olea Europaea (Olive) Oil and PEG-7
Olive Oil PEG-8 Esters	Olive Oil PEG-8 Esters is a product obtained by the transesterification of Olea Europaea (Olive) Oil and PEG-8.
Olive Oil PEG-10 Esters	Olive Oil PEG-10 Esters is a product obtained by the transesterification of Olea Europaea (Olive) Oil and PEG-10.
Orbignya Oleifera Seed Oil PEG-8 Esters	Orbignya Oleifera Seed Oil PEG-8 Esters is the product obtained by the transesterification of Orbignya Oleifera Seed Oil and PEG-8.
Palm Oil PEG-8 Esters	Palm Oil PEG-8 Esters is the product obtained by the transesterification of Elaeis Guineensis (Palm) Oil and PEG-8.
Passiflora Edulis/Passiflora Incarnata Seed Oils PEG-8 Esters	Passiflora Edulis/Passiflora Incarnata Seed Oils PEG-8 Esters is a product obtained by the transesterification of a blend of Passiflora Edulis Seed Oil and Passiflora Incarnata Seed Oil with PEG-8.
Peanut Oil PEG-6 Esters	Peanut Oil PEG-6 Esters is the product obtained by the transesterification of Arachis Hypogaea (Peanut) Oil and PEG-6.
PEG-75 Crambe Abyssinica Seed Oil	PEG-75 Crambe Abyssinica Seed Oil is a polyethylene glycol derivative of Crambe Abyssinica Seed Oil with an average of 75 moles of ethylene oxide. *PEG-75 Crambe Abyssinica Seed Oil is a mixture of the etherification and esterification products of crambe abyssinica seed oil glycerides and fatty acids from crambe abyssinica seed oil, with seventy-five equivalents of ethylene oxide.*
PEG-75 Meadowfoam Oil	PEG-75 Meadowfoam Oil is a polyethylene glycol derivative of Limnanthes Alba (Meadowfoam) Seed Oil with an average of 75 moles of ethylene oxide. *PEG-75 Meadowfoam Oil is a mixture of the etherification and esterification products of meadowfoam oil glycerides and fatty acids from meadowfoam oil, with seventy-five equivalents of ethylene oxide.*
Pumpkin Seed Oil PEG-8 Esters	Pumpkin Seed Oil PEG-8 Esters is the product obtained by the transesterification of Cucurbita Pepo (Pumpkin) Seed Oil and PEG-8.
Rapeseed Oil PEG-3 Esters	Rapeseed Oil PEG-3 Esters is the product obtained by the transesterification of Brassica Campestris (Rapeseed) Oil and PEG-3.
Rapeseed Oil PEG-20 Esters	Rapeseed Oil PEG-20 Esters is the product obtained by the transesterification of Brassica Campestris (Rapeseed) Oil and PEG-20.
Raspberry Seed Oil PEG-8 Esters	Raspberry Seed Oil PEG-8 Esters is the product obtained by the transesterification of Rubus Idaeus (Raspberry) Seed Oil and PEG-8.
Safflower Seed Oil PEG-8 Esters	Safflower Seed Oil PEG-8 Esters is the product obtained by the transesterification of Carthamus Tinctorius (Safflower) Seed Oil and PEG-8.
Schinziophyton Rautanenii Kernel Oil PEG-8 Esters	Schinziophyton Rautanenii Kernel Oil PEG-8 Esters is the product obtained by the transesterification of Schinziophyton Rautanenii Kernel Oil and PEG-8.
Sclerocarya Birrea Seed Oil PEG-8 Esters	Sclerocarya Birrea Seed Oil PEG-8 Esters is the product obtained by the transesterification of PEG-8 with Sclerocarya Birrea Seed Oil.
Sesame Seed Oil PEG-8 Esters	Sesame Seed Oil PEG-8 Esters is the product obtained by the transesterification of PEG-8 with Sesamum Indicum Seed Oil.
Soybean Oil PEG-8 Esters	Soybean Oil PEG-8 Esters is the product obtained by the transesterification of Glycine Soja (Soybean) Oil and PEG-8.
Soybean Oil PEG-20 Esters	Soybean Oil PEG-20 Esters is the product obtained by the transesterification of Glycine Soja (Soybean) Oil and PEG-20
Soybean Oil PEG-36 Esters	Soybean Oil PEG-36 Esters is the product obtained by the transesterification of Glycine Soja (Soybean) Oil and PEG-36.
Sunflower Seed Oil PEG-8 Esters	Sunflower Seed Oil PEG-8 Esters is the product obtained by the transesterification of Helianthus Annuus (Sunflower) Seed Oil and PEG-8.

Table 3. Names, CAS registry numbers, and definitions of the PEGylated Oil ingredients

Ingredient CAS No.	Definition[7] (*italicized text has been generated by CIR*)
Sunflower Seed Oil PEG-32 Esters	Sunflower Seed Oil PEG-32 Esters is the product obtained by the transesterification of Helianthus Annuus (Sunflower) Seed Oil and PEG-32.
Sweet Almond Oil PEG-8 Esters	Sweet Almond Oil PEG-8 Esters is the product obtained by the transesterification of Prunus Amygdalus (Sweet Almond) Oil and PEG-6.
Watermelon Seed Oil PEG-8 Esters	Watermelon Seed Oil PEG-8 Esters is the product obtained by the transesterification of PEG-8 with Citrillus Lanatus (Watermelon) Seed Oil.
Wheat Germ Oil PEG-40 Butyloctanol Esters	Wheat Germ Oil PEG-40 Butyloctanol Esters is a the product obtained by the reaction of a mixture of Triticum Vulgare (Wheat) Germ Oil (q.v.) and Butyloctanol with PEG-40. *Wheat Germ Oil PEG-40 Butyloctanol Esters is the transesterification product obtained by the reaction of a mixture of Triticum Vulgare (Wheat) Germ Oil with 2-butyloctanol and PEG-40.*
Wheat Germ Oil PEG-8 Esters	Wheat Germ Oil PEG-8 Esters is the product obtained by the transesterificaton of Triticum Vulgare (Wheat) Germ Oil and PEG-8.

Table 4a. Historical and current use and concentration of use data for PEG-30, -33, -35, -36, -40 Castor Oil and PEG-30 and-40 Hydrogenated Castor Oil.[1,8]

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	PEG-30 Castor Oil				PEG-33 Castor Oil				PEG-35 Castor Oil			
Data Year	**1997**	**2012**	**1997**	**2012**	**1997**	**2012**	**1997**	**2012**	**1997**	**2012**	**1997**	**2012**
Totals*	**77[a]**	**1**	**≥ 50[b]**	**0.1**	**13**	**41**	**NR**	**NR**	**4**	**35**	**NR**	**0.001-1**
Duration of Use												
Leave-On	NR	NR	[b]	NR	10	30	NR	NR	4	21	NR	0.005-1
Rinse-Off	73	1	[b]	0.1	3	11	NR	NR	NR	14	NR	0.001-1
Diluted for (Bath) Use	NR	NR	[b]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Exposure Type												
Eye Area	NR	NR	[b]	NR	NR	1	NR	NR	NR	2	NR	NR
Incidental Ingestion	NR	NR	[b]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	[b]	NR	NR	NR	NR	NR	1	1	NR	NR
Incidental Inhalation-Powder	NR	NR	[b]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	1	NR	[b]	NR	8	35	NR	NR	3	24	NR	0.005
Deodorant (underarm)	NR	NR	[b]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	1	[b]	0.1	5	6	NR	NR	1	11	NR	0.001-1
Hair-Coloring	72	NR	[b]	NR	NR	NR	NR	NR	NR	NR	NR	0.2-0.4
Nail	NR	NR	[b]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	[b]	NR	NR	NR	NR	NR	NR	1	NR	0.005
Baby Products	NR	NR	[b]	NR	NR	NR	NR	NR	NR	NR	NR	NR

	PEG-36 Castor Oil				PEG-40 Castor Oil				PEG-30 Hydrogenated Castor Oil			
Data Year	**1997**	**2012**	**1997**	**2012**	**1997**	**2012**	**1997**	**2012**	**1997**	**2012**	**1997**	**2012**
Totals*	**3**	**6**	**NR**	**NR**	**170[c]**	**95**	**≤ 10[b]**	**NR**	**5**	**3**	**≤ 0.1[b]**	**0.06-10**
Duration of Use												
Leave-On	3	6	NR	NR	60	59	[b]	NR	2	1	[b]	0.06-2
Rinse Off	NR	NR	NR	NR	46	36	[b]	NR	3	2	[b]	2-10
Diluted for (Bath) Use	NR	NR	NR	NR	1	NR	[b]	NR	NR	NR	[b]	NR
Exposure Type												
Eye Area	NR	NR	NR	NR	1	1	[b]	NR	NR	NR	[b]	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	[b]	NR	NR	NR	[b]	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	7	1	[b]	NR	1	NR	[b]	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	[b]	NR	NR	NR	[b]	NR
Dermal Contact	3	6	NR	NR	74	63	[b]	NR	5	2	[b]	2-10
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	[b]	NR	1	NR	[b]	NR
Hair - Non-Coloring	NR	NR	NR	NR	33	29	[b]	NR	NR	NR	[b]	NR
Hair-Coloring	NR	NR	NR	NR	NR	2	[b]	NR	NR	1	[b]	NR
Nail	NR	NR	NR	NR	NR	1	[b]	NR	NR	NR	[b]	0.06
Mucous Membrane	NR	NR	NR	NR	2	14	[b]	NR	NR	NR	[b]	10
Baby Products	NR	NR	NR	NR	NR	NR	[b]	NR	NR	NR	[b]	NR

	PEG-40 Hydrogenated Castor Oil			
	1997	**2012**	**1997**	**2012**
Totals*	**268[d]**	**2107**	**≤ 5[b]**	**0.00007-22**
Duration of Use				
Leave-On	186	1319	[b]	0.0007-22
Rinse-Off	50	754	[b]	0.00007-14
Diluted for (Bath) Use	20	34	[b]	0.001-5
Exposure Type				
Eye Area	9	53	[b]	0.002-15
Incidental Ingestion	NR	4	[b]	0.9-4
Incidental Inhalation-Spray	31	279	[b]	0.003-6[e]
Incidental Inhalation-Powder	3	3	[b]	0.002-2
Dermal Contact	197	1461	[b]	0.00007-10
Deodorant (underarm)	2	27	[b]	0.02-4
Hair - Non-Coloring	54	537	[b]	0.008-22
Hair-Coloring	2	93	[b]	0.06-14
Nail	NR	4	[b]	0.8
Mucous Membrane	30	390	[b]	0.001-10
Baby Products	1	18	[b]	0.5-4

*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.

NR = Not reported

a Total includes4 uses listed under trade name of mixtures, exact duration of use and exposure type could not be determined.

b Breakdown not available.

c Total includes 63 uses listed under trade name of mixtures, exact duration of use and exposure type could not be determined.

d Total includes 11 uses listed under trade name, exact duration of use and exposure type could not be determined.

e 0.5% in a baby detangling spray; 0.003% in an other spray fragrance; 6% in an other pump spray fragrance; 0.02-0.4% in an aerosol hair spray; 0.2-0.7% in a pump hair spray; 0.5% in a tonic, dressing, and other hair grooming aids spray; 4% in an aerosol deodorant spray; 3% in a body and hand cream spray; 3% in a foot spray; and 2% in a skin freshener spray.

Table 4b. Frequency and concentration of use according to duration and type of exposure for proposed expansion of PEGylated Oils.[8]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	PEG-9 Castor Oil		**PEG-25 Castor Oil**		**PEG-50 Castor Oil**	
Totals*	**1**	**0.3**	**NR**	**3-17**	**2**	**NR**
Duration of Use						
Leave-On	1	0.3	NR	3-17	2	NR
Rinse-Off	NR	NR	NR	NR	NR	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1	NR	NR	3[a]	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	NR	NR	NR	2	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	0.3	NR	3-17	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

	PEG-60 Castor Oil		**PEG-2 Hydrogenated Castor Oil**		**PEG-7 Hydrogenated Castor Oil**	
Totals*	**NR**	**0.002-23**	**5**	**NR**	**11**	**0.05-8**
Duration of Use						
Leave-On	NR	0.04-23	5	NR	9	0.05-8
Rinse Off	NR	0.002-11	NR	NR	2	NR
Diluted for (Bath) Use	NR	6	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	0.08-1	5	NR	NR	5
Incidental Ingestion	NR	0.06-2	NR	NR	NR	8
Incidental Inhalation-Spray	NR	0.04-16[b]	NR	NR	4	NR
Incidental Inhalation-Powder	NR	0.2	NR	NR	NR	NR
Dermal Contact	NR	0.002-11	NR	NR	9	0.6-5
Deodorant (underarm)	NR	0.04-0.5	NR	NR	NR	NR
Hair - Non-Coloring	NR	0.5-23	NR	NR	2	0.05
Hair-Coloring	NR	0.6-8	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	0.06-6	NR	NR	2	8
Baby Products	NR	NR	NR	NR	NR	NR

	PEG-10 Hydrogenated Castor Oil		**PEG-16 Hydrogenated Castor Oil**		**PEG-20 Hydrogenated Castor Oil**	
Totals*	**5**	**3**	**1**	**NR**	**5**	**0.05-0.5**
Duration of Use						
Leave-On	5	*3*	1	NR	4	0.05-0.5
Rinse-Off	NR	*NR*	NR	NR	1	NR
Diluted for (Bath) Use	NR	*NR*	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	1	NR	1	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	3	3	NR	NR	5	0.05-0.5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	NR	1	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

Table 4b. Frequency and concentration of use according to duration and type of exposure for proposed expansion of PEGylated Oils.[8]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	PEG-25 Hydrogenated Castor Oil		**PEG-35 Hydrogenated Castor Oil**		**PEG-45 Hydrogenated Castor Oil**	
Totals	**39**	**0.01-23**	**1**	**NR**	**2**	**NR**
Duration of Use						
Leave-On	34	0.01-23	1	NR	1	NR
Rinse Off	5	0.3	NR	NR	1	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	4	NR	1	NR	NR	NR
Incidental Inhalation-Aerosol	NR	NR	NR	NR	NR	NR
Dermal Contact	16	0.01-2	1	NR	1	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	23	3-23	NR	NR	1	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	3	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	1	NR

	PEG-60 Hydrogenated Castor Oil		**PEG-80 Hydrogenated Castor Oil**		**PEG-100 Hydrogenated Castor Oil**	
Totals*	**349**	**0.00004-18**	**4**	**NR**	**NR**	**0.02-4**
Duration of Use						
Leave-On	251	0.00004-18	3	NR	NR	0.02-3
Rinse-Off	94	0.00004-0.5	1	NR	NR	1-2
Diluted for (Bath) Use	4	NR	NR	NR	NR	4
Exposure Type						
Eye Area	9	3-5	NR	NR	NR	NR
Incidental Ingestion	1	6	NR	NR	NR	0.5
Incidental Inhalation-Spray	13	0.3-1[c]	NR	NR	NR	0.3[d]
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	307	0.00004-5	4	NR	NR	0.02-4
Deodorant (underarm)	2	NR	NR	NR	NR	NR
Hair - Non-Coloring	41	0.3-18	NR	NR	NR	0.2-3
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	3	NR	NR	NR	NR
Mucous Membrane	37	0.004-6	NR	NR	NR	0.5-4
Baby Products	1	NR	NR	NR	NR	NR

	PEG-20 Hydrogenated Castor Oil Triisostearate		**PEG-40 Hydrogenated Castor Oil Triisostearate**		**PEG-50 Hydrogenated Castor Oil Succinate**	
Totals*	**3**	**NR**	**NR**	**0.002-0.003**	**NR**	**1-40**
Duration of Use						
Leave-On	3	NR	NR	NR	NR	40
Rinse-Off	NR	NR	NR	0.002-0.003	NR	1
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	3	NR	NR	NR	NR	1
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	NR	NR	0.002-0.003	NR	1
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	0.003	NR	40
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	0.002-0.003	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

Table 4b. Frequency and concentration of use according to duration and type of exposure for proposed expansion of PEGylated Oils.[8]

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	PEG-40 Hydrogenated Castor Oil PCA Isostearate		**Apricot Kernel Oil PEG-6 Esters**		**Avocado Oil PEG-11 Esters**	
Totals*	**2**	**NR**	**24**	**0.8-1**	**NR**	**0.1**
Duration of Use						
Leave-On	1	NR	23	0.8-1	NR	0.1
Rinse-Off	1	NR	NR	NR	NR	NR
Diluted for (Bath) Use	NR	NR	1	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	1	1	NR	NR
Incidental Ingestion	NR	NR	4	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	1	NR	20	0.8-1	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	NR	NR	NR	NR	0.1
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	5	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Coconut Oil PEG-10 Esters		**Grape Seed Oil PEG-8 Esters**		**Hydrogenated Palm/Palm Kernel Oil PEG-6 Esters**	
Totals*	**8**	**NR**	**18**	**NR**	**4**	**0.6-24**
Duration of Use						
Leave-On	2	NR	10	NR	4	0.6-24
Rinse-Off	6	NR	8	NR	NR	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	1	9-24
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	1	NR	NR	0.6
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	16
Dermal Contact	2	NR	18	NR	4	0.6-24
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	6	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	6	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Jojoba Oil PEG-8 Esters		**Olive Oil PEG-7 Esters**		**Olive Oil PEG-10 Esters**	
Totals*	**40**	**0.5**	**97**	**0.05-97**	**NR**	**0.002-0.009**
Duration of Use						
Leave-On	26	NR	45	0.9-12	NR	0.002
Rinse Off	7	0.5	52	0.05-97	NR	0.003-0.009
Diluted for (Bath) Use	7	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	3	NR	NR	NR
Incidental Ingestion	NR	NR	NR	0.9	NR	NR
Incidental Inhalation-Spray	NR	NR	2	1[e]	NR	NR
Incidental Inhalation-Powder	1	NR	NR	NR	NR	NR
Dermal Contact	34	NR	74	0.1-97	NR	0.002-0.009
Deodorant (underarm)	NR	NR	1	NR	NR	NR
Hair - Non-Coloring	6	0.5	23	0.05-1	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	7	NR	22	0.1-0.9	NR	0.003-0.009
Baby Products	3	NR	1	NR	NR	NR

Table 4b. Frequency and concentration of use according to duration and type of exposure for proposed expansion of PEGylated Oils.[8]

	# of Uses	*Max Conc of Use (%)*
	PEG-75 Meadowfoam Oil	
Totals*	**1**	**0.08**
Duration of Use		
Leave-On	1	0.08
Rinse-Off	NR	NR
Diluted for (Bath) Use	NR	NR
Exposure Type		
Eye Area	NR	NR
Incidental Ingestion	NR	NR
Incidental Inhalation-Spray	NR	0.08[f]
Incidental Inhalation-Powder	NR	NR
Dermal Contact	NR	NR
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	1	0.08
Hair-Coloring	NR	NR
Nail	NR	NR
Mucous Membrane	NR	NR
Baby Products	NR	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
NR = Not reported
a 3% in a pump hair spray.
b 0.5% in a pump hair spray and 16% in an aerosol hair spray; 0.04% in an aerosol deodorant; and 0.4% in a face and neck cream spray.
c 0.3% in an aerosol Hairspray, 0.9% in a pump Hairspray, and 1% in a face and Neck cream spray
d0.3% in an aerosol other fragrance preparation.
e 1% in a pump spray
f 0.08% in a pump spray

Table 4c. Not reported to be in use

PEG-2 Castor Oil	PEG-15 Hydrogenated Castor Oil Isostearate	Corn Oil PEG-8 Esters
PEG-3 Castor Oil	PEG-20 Hydrogenated Castor Oil Isostearate	Hazel Seed Oil PEG-8 Esters
PEG-4 Castor Oil	PEG-30 Hydrogenated Castor Oil Isostearate	Jojoba Oil PEG-150 Esters
PEG-5 Castor Oil	PEG-40 Hydrogenated Castor Oil Isostearate	Linseed Oil PEG-8 Esters
PEG-8 Castor Oil	PEG-50 Hydrogenated Castor Oil Isostearate	Macadamia Ternifolia Seed Oil PEG-8 Esters
PEG-10 Castor Oil	PEG-58 Hydrogenated Castor Oil Isostearate	Mango Seed Oil PEG-70 Esters
PEG-11 Castor Oil	PEG-20 Hydrogenated Castor Oil Laurate	Mink Oil PEG-13 Esters
PEG-15 Castor Oil	PEG-30 Hydrogenated Castor Oil Laurate	Olive Oil PEG-6 Esters
PEG-16 Castor Oil	PEG-40 Hydrogenated Castor Oil Laurate	Olive Oil PEG-8 Esters
PEG-20 Castor Oil	PEG-50 Hydrogenated Castor Oil Laurate	Orbignya Oleifera Seed Oil PEG-8 Esters
PEG-26 Castor Oil	PEG-60 Hydrogenated Castor Oil Laurate	Palm Oil PEG-8 Esters
PEG-29 Castor Oil	PEG-20 Hydrogenated Castor Oil PCA Isostearate	Passiflora Edulis/Passiflora Incarnata Seed Oils
PEG-44 Castor Oil	PEG-30 Hydrogenated Castor Oil PCA Isostearate	PEG-8 Esters
PEG-54 Castor Oil	PEG-60 Hydrogenated Castor Oil PCA Isostearate	Peanut Oil PEG-6 Esters
PEG-55 Castor Oil	Potassium PEG-50 Hydrogenated Castor Oil Succinate	PEG-75 Crambe Abyssinica Seed Oil
PEG-75 Castor Oil	Sodium PEG-50 Hydrogenated Castor Oil Succinate	Pumpkin Seed Oil PEG-8 Esters
PEG-80 Castor Oil	PEG-5 Hydrogenated Castor Oil Triisostearate	Rapeseed Oil PEG-3 Esters
PEG-100 Castor Oil	PEG-10 Hydrogenated Castor Oil Triisostearate	Rapeseed Oil PEG-20 Esters
PEG-200 Castor Oil	PEG-15 Hydrogenated Castor Oil Triisostearate	Raspberry Seed Oil PEG-8 Esters
PEG-18 Castor Oil Dioleate	PEG-30 Hydrogenated Castor Oil Triisostearate	Safflower Seed Oil PEG-8 Esters
PEG-60 Castor Oil Isostearate	PEG-50 Hydrogenated Castor Oil Triisostearate	Schinziophyton Rautanenii Kernel Oil PEG-8 Esters
PEG-5 Hydrogenated Castor Oil	PEG-60 Hydrogenated Castor Oil Triisostearate	Sclerocarya Birrea Seed Oil PEG-8 Esters
PEG-6 Hydrogenated Castor Oil	Adansonia Digitata Seed Oil PEG-8 Esters	Sesame Seed Oil PEG-8 Esters
PEG-8 Hydrogenated Castor Oil	Almond Oil PEG-6 Esters	Soybean Oil PEG-8 Esters
Hydrogenated Castor Oil PEG-8 Esters	Almond Oil PEG-8 Esters	Soybean Oil PEG-20 Esters
PEG-54 Hydrogenated Castor Oil	Apricot Kernel Oil PEG-8 Esters	Soybean Oil PEG-36 Esters
PEG-55 Hydrogenated Castor Oil	Apricot Kernel Oil PEG-40 Esters	Sunflower Seed Oil PEG-8 Esters
PEG-65 Hydrogenated Castor Oil	Argan Oil PEG-8 Esters	Sunflower Seed Oil PEG-32 Esters
PEG-200 Hydrogenated Castor Oil	Avocado Oil PEG-8 Esters	Sweet Almond Oil PEG-8 Esters
PEG-5 Hydrogenated Castor Oil Isostearate	Bertholletia Excelsa Seed Oil PEG-8 Esters	Watermelon Seed Oil PEG-8 Esters
PEG-10 Hydrogenated Castor Oil Isostearate	Borage Seed Oil PEG-8 Esters	Wheat Germ Oil PEG-40 Butyloctanol Esters
	Corn Oil PEG-6 Esters	Wheat Germ Oil PEG-8 Esters

References

1. Andersen FA (ed.). Final report on the safety assessment of PEG-30, -35, -36, and -40 castor oil and PEG-30 and -40 hydrogenated castor oil. *IJT*. 1997;16:269-306.

2. O'Lenick AJ and Parkinson JK. Group selectivity of ethyoxylation of hydroxy acids. *J Soc Cosmet Chem*. 1993;44(6):319-328.

3. Nasioudis A, van Velde JW, Heeren RMA, and van den Brink OF. Detailed molecular characterization of castor oil ethoxylates by liquid chromatography multistage mass spectrometry. *J Chromatogr A*. 2011;1218:7166-7172.

4. Shree Vallabh Chemicals. Castor Oil Ethoxylate. http://www.shreechem.in/castor_oil_ethoxylates.html. Date Accessed 1-23-2012.

5. Kociba RJ, McCollister SB, Park C, Torkelson TR, and Gehring PJ. 1,4-Dioxane. I. Results of a 2-year ingestion study in rats. *Toxicol Appl Pharmacol*. 1974;30:275-286.

6. Elder RL (ed). Final Report on the Safety Assessment of PEG-2, -6, -8, -12, -20, -32, -40, -50, -100, and -150 Stearates. *JACT*. 1983;2(7):17-34.

7. Gottschalck TE and Bailey JE eds. International Cosmetic Ingredient Dictionary and Handbook. 13th ed. Washington, D.C.: Personal Care Products Council; 2010.

8. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. *FDA Database.* 2012. Washington, DC: FDA.

9. Personal Care Products Council. 4-24-2012. Concentration of Use by FDA product category: PEGylated Castor Oil Ingredients. 8 pages.

10. Personal Care Products Council. 8-1-2012. Concentration of use by FDA Product Category PEGylated Oils, April 2012 Survey. 4 pages.

11. Rothe H, Fautz R, Gerber E, Neumann L, Rettinger K, Schuh W, and Gronewold C. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. *Toxicol Lett*. 2011;205(2):97-104.

12. Rothe H. Special Aspects of Cosmetic Spray Evalulation. 9-26-2011.

13. Bremmer HJ, Prud'homme de Lodder LCH, and Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. 2006. Report No. RIVM 320104001/2006. pp. 1-77.

14. Johnsen MA. The influence of particle size. *Spray Technology and Marketing*. 2004;November:24-27.

15. Bremmer HJ, Prud'homme de Lodder LCH, and van Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. 2006. http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf. Date Accessed 8-24-2011. Report No. RIVM 320104001/2006. pp. 1-77.

16. European Union. 1976, Council Directive 1976/768/EEC of 27 July 1976 on the Approximation of the Laws of the Member States Relating to Cosmetic Products, as amended through Commission Directive 2008/42/EC. 2008. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1976L0768:20080424:en:PDF.

17. Waghmare N, Waghmare P, Wani S, and Yerawar A. Development of isotretinoin gel for the treatment of acne vulgaris. *Res J Pharm Biol Chem Sci*. 2011;2(1):220-230.

18. Zhu W, Yu A, Wang W, Dong R, Wu J, and Zhai G. Formulation design of microemulsion for dermal delivery of penciclovir. *Int J Pharm*. 2008;360(1-2):184-190.

19. Chen H, Xiao L, Du D, Mou D, Xu H, and Yang X. A facile construction strategy of stable lipid nanoparticle for drug delivery using a hydrogel-thickened microemulsion system. *Nanotechnology*. 2010;21(1):1-9.

20. Casiraghi A, Ardovino P, Minghetti P, Botta C, Gattini A, and Montanari L. Semisolid formulations containing dimethyl sulfoxide and alpha-tocopherol for the treatment of extravasationof antiblastic agents. *Arch Dermatol Res*. 2007;299:201-207.

21. Nielloud F, Mestres JP, and Marti-Mestres G. Consideration of the formulation of benzoyl peroxide at ambient temperature: Choice of non-polar solvent and preparation of submicron emulsion gels. *Drug Dev Ind Pharm*. 2002;28(7):863-870.

22. D'Cruz OJ, Yiv SH, and Uckum FM. GM-144, a novel lipophilic vaginal contraceptive gel-microemulsion. *AAPS Pharm Sci Tech*. 2001;2(1):1-10.

23. Hua L, Weisan P, Jiayu L, and Hongfei L. Prepartion and evaluation of microemulsion of vinpocetine for transdermal delivery. *Pharmazie*. 2004;59(4):274-278.

24. Elder RL ed. Final report on the safety assessment of laneth-10 acetate group. *International Journal of Toxicology*. 1982;1(4):1-23.

25. ten Tije AJ, Loos WJ, Verweij J, Baker SD, Dinh K, Figg WD, and Sparreboom A. Disposition of polyoxyethylated excipients in humans: Implications for drug safety and formulation approaches. *Clin Pharmacol Ther*. 2003;74:509-510.

26. Bonina FP, Carelli V, Di Colo G, Montenegro L, and Nannipieri E. Vehicle effects on in vitro skin permeation of and stratum corneum affinity for model drugs caffeine and testosterone. *Int J Pharm*. 1993;100:41-47.

27. Moreau JP, Vachon PJ, and Huneau MC. Elevated glycemia and local inflammation after injectingN-methyl-2-pyrrolidone (NMP) into the marginal ear vein of rabbits. *Contemp Top Lab Anim Sci*. 2001;40(1):38-40.

28. Hisatomi A, Kimura M, Maeda M, Matsumoto M, Ohara K, and Noguchi H. Toxicity of polyoxyethylene hydrogenated castor oil 60 (HCO-60) in experimental animals. *J Toxicol Sci*. 1993;18(Suppl. 3):1-9.

29. Sanchez H, Bigard X, Veksler V, Mettauer B, Lampert E, Lonsdorfer J, and Ventura-Clapier R. Immunosuppressive treatment affects cardiac and skeletal muscle mitochondria by the toxic effect of vehicle. *J Mol Cell Cardiol*. 2000;32:323-331.

30. Tatou E, Mossiat C, Maupoil V, Gabrielle F, David M, and Rochette L. Effects of cyclosporin and cremophor on working rat heart and incidence of myocardial lipid peroxidation. *Pharmacology*. 1996;52:1-7.

31. Jaramillo-Juarez F, Rodriguez-Vazquez ML, Namorado MC, and Reyes JL. Acidosis and weight loss are induced by cyclosporin A in uninephrectomized rats. *Pediatr Nephrol*. 2000;14(2):122-127.

32. Chan FK and Shaffer EA. Cholestatic effects of cyclosporine in the rat. *Transplantation*. 1997;63(11):1574-1578.

33. Hirai O, Miyamae Y, Zaizen K, Miyamoto A, Takashima M, Hattori Y, Ohara K, and Mine Y. Mutagenicity tests of polyoxyethylene hydrogenated castor oil 60 (HCO-60). *J Toxicol Sci*. 1994;19(2):89-96.

34. Yu A, Guo C, Zhou Y, Cao F, Zhu W, Sun M, and Zhai G. Skin irritation and the inhibition effect on HSV-1 in vivo of penciclovir-loaded microemulsion. *Int Immunopharmacol*. 2010;10:1305-1309.

35. Soliman SM, Malak NSA, El-Gazayerly ON, and Rehim AAA. Formulation of microemulsion gel systems for transdermal delivery of celecoxib: In vitro permeation, anti-inflammatory activity and skin irritation tests. *Drug Discov Ther*. 2010;4(6):459-471.

36. Ammar HO, Salama HA, Ghorab M, and Mahmoud AA. Nanoemulsion as a potential ophthalmic delivery system for dorzolamide hydrochloride. *AAPS Pharm Sci Tech*. 2009;10(3):808-819.

37. Bushy Run Research Center. Tergitol nonionic surfactant 24-L-60N: Nine-day cutaneous dose toxicity study with neurotoxicity evaluation in albino rats. 1-29-1990.

38. Organisation of Economic Co-operation and Development. SIDS Intial Assessment Report for SIAM 4. 2-(2-(2-Methoxyethoxy)-ethanol. CAS NO. 112-35-6. (PEG-3 Methyl Ether). http://www.chem.unep.ch/irptc/sids/OECDSIDS/112356.pdf. Date Accessed 10-26-2010.

39. Scientific Committee on Consumer Products. Opinion on polidocanol (laureth-9). http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_113.pdf. Date Accessed 5-13-2010.

40. Shell Oil Company. Initial submission. Toxicology of detergents: Acute mammalian toxicity, skin and eye irritancy and skin sensitizing potential of Dobanol 25-3 (Final report). W-attaqch & lttr 011792. 1-20-1978.

41. Kleyn, C. E., Bharati, A., and King, C. M. Contact dermatitis from 3 different allergens in Solaraze gel. *Contact Derm*. 2004;51:215-216.

42. Suzuki, M., Machida, M., Adachi, K., Otabe, K., Sugimoto, T., Hayashi, M., and Awazu, S. Histopathological study of the effects of a single intratracheal instillation of surface active agents on lung in rats. *J Toxicol Sci*. 2000;25(1):49-55.

43. Zhou, M. and Donovan, M. D. Recovery of the nasal mucosa following laureth 9 induced damage. *Int.J.Pharm.* 1996;130:93-102.

44. Pham AQ, Berz D, Karwan P, and Colvin GA. Cremophor-induced lupus erythematosus-like reaction with taxol administration: A case report and review of the literature. *Case Rep Oncol*. 2011;4(3):526-530.

45. Kalavala M, Hughes TM, and Stone NM. Allergic contact dermatitis to polyethylene glycol-7 hydrogenated castor oil. *Contact Derm*. 2007;56:287-288.

46. Ninomiya H, Hanada T, Nakazawa M, Aoki Y, Shibuya A, Nagasawa T, and Abe T. Immunological erythroblastopenia induced by HCO-60 as a solvent of enocitabine (BH-AC). *Acta Haematol Jpn*. 1987;50(4):777-783.

Data

2012 FDA VCRP RAW DATA

05G - Tonics, Dressings, and Other Hair Grooming Aids	PEG-10 HYDROGENATED CASTOR OIL	1
07E - Lipstick	PEG-10 HYDROGENATED CASTOR OIL	1
12C - Face and Neck (exc shave)	PEG-10 HYDROGENATED CASTOR OIL	1
12F - Moisturizing	PEG-10 HYDROGENATED CASTOR OIL	1
12I - Skin Fresheners	PEG-10 HYDROGENATED CASTOR OIL	1
07E - Lipstick	PEG-16 HYDROGENATED CASTOR OIL	1
03F - Mascara	PEG-2 HYDROGENATED CASTOR OIL	5
12A - Cleansing	PEG-20 HYDROGENATED CASTOR OIL	1
12C - Face and Neck (exc shave)	PEG-20 HYDROGENATED CASTOR OIL	1
12D - Body and Hand (exc shave)	PEG-20 HYDROGENATED CASTOR OIL	1
12F - Moisturizing	PEG-20 HYDROGENATED CASTOR OIL	2
03F - Mascara	PEG-20 HYDROGENATED CASTOR OIL TRIISOSTEARATE	3
04E - Other Fragrance Preparation	PEG-25 HYDROGENATED CASTOR OIL	4
05A - Hair Conditioner	PEG-25 HYDROGENATED CASTOR OIL	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	PEG-25 HYDROGENATED CASTOR OIL	21
05I - Other Hair Preparations	PEG-25 HYDROGENATED CASTOR OIL	1
10A - Bath Soaps and Detergents	PEG-25 HYDROGENATED CASTOR OIL	3
11A - Aftershave Lotion	PEG-25 HYDROGENATED CASTOR OIL	1
12A - Cleansing	PEG-25 HYDROGENATED CASTOR OIL	1
12D - Body and Hand (exc shave)	PEG-25 HYDROGENATED CASTOR OIL	1
12F - Moisturizing	PEG-25 HYDROGENATED CASTOR OIL	4
12I - Skin Fresheners	PEG-25 HYDROGENATED CASTOR OIL	2
05F - Shampoos (non-coloring)	PEG-30 CASTOR OIL	1
06B - Hair Tints	PEG-30 HYDROGENATED CASTOR OIL	1
12A - Cleansing	PEG-30 HYDROGENATED CASTOR OIL	1
12F - Moisturizing	PEG-30 HYDROGENATED CASTOR OIL	1
03G - Other Eye Makeup Preparations	PEG-33 CASTOR OIL	1
05F - Shampoos (non-coloring)	PEG-33 CASTOR OIL	3
05G - Tonics, Dressings, and Other Hair Grooming Aids	PEG-33 CASTOR OIL	2
05I - Other Hair Preparations	PEG-33 CASTOR OIL	1
12A - Cleansing	PEG-33 CASTOR OIL	1
12C - Face and Neck (exc shave)	PEG-33 CASTOR OIL	16
12D - Body and Hand (exc shave)	PEG-33 CASTOR OIL	3

12F - Moisturizing	PEG-33 CASTOR OIL	2
12H - Paste Masks (mud packs)	PEG-33 CASTOR OIL	7
12I - Skin Fresheners	PEG-33 CASTOR OIL	3
12J - Other Skin Care Preps	PEG-33 CASTOR OIL	2
03D - Eye Lotion	PEG-35 CASTOR OIL	1
03G - Other Eye Makeup Preparations	PEG-35 CASTOR OIL	1
05A - Hair Conditioner	PEG-35 CASTOR OIL	2
05D - Permanent Waves	PEG-35 CASTOR OIL	4
05F - Shampoos (non-coloring)	PEG-35 CASTOR OIL	5
10A - Bath Soaps and Detergents	PEG-35 CASTOR OIL	1
12A - Cleansing	PEG-35 CASTOR OIL	2
12C - Face and Neck (exc shave)	PEG-35 CASTOR OIL	11
12D - Body and Hand (exc shave)	PEG-35 CASTOR OIL	3
12G - Night	PEG-35 CASTOR OIL	1
12J - Other Skin Care Preps	PEG-35 CASTOR OIL	3
13B - Indoor Tanning Preparations	PEG-35 CASTOR OIL	1
13B - Indoor Tanning Preparations	PEG-35 HYDROGENATED CASTOR OIL	1
12C - Face and Neck (exc shave)	PEG-36 CASTOR OIL	1
12D - Body and Hand (exc shave)	PEG-36 CASTOR OIL	1
12F - Moisturizing	PEG-36 CASTOR OIL	1
12I - Skin Fresheners	PEG-36 CASTOR OIL	1
12J - Other Skin Care Preps	PEG-36 CASTOR OIL	2
03G - Other Eye Makeup Preparations	PEG-40 CASTOR OIL	1
05A - Hair Conditioner	PEG-40 CASTOR OIL	8
05F - Shampoos (non-coloring)	PEG-40 CASTOR OIL	3
05G - Tonics, Dressings, and Other Hair Grooming Aids	PEG-40 CASTOR OIL	14
05I - Other Hair Preparations	PEG-40 CASTOR OIL	4
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	PEG-40 CASTOR OIL	1
06G - Hair Bleaches	PEG-40 CASTOR OIL	1
07F - Makeup Bases	PEG-40 CASTOR OIL	1
07G - Rouges	PEG-40 CASTOR OIL	1
08C - Nail Creams and Lotions	PEG-40 CASTOR OIL	1
10A - Bath Soaps and Detergents	PEG-40 CASTOR OIL	6
10E - Other Personal Cleanliness Products	PEG-40 CASTOR OIL	8
12A - Cleansing	PEG-40 CASTOR OIL	7
12C - Face and Neck (exc shave)	PEG-40 CASTOR OIL	3
12D - Body and Hand (exc shave)	PEG-40 CASTOR OIL	11
12F - Moisturizing	PEG-40 CASTOR OIL	13

12H - Paste Masks (mud packs)	PEG-40 CASTOR OIL	2
12J - Other Skin Care Preps	PEG-40 CASTOR OIL	9
13B - Indoor Tanning Preparations	PEG-40 CASTOR OIL	1
01A - Baby Shampoos	PEG-40 HYDROGENATED CASTOR OIL	1
01B - Baby Lotions, Oils, Powders, and Creams	PEG-40 HYDROGENATED CASTOR OIL	3
01C - Other Baby Products	PEG-40 HYDROGENATED CASTOR OIL	14
02A - Bath Oils, Tablets, and Salts	PEG-40 HYDROGENATED CASTOR OIL	3
02B - Bubble Baths	PEG-40 HYDROGENATED CASTOR OIL	18
02D - Other Bath Preparations	PEG-40 HYDROGENATED CASTOR OIL	13
03A - Eyebrow Pencil	PEG-40 HYDROGENATED CASTOR OIL	1
03B - Eyeliner	PEG-40 HYDROGENATED CASTOR OIL	5
03C - Eye Shadow	PEG-40 HYDROGENATED CASTOR OIL	3
03D - Eye Lotion	PEG-40 HYDROGENATED CASTOR OIL	14
03E - Eye Makeup Remover	PEG-40 HYDROGENATED CASTOR OIL	7
03F - Mascara	PEG-40 HYDROGENATED CASTOR OIL	7
03G - Other Eye Makeup Preparations	PEG-40 HYDROGENATED CASTOR OIL	16
04A - Cologne and Toilet waters	PEG-40 HYDROGENATED CASTOR OIL	82
04B - Perfumes	PEG-40 HYDROGENATED CASTOR OIL	7
04E - Other Fragrance Preparation	PEG-40 HYDROGENATED CASTOR OIL	126
05A - Hair Conditioner	PEG-40 HYDROGENATED CASTOR OIL	37
05B - Hair Spray (aerosol fixatives)	PEG-40 HYDROGENATED CASTOR OIL	16
05C - Hair Straighteners	PEG-40 HYDROGENATED CASTOR OIL	1
05D - Permanent Waves	PEG-40 HYDROGENATED CASTOR OIL	3
05E - Rinses (non-coloring)	PEG-40 HYDROGENATED CASTOR OIL	3
05F - Shampoos (non-coloring)	PEG-40 HYDROGENATED CASTOR OIL	71
05G - Tonics, Dressings, and Other Hair Grooming Aids	PEG-40 HYDROGENATED CASTOR OIL	226
05H - Wave Sets	PEG-40 HYDROGENATED CASTOR OIL	21
05I - Other Hair Preparations	PEG-40 HYDROGENATED CASTOR OIL	158
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	PEG-40 HYDROGENATED CASTOR OIL	65
06B - Hair Tints	PEG-40 HYDROGENATED CASTOR OIL	22
06D - Hair Shampoos (coloring)	PEG-40 HYDROGENATED CASTOR OIL	2
06G - Hair Bleaches	PEG-40 HYDROGENATED CASTOR OIL	2
06H - Other Hair Coloring Preparation	PEG-40 HYDROGENATED CASTOR OIL	2
07A - Blushers (all types)	PEG-40 HYDROGENATED CASTOR OIL	1
07C - Foundations	PEG-40 HYDROGENATED CASTOR OIL	7
07D - Leg and Body Paints	PEG-40 HYDROGENATED CASTOR OIL	1
07E - Lipstick	PEG-40 HYDROGENATED CASTOR OIL	1
07F - Makeup Bases	PEG-40 HYDROGENATED CASTOR OIL	1
07H - Makeup Fixatives	PEG-40 HYDROGENATED CASTOR OIL	1
07I - Other Makeup Preparations	PEG-40 HYDROGENATED CASTOR OIL	7
08B - Cuticle Softeners	PEG-40 HYDROGENATED CASTOR OIL	1

08G - Other Manicuring Preparations	PEG-40 HYDROGENATED CASTOR OIL	3
09A - Dentifrices	PEG-40 HYDROGENATED CASTOR OIL	1
09B - Mouthwashes and Breath Fresheners	PEG-40 HYDROGENATED CASTOR OIL	2
10A - Bath Soaps and Detergents	PEG-40 HYDROGENATED CASTOR OIL	248
10B - Deodorants (underarm)	PEG-40 HYDROGENATED CASTOR OIL	27
10C - Douches	PEG-40 HYDROGENATED CASTOR OIL	1
10D - Feminine Deodorants	PEG-40 HYDROGENATED CASTOR OIL	1
10E - Other Personal Cleanliness Products	PEG-40 HYDROGENATED CASTOR OIL	102
11A - Aftershave Lotion	PEG-40 HYDROGENATED CASTOR OIL	131
11B - Beard Softeners	PEG-40 HYDROGENATED CASTOR OIL	1
11E - Shaving Cream	PEG-40 HYDROGENATED CASTOR OIL	2
11G - Other Shaving Preparation Products	PEG-40 HYDROGENATED CASTOR OIL	8
12A - Cleansing	PEG-40 HYDROGENATED CASTOR OIL	111
12B - Depilatories	PEG-40 HYDROGENATED CASTOR OIL	7
12C - Face and Neck (exc shave)	PEG-40 HYDROGENATED CASTOR OIL	140
12D - Body and Hand (exc shave)	PEG-40 HYDROGENATED CASTOR OIL	75
12E - Foot Powders and Sprays	PEG-40 HYDROGENATED CASTOR OIL	3
12F - Moisturizing	PEG-40 HYDROGENATED CASTOR OIL	98
12G - Night	PEG-40 HYDROGENATED CASTOR OIL	11
12H - Paste Masks (mud packs)	PEG-40 HYDROGENATED CASTOR OIL	35
12I - Skin Fresheners	PEG-40 HYDROGENATED CASTOR OIL	43
12J - Other Skin Care Preps	PEG-40 HYDROGENATED CASTOR OIL	71
13A - Suntan Gels, Creams, and Liquids	PEG-40 HYDROGENATED CASTOR OIL	1
13B - Indoor Tanning Preparations	PEG-40 HYDROGENATED CASTOR OIL	14
13C - Other Suntan Preparations	PEG-40 HYDROGENATED CASTOR OIL	2
05G - Tonics, Dressings, and Other Hair Grooming Aids	PEG-40 HYDROGENATED CASTOR OIL PCA ISOSTEARATE	1
12A - Cleansing	PEG-40 HYDROGENATED CASTOR OIL PCA ISOSTEARATE	1
01C - Other Baby Products	PEG-45 HYDROGENATED CASTOR OIL	1
05A - Hair Conditioner	PEG-45 HYDROGENATED CASTOR OIL	1
12C - Face and Neck (exc shave)	PEG-50 CASTOR OIL	2
01C - Other Baby Products	PEG-60 HYDROGENATED CASTOR OIL	1
02A - Bath Oils, Tablets, and Salts	PEG-60 HYDROGENATED CASTOR OIL	3
02D - Other Bath Preparations	PEG-60 HYDROGENATED CASTOR OIL	1
03B - Eyeliner	PEG-60 HYDROGENATED CASTOR OIL	2
03D - Eye Lotion	PEG-60 HYDROGENATED CASTOR OIL	4
03E - Eye Makeup Remover	PEG-60 HYDROGENATED CASTOR OIL	1
03G - Other Eye Makeup Preparations	PEG-60 HYDROGENATED CASTOR OIL	2
04A - Cologne and Toilet waters	PEG-60 HYDROGENATED CASTOR OIL	1

04B - Perfumes	PEG-60 HYDROGENATED CASTOR OIL	3
04E - Other Fragrance Preparation	PEG-60 HYDROGENATED CASTOR OIL	4
05A - Hair Conditioner	PEG-60 HYDROGENATED CASTOR OIL	5
05C - Hair Straighteners	PEG-60 HYDROGENATED CASTOR OIL	3
05F - Shampoos (non-coloring)	PEG-60 HYDROGENATED CASTOR OIL	19
05G - Tonics, Dressings, and Other Hair Grooming Aids	PEG-60 HYDROGENATED CASTOR OIL	9
05I - Other Hair Preparations	PEG-60 HYDROGENATED CASTOR OIL	5
07D - Leg and Body Paints	PEG-60 HYDROGENATED CASTOR OIL	1
07E - Lipstick	PEG-60 HYDROGENATED CASTOR OIL	1
07F - Makeup Bases	PEG-60 HYDROGENATED CASTOR OIL	1
10A - Bath Soaps and Detergents	PEG-60 HYDROGENATED CASTOR OIL	28
10B - Deodorants (underarm)	PEG-60 HYDROGENATED CASTOR OIL	2
10D - Feminine Deodorants	PEG-60 HYDROGENATED CASTOR OIL	1
10E - Other Personal Cleanliness Products	PEG-60 HYDROGENATED CASTOR OIL	3
11A - Aftershave Lotion	PEG-60 HYDROGENATED CASTOR OIL	35
11G - Other Shaving Preparation Products	PEG-60 HYDROGENATED CASTOR OIL	2
12A - Cleansing	PEG-60 HYDROGENATED CASTOR OIL	23
12C - Face and Neck (exc shave)	PEG-60 HYDROGENATED CASTOR OIL	60
12D - Body and Hand (exc shave)	PEG-60 HYDROGENATED CASTOR OIL	9
12F - Moisturizing	PEG-60 HYDROGENATED CASTOR OIL	54
12G - Night	PEG-60 HYDROGENATED CASTOR OIL	4
12H - Paste Masks (mud packs)	PEG-60 HYDROGENATED CASTOR OIL	10
12I - Skin Fresheners	PEG-60 HYDROGENATED CASTOR OIL	23
12J - Other Skin Care Preps	PEG-60 HYDROGENATED CASTOR OIL	27
13B - Indoor Tanning Preparations	PEG-60 HYDROGENATED CASTOR OIL	2
05G - Tonics, Dressings, and Other Hair Grooming Aids	PEG-7 HYDROGENATED CASTOR OIL	1
05I - Other Hair Preparations	PEG-7 HYDROGENATED CASTOR OIL	1
10E - Other Personal Cleanliness Products	PEG-7 HYDROGENATED CASTOR OIL	2
12D - Body and Hand (exc shave)	PEG-7 HYDROGENATED CASTOR OIL	1
12F - Moisturizing	PEG-7 HYDROGENATED CASTOR OIL	1
12G - Night	PEG-7 HYDROGENATED CASTOR OIL	1
13A - Suntan Gels, Creams, and Liquids	PEG-7 HYDROGENATED CASTOR OIL	3
13C - Other Suntan Preparations	PEG-7 HYDROGENATED CASTOR OIL	1
12A - Cleansing	PEG-80 HYDROGENATED CASTOR OIL	1
12D - Body and Hand (exc shave)	PEG-80 HYDROGENATED CASTOR OIL	2
12F - Moisturizing	PEG-80 HYDROGENATED CASTOR OIL	1
05B - Hair Spray (aerosol fixatives)	PEG-9 CASTOR OIL	1
02A - Bath Oils, Tablets, and Salts	APRICOT KERNEL OIL PEG-6 ESTERS	1
03D - Eye Lotion	APRICOT KERNEL OIL PEG-6 ESTERS	1

07E - Lipstick	APRICOT KERNEL OIL PEG-6 ESTERS	4
07I - Other Makeup Preparations	APRICOT KERNEL OIL PEG-6 ESTERS	12
12C - Face and Neck (exc shave)	APRICOT KERNEL OIL PEG-6 ESTERS	2
12F - Moisturizing	APRICOT KERNEL OIL PEG-6 ESTERS	3
12G - Night	APRICOT KERNEL OIL PEG-6 ESTERS	1
05A - Hair Conditioner	PEG-10 COCONUT OIL ESTER	2
05F - Shampoos (non-coloring)	PEG-10 COCONUT OIL ESTER	4
12F - Moisturizing	PEG-10 COCONUT OIL ESTER	2
04E - Other Fragrance Preparation	GRAPE SEED OIL PEG-8 ESTERS	1
10A - Bath Soaps and Detergents	GRAPE SEED OIL PEG-8 ESTERS	3
10E - Other Personal Cleanliness Products	GRAPE SEED OIL PEG-8 ESTERS	3
12D - Body and Hand (exc shave)	GRAPE SEED OIL PEG-8 ESTERS	3
12F - Moisturizing	GRAPE SEED OIL PEG-8 ESTERS	4
12H - Paste Masks (mud packs)	GRAPE SEED OIL PEG-8 ESTERS	2
12J - Other Skin Care Preps	GRAPE SEED OIL PEG-8 ESTERS	2
03C - Eye Shadow	HYDROGENATED PALM/PALM KERNEL OIL PEG-6 ESTERS	1
07C - Foundations	HYDROGENATED PALM/PALM KERNEL OIL PEG-6 ESTERS	1
07I - Other Makeup Preparations	HYDROGENATED PALM/PALM KERNEL OIL PEG-6 ESTERS	1
12I - Skin Fresheners	HYDROGENATED PALM/PALM KERNEL OIL PEG-6 ESTERS	1
01B - Baby Lotions, Oils, Powders, and Creams	JOJOBA OIL PEG-8 ESTERS	1
01C - Other Baby Products	JOJOBA OIL PEG-8 ESTERS	2
02A - Bath Oils, Tablets, and Salts	JOJOBA OIL PEG-8 ESTERS	7
05A - Hair Conditioner	JOJOBA OIL PEG-8 ESTERS	3
05C - Hair Straighteners	JOJOBA OIL PEG-8 ESTERS	1
05F - Shampoos (non-coloring)	JOJOBA OIL PEG-8 ESTERS	2
07I - Other Makeup Preparations	JOJOBA OIL PEG-8 ESTERS	8
12A - Cleansing	JOJOBA OIL PEG-8 ESTERS	1
12C - Face and Neck (exc shave)	JOJOBA OIL PEG-8 ESTERS	2
12D - Body and Hand (exc shave)	JOJOBA OIL PEG-8 ESTERS	1
12F - Moisturizing	JOJOBA OIL PEG-8 ESTERS	12
01A - Baby Shampoos	OLIVE OIL PEG-7 ESTERS	1
03D - Eye Lotion	OLIVE OIL PEG-7 ESTERS	1
03E - Eye Makeup Remover	OLIVE OIL PEG-7 ESTERS	1
03G - Other Eye Makeup Preparations	OLIVE OIL PEG-7 ESTERS	1
05A - Hair Conditioner	OLIVE OIL PEG-7 ESTERS	3
05F - Shampoos (non-coloring)	OLIVE OIL PEG-7 ESTERS	9

05G - Tonics, Dressings, and Other Hair Grooming Aids	OLIVE OIL PEG-7 ESTERS	6
05I - Other Hair Preparations	OLIVE OIL PEG-7 ESTERS	4
10A - Bath Soaps and Detergents	OLIVE OIL PEG-7 ESTERS	15
10B - Deodorants (underarm)	OLIVE OIL PEG-7 ESTERS	1
10E - Other Personal Cleanliness Products	OLIVE OIL PEG-7 ESTERS	7
11G - Other Shaving Preparation Products	OLIVE OIL PEG-7 ESTERS	1
12A - Cleansing	OLIVE OIL PEG-7 ESTERS	14
12C - Face and Neck (exc shave)	OLIVE OIL PEG-7 ESTERS	1
12D - Body and Hand (exc shave)	OLIVE OIL PEG-7 ESTERS	13
12F - Moisturizing	OLIVE OIL PEG-7 ESTERS	6
12G - Night	OLIVE OIL PEG-7 ESTERS	2
12H - Paste Masks (mud packs)	OLIVE OIL PEG-7 ESTERS	1
12I - Skin Fresheners	OLIVE OIL PEG-7 ESTERS	4
12J - Other Skin Care Preps	OLIVE OIL PEG-7 ESTERS	5
13B - Indoor Tanning Preparations	OLIVE OIL PEG-7 ESTERS	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	PEG-75 MEADOWFOAM OIL	1

FINAL REPORT ON THE SAFETY ASSESSMENT OF PEG-30, -33, -35, -36, AND -40 CASTOR OIL AND PEG-30 AND -40 HYDROGENATED CASTOR OIL[1]

PEG Castor Oils and PEG Hydrogenated Castor Oils are a family of polyethylene glycol derivatives of castor oil and hydrogenated castor oil that are used in over 500 formulations representing a wide variety of cosmetic products. They are used as skin conditioning agents and as surfactants (emulsifying and/or solubilizing agents). The PEG Castor Oils and PEG Hydrogenated Castor Oils include various chain lengths, depending on the quantity of ethylene oxide used in synthesis. Although not all polymer lengths have been studied, it is considered acceptable to extrapolate the results of the few that have been studied to all ingredients in the family. Because a principal noncosmetic use of PEG Castor Oils is as solvents for intravenous drugs, clinical data are available that indicate intravenous exposure can result in cardiovascular changes. Results from animal studies indicate very high LD_{50} values, with some evidence of acute nephrotoxicity in rats but not in rabbits. Short-term studies with intravenous exposure produced some evidence of toxicity in dogs but not in rabbits. Intramusuclar injection produced no toxicity in several species, including dogs. Subchronic oral studies also were negative. No dermal or ocular irritation was observed in studies in rabbits. Irritation was seen during induction, but no sensitization was found on challenge in guinea-pig studies using up to 50% PEG-35 Castor Oil; however, this ingredient was found to be a potent adjuvant in guinea pigs and mice. No evidence of developmental toxicity was seen in mice and rat feeding studies. These ingredients, tested as vehicle controls, produced no mutagenic or carcinogenic effect. Clinical data are generally negative for irritation and sensitization, although some anaphylactoid reactions have been seen in studies of intravenous drugs in which PEG-35 Castor Oil was used as the vehicle. Because the maximum concentration used in animal sensitization studies was 50% for PEG Castor Oils and 100% for PEG Hydrogenated Castor Oils, it was concluded that PEG Castor Oils are safe for use in cosmetic formulations up to a concentration of 50% and that PEG Hydrogenated Castor Oils are safe as used in cosmetic formulations.

PEG-30, -33, -35, -36, and -40 Castor Oil and PEG-30 and -40 Hydrogenated Castor Oil are polyethylene glycol derivatives of castor

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

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International Journal of Toxicology, 16:269–306, 1997

1091-5818/97 $12.00 + .00

oil (q.v.) and hydrogenated castor oil (q.v.) that are used in a variety of cosmetic products. This report reviews the safety data on these ingredients.

CHEMISTRY

Definition and Structure

PEG-30, -33, -35, -36, and -40 Castor Oil (generic CAS No. 61791-12-6) and PEG-30 and -40 Hydrogenated Castor Oil (generic CAS No. 61788-85-0) are polyethylene glycol derivatives of castor oil (q.v.) and hydrogenated castor oil (q.v.). The number associated with the name of the compound represents the average number of moles of ethylene oxide consumed in the reaction to form the compound. Other respective chemical names for the castor oil and hydrogenated castor oil compounds include (X = the number of moles of ethylene oxide) Polyethylene Glycol X Castor Oil; Polyethylene Glycol X Hydrogenated Castor Oil; Polyethylene Glycol X; and Polyethylene Glycol X Hydrogenated Castor Oil (Wenninger and McEwen, 1995a).

Chemical and Physical Properties

Because castor oil is a triglyceride containing approximately 87% ricinoleic acid, 7% oleic acid, 3% linoleic acid, 2% palmitic acid, 1% stearic acid, and a trace of dihydroxysteric acid (Budavari, 1989), PEG Castor Oils are predominantly glyceryl triricinoleyl polyethylene glycol and PEG Hydrogenated Castor Oils are predominantly tri-12-hydroxylstearyl polyethylene glycol.

PEG-36 Castor Oil is a light yellow and slightly viscous liquid with a mild fatty odor. It has a specific gravity of 1.05 to 1.06 at 25°/25°C and is soluble in water. A 1% aqueous (aq) solution of this ingredient has a pH range of 7.0 to 8.0 (Nikitakis and McEwen, 1990). PEG-40 Castor Oil is a nonionic amber colored liquid that is miscible in water and aqueous buffer solution. It has a density of 1057.0 kg^{-3}, a viscosity of 450 cps at 20°C, and a melting point of approximately 10°C. Over a concentration range of 0.0005% to 1.0% (w/v), the pH of PEG-40 Castor Oil aq is 5.0 to 6.0 (Yalabik-Kas et al., 1982).

Spectral Data

The ultraviolet spectra of PEG-40 Castor Oil has a maximum peak at 234 to 236 nm (Yalabik-Kas et al., 1982).

Method of Manufacture

In general, PEG Castor Oils are made by reacting ethylene oxide with castor oil. The number (X) in the name of the compound refers to the molar ratio (X:1) of ethylene oxide to castor oil (Au et al., 1991).

USE

Cosmetic

The PEG Castor Oils and PEG Hydrogenated Castor Oils are used as skin-conditioning agents and as surfactants that function as emulsifying or solubilizing agents in cosmetic formulations (Wenninger and McEwen, 1995b). The product formulation data submitted to the Food and Drug Administration (FDA) in 1995 are listed in Tables 1 and 2 (FDA, 1995). Collectively, these ingredients are used in more than 500 cosmetic products. Concentration of use values are no longer reported to the FDA by the cosmetic industry (Federal Register, 1992). Product formulation data submitted to the FDA in 1984 stated, however, that PEG-30 Castor Oil was used at concentrations of up to 50% and more and that PEG-40 Castor Oil was used at concentrations of up to 10%. PEG-30 Hydrogenated Castor Oil was used at concentrations of up to 0.1%, and PEG-40 Castor Oil was used at concentrations of up to 5% (FDA, 1984).

Noncosmetic

In the pharmaceutical industry, PEG-35 Castor Oil is used as an emulsifier and solubilizer in pharmaceuticals containing volatile oils, fat-soluble vitamins, diazepam, propanidid, alfaxolone/alfadolone acetate, miconazole, methotrimeprazine, thiopental, and glycerin suppositories (Smolinske, 1992).

BIOLOGY

Cell Function

Nässberger (1990) reported that PEG-35 Castor Oil (diluted 1:1) decreased the spontaneous production of adenosine triphosphate (ATP) in isolated rat kidney mitochondria by 4%. At greater dilutions no such effect was observed. During oxidative phosphorylation, PEG-35 Castor Oil inhibited ATP production by 9.0% to 36.9% at dilutions of 1:160 to 1:1. A dilution of 1:640 caused only minimal inhibition.

PEG-35 Castor Oil selectively inhibited the activation of protein kinase C (PKC) at submicromolar concentrations in vitro. In a study

with PKC isolated from human leukemia ML-1 cells, PEG-35 Castor Oil interacted with the main enzyme activator of PKC, diacylglycerol, and prevented the enzyme from binding to and activating PKC. These inhibitory effects were not observed with studies of other polyoxyethylated nonionic solvents, which the investigators believed ruled out the possibility that PEG-35 Castor Oil acted by virtue of a detergent effect (Zhao et al., 1989).

The inhibitory effects of PEG-35 Castor Oil on PKC activity were tested further using 12-*o*-tetradecanolyphorbol-13-acetate (TPA), which mimicked the effects of intracellular diacylglycerol in activating PKC and inducing phosphorylation of cellular proteins. When added

Table 1. Cosmetic product formulation data on the PEG Castor Oil Family

Castor Oil	Product category	Total no. of formulations in category	Total no. of formulations containing ingredient
PEG-30 Castor Oil	Hair dyes and colors (all types requiring caution statements and patch tests)	1437	72
	Cleansing	771	1
	Listing under		4
	1995 Total		***77***
PEG-33 Castor Oil	Hair conditioners	624	1
	Shampoos (noncoloring)	916	2
	Tonics, dressings, and other hair-grooming aids	624	1
	Other hair preparations	382	1
	Other skin-care preparations	782	8
	1995 Total		***13***
PEG-35 Castor Oil	Tonics, dressings, and other hair-grooming aids	624	1
	Face and neck (excluding shaving preparations	261	1
	Skin fresheners	228	1
	Indoor tanning preparations	62	1
	1995 Total		***4***
PEG-36 Castor Oil	Body and hand (excluding shaving)	987	1
	Other skin-care preparations	782	2
	1995 Total		***3***

Table 1. Cosmetic product formulation data on the PEG Castor Oil Family (*continued*)

Castor Oil	Product category	Total no. of formulations in category	Total no. of formulations containing ingredient
PEG-40 Castor Oil	Other bath preparations	144	1
	Eye makeup remover	89	1
	Other fragrance preparations	158	1
	Hair conditioners	693	8
	Hair sprays (aerosol fixatives)	348	2
	Permanent waves	423	10
	Tonics, dressings, and other hair-grooming aids	624	6
	Wave sets	104	3
	Other hair preparations	382	4
	Bath soaps and detergents	339	1
	Cleansing	771	15
	Face and neck (excluding shaving preparations)	261	3
	Body and hand (excluding shaving preparations	987	10
	Moisturizing	873	8
	Night	220	2
	Paste masks (mud packs)	276	8
	Skin fresheners	228	2
	Other skin-care preparations	782	18
	Suntan gels, creams, and liquids	196	2
	Indoor tanning preparations	62	2
	Listing under trade name of mixtures		63
	1995 Total		***170***

Source. FDA (1995).

extracellularly to human myeloblast ML-1 cells, PEG-35 Castor Oil greatly reduced the phosphorylation of proteins induced by TPA. It also inhibited the growth of ML-1 cells dose dependently but had no effect on TPA-induced cell differentiation. Because PKC is involved with cellular regulation, the researchers suggested that inhibition of PKC by PEG-35 Castor Oil may alter cellular functions (Chuang et al., 1991).

PEG-35 Castor Oil also affects the physiologic functioning of renal proximal tubule cells. Primary proximal tubule cells from the kidneys of New Zealand White rabbits were cultured to retain the functional polarity of the proximal tubule, and the effects of 156, 391, and 782

Table 2. Cosmetic product formulation data on the PEG Hydrogenated Castor Oils

Castor oil	Product category	Total no. of formulations in category	Total no. of formulations containing ingredient
PEG-30 Hydrogenated Castor Oil	Deodarants (underarm)	293	1
	Shaving cream	152	1
	Cleansing	771	2
	Moisturizing	873	1
	1995 Total		***5***
PEG-40 Hydrogenated Castor Oils	Other baby products	30	1
	Bubble baths	204	2
	Other bath preparations	144	18
	Eye shadow	597	3
	Eye makeup remover	89	1
	Mascara	211	3
	Other eye makeup preparations	130	2
	Colognes and toilet waters	776	18
	Other fragarance preparations	158	2
	Hair conditioners	693	1
	Hair sprays (aerosol fixatives)	348	3
	Shampoos (noncoloring)	916	2
	Tonics, dressings, and other hair-grooming aaids	624	31
	Wave sets	104	6
	Other hair preparations	382	11
	Hair bleaches	112	2
	Blushers (all types)	283	1
	Face powders	305	3
	Foundations	333	1
	Makeup bases	159	1
	Bath soaps and detergents	339	3
	Deodorants (underarm)	293	2
	Other personal cleanliness products	317	7
	Aftershave lotion	236	22
	Other shaving preparation products	60	4
	Cleansing	771	19
	Face and neck (excluding shaving preparations)	261	3

Table 2. Cosmetic product formulation data on the PEG Hydrogenated Castor Oils (*continued*)

Castor oil	Product category	Total no. of formulations in category	Total no. of formulations containing ingredient
PEG-40 Hydrogenated Castor oils	Body and hand (excluding shaving preparations)	987	32
	Moisturizing	873	9
	Paste masks (mud packs)	276	5
	Skin fresheners	228	11
	Other skin-care preparations	782	21
	Suntan gels, creams, and liquids	196	2
	Indoor tanning preparations	62	3
	Other suntan preparations	62	1
	Listing under trade name		11
	1995 Total		***268***

Source. FDA (1995).

μg/mL PEG-35 Castor Oil on the capacity of these cells to generate a pH gradient was determined. PEG-35 Castor Oil significantly inhibited the development of a pH gradient after 24 h and essentially eliminated it by 72 h. This effect was reversible. A decrease of 15% also occurred in cell viability following 72 h of exposure to 782 μg/mL PEG-35 Castor Oil. The investigators concluded that PEG-35 Castor Oil affected the capacity of rabbit primary proximal tubular cell cultures to carry out a characteristic physiologic function and proposed that the toxicity of the compound itself may contribute to nephrotoxicity observed with cyclosporine A, the drug for which it is a vehicle (Sokol et al., 1990).

PEG-35 Castor Oil also has been reported to affect neurites in vitro. In cultures of differentiating N1E.115 neuroblastoma cells treated with 0.005% PEG-35 Castor Oil, neurite outgrowth was inhibited 50% in serum-free medium. Surviving neurites were shorter in length and were disfigured. Deficits in rapid axonal transport also were detected. The investigators concluded that PEG-35 Castor Oil "impairs neurite outgrowth and disrupts organellar motility in a fashion that might account for neuropathologic effects *in vivo*" (Brat et al., 1992).

The effect of PEG-40 Hydrogenated Castor Oil on epithelial integrity was investigated using monolayers of human intestinal epithelial cells. Specifically, intracellular enzyme activity and morphology were studied, and cell monolayer permeability was determined by measuring the transport of marker molecules and by measuring transepithelial electrical resistance. At concentrations of 0.010

to 7.1 mM, PEG-40 Hydrogenated Castor Oil had no effect on permeability; however, it caused a dose-dependent decrease in dehydrogenase activity, and, at a concentration of 7.1 mM, it caused alterations in a monolayer morphology (Anderberg et al., 1992).

Cytotoxicity

The toxicity of PEG-30 Castor Oil to hepatocytes was investigated by O'Hara et al. (1989). Hepatocytes isolated from male CD rats were treated with 0.063% to 1.0% PEG-30 Castor Oil for 5 h. Cell injury was measured by intracellular K^+, and cell death was measured by lactate dehydrogenase leakage. Cell injury and leakage were observed at concentrations between 0.25% and 1.0% after 5 h. The maximum no-effect concentration was 0.125%.

PEG-35 Castor Oil was cytotoxic to the porcine renal epithelial cell line LLC-PK_1. Using electron and fluorescence microscopy, a reduction in cell adherence at concentrations between 0.01% and 0.1% and alterations in intracellular morphology at lower concentrations were observed. The investigators stated, "This finding supports suggestions based on clinical experience that [PEG-35 Castor Oil] may be responsible for a part of the nephrotoxic effects associated with cyclosporin A treatment" (Nässberger et al., 1991).

Hemodynamic Effects

In Vitro

In a study by Board (1993), PEG-35 Castor Oil inhibited the transport of 2,4-dinitrophenyl glutathione (GSDNP) out of intact human erythrocytes. Approximately 20% of the total transport activity was not inhibited, which the investigators suggested was caused by the inhibitory effect differentiating between glutathione transporters. No hemolysis occurred at concentrations of up to 10% (v/v), the maximum concentration tested. Inhibition was not caused by a depletion of intracellular ATP because studies using a 1:1000 dilution of PEG-35 Castor Oil did not change the intracellular ATP concentrations.

Kongshaug et al. (1991) studied the interaction of PEG-35 Castor Oil with human plasma lipoproteins and nonlipoproteins using ultracentrifugation. They found that at concentrations of 1 to 3 mg/mL PEG-35 Castor Oil associates substantially with low-density lipoproteins; however, such an association was not observed at concentrations between 12 and 116 mg/mL. PEG-35 Castor Oil has a destructive effect on high-density lipoproteins, which was observable at all concentrations tested but was particularly severe at concentrations of 3.6 mg/mL or more PEG-35 Castor Oil. PEG-35 Castor Oil had no observable effect on human serum albumin or other heavy proteins.

The effect of PEG-35 Castor Oil on endothelial function and vascular smooth muscle was investigated using isolated rat hearts. Hearts from AO/Olac rats were perfused using a modified Langendorf preparation (Langendorf, 1935). Groups of eight hearts were perfused with 50, 100, 500, and 1000 ng/mL PEG-35 Castor Oil, and basal coronary flow during perfusion was determined. Each heart was perfused separately with 5-hydroxytryptamine (5-HT) and nitroglycerine (GTN), and coronary flow was monitored to determine the effects of PEG-35 Castor Oil on changes induced by these vasodilators. A control group of hearts was perfused with buffer only, followed by perfusion with the two vasodilators.

At a dose of 50 ng/mL, PEG-35 Castor Oil caused a slight decrease in coronary flow, which was similar to that observed with the control experiment. At greater concentrations, however, PEG-35 Castor Oil caused dose-dependent coronary vasodilation. The greatest increase observed was a 24.8% increase in flow with 1000 ng/mL PEG-35 Castor Oil. No change occurred in the vasodilatory response to 5-HT and GTN in the control experiment; however, in the experiments with 500 and 1000 ng/mL PEG-35 Castor Oil, a significant reduction occurred in the 5-HT response, but no appreciable change occurred in the GTN response. The researchers concluded that PEG-35 Castor Oil caused endothelial dysfunction (Mankad et al., 1992).

In Vivo

The effect of PEG-35 Castor Oil on blood flow to various organs was studied using dogs. A group of five dogs was anesthetized and intravenously injected with 2 mL of a solution containing 1 g/mL PEG-35 Castor Oil over a 90-min period. Cardiac output; mean arterial pressure; and renal, hepatic, and pancreatic blood flow were monitored. A control group of five dogs also was anesthetized but received no infusions. Statistically significant changes were observed in the cardiac output, mean arterial pressure, and hepatic blood flow of the treated group compared with the control group. Curves for cardiac output and mean arterial blood pressure over the 90-min infusion period indicated a marked decrease immediately following the infusion of a few milliliters of PEG-35 Castor Oil, followed by a recovery toward baseline and then another rapid fall with time. A precipitous decline in hepatic blood flow occurred, which returned to baseline rate after approximately 60 min. In the control group, cardiac output, mean arterial blood pressure, and hepatic blood flow were relatively stable. The curve for pancreatic blood flow was similar to the bimodal pattern seen with cardiac output and mean arterial blood flow. The difference between this curve and that of the control group approached, but did not reach, statistical significance. A rapid linear decline occurred in renal blood flow over time in the PEG-35 Castor Oil–treated group, but this decline was not sta-

tistically different from that observed with the control group (Bowers et al., 1991).

In a study with different types of species, PEG-35 Castor Oil depressed the blood pressure of dogs and cats, but not of rabbits, following intravenous administration at concentrations of 30 to 100 mg/kg and 100 mg/kg, respectively. The depressant effects observed with the dogs and cats was thought to be of allergic nature (BASF, no date, a).

Histamine Release

In in vitro studies with rat peritoneal mast cells, PEG-35 Castor Oil alone did not stimulate histamine release (Ennis et al., 1985). When administered in conjunction with histamine-releasing agents, however, PEG-35 Castor Oil potentiated the release of histamine with some agents but inhibited the release with others (Ennis et al., 1986).

PEG-30 Castor Oil (Constantine and Lebel, 1979) and PEG-35 Castor Oil (Lorenz et al., 1977; Lorenz et al., 1982; Ennis et al., 1985) caused histamine release and severe hypotension when administered intravenously to dogs. Oxethylated oleic acid was the most effective constituent of PEG-35 Castor Oil (Lorenz et al., 1977). In studies with miniature pigs, PEG-35 Castor Oil was also a histamine releaser, but only after a second exposure to the compound. In addition, hypertension, as opposed to hypotension, was observed (Glen et al., 1979). Although PEG-35 Castor Oil alone did not cause histamine release in studies with humans (Doenicke et al., 1973; Lorenz, 1975), this compound is believed to cause histamine release when administered in combination with certain anaesthetic drugs (Lorenz, 1975). This effect is thought to play a role in clinical anaphylactoid reactions caused by drugs dissolved in PEG-35 Castor Oil (Lorenz et al., 1982).

Pharmacologic Effects

In Vitro

Multidrug resistance was reversed in vitro by PEG-35 Castor Oil in studies with human myeloma cells (Schuurhuis et al., 1990), Ehrlich ascites tumor cells (Friche et al., 1990), and the R100 and K562 cell lines (Woodcock et al., 1990). PEG-35 Castor Oil is thought to modulate resistance by binding to the plasma membrane P-glycoproteins and preventing the efflux of drugs from cells (Friche et al., 1990; Woodcock et al., 1992).

In Vivo

Antidiuretic effects were observed when Sprague-Dawley rats were orally administered 2.5 mL/kg PEG-35 Castor Oil. The researchers

attributed this observation to the laxative action induced by this compound (Coppi et al., 1971).

ANIMAL TOXICITY

Acute Toxicity

Oral

LD_{50} values of formulations containing 2.0% PEG-25 Hydrogenated Castor Oil and 0.25% PEG-40 Hydrogenated Castor Oil were reported to be more than 15.0 g/kg for rats (CTFA, 1982a; CTFA, 1982b). For a formulation containing 3.0% PEG-60 Hydrogenated Castor Oil, the LD_{50} for rats was more than 5.0 g/kg (CTFA, 1976a).

Intravenous

PEG-35 Castor Oil impaired renal function following intravenous administration in male Wistar rats. Five rats were injected with 0.7 mg/kg/min PEG-35 Castor Oil for 2 h, and a control group of five rats was injected with the same volume of 0.9% NaCl. Control measurements of blood pressure, renal blood flow, creatinine clearance, and urine output were determined prior to infusion. Then blood pressure and renal blood flow were determined five times during infusion and urine was collected at 30-min intervals for clearance determination. A slight decrease occurred in renal blood flow in some of the rats during the first 30 min of infusion, but no changes in arterial blood pressure or creatinine clearance were detected. Renal blood flow and creatinine clearance decreased at 45 min and decreased to 50% of their initial values at 90 min. Arterial blood pressure was only modestly reduced. Urine volume initially increased during the first 30 min of infusion but began to decrease after 45 min. It decreased to less than 50% of initial control values at 105 min, whereas in the control group urine flow doubled. The investigators concluded that PEG-35 Castor Oil caused vasoconstriction of renal arteries, which induced a more than 50% decrease in renal blood flow and glomerular filtration rate without affecting blood pressure (Thiel et al., 1986).

Short-Term Toxicity

Intravenous

Transient cholestasis occurred when PEG-35 Castor Oil was administered intravenously to rats. This condition was both dependent and independent of bile acid secretion and was accompanied by a marked

reduction in bilirubin excretion with no significant changes in serum bilirubin concentrations (Roman et al., 1989).

PEG-30 and PEG-35 Castor Oil (0.5 mL/kg) each were administered intravenously to one male and one female beagle dog. A pair of control dogs was injected with 0.9% NaCl. Injections were performed daily for 30 days. The dogs were observed daily for signs of toxicity, and blood samples were taken after 9, 16, 23, and 31 days. All of the dogs were killed on day 31 for necropsy. Clinical signs of toxicity were observed in both treatment groups and included edematous wrinkling of the skin above the eyes, flushing of the skin of the external ears, and shaking or rubbing of the head. These signs were more pronounced in the dogs treated with PEG-35 Castor Oil. Salivation and rhinorrhea also were observed in both treatment groups but only for the first 10 days. Thrombocytopenia occurred in the dogs treated with PEG-30 Castor Oil and increased platelet counts were observed in the dogs administered PEG-35 Castor Oil. Clinical chemistry changes included increases in serum concentrations of total cholesterol, triglycerides, total lipids, and percentage of chylomicrons. Electrophoretic patterns indicated a decrease in the percentage of α-lipoproteins and demonstrated the appearance of a new peak near the origin. Changes in the lipid and lipoprotein values were more marked in the PEG-35 Castor Oil–treated dogs. Excessive amounts of lipid were present in the spleen, lymph nodes, liver, and kidneys at histopathologic examination (Hacker et al., 1981).

Six male and six female rabbits were intravenously injected in the ear vein with 4.0 mL/kg of 25% aq PEG-35 Castor Oil (= 1.0 g/kg) for 5 consecutive days. A control group of two male and two female rabbits was injected with the same volume of saline solution following the same protocol. The animals were weighed daily, and hematologic evaluations were performed prior to the study and on day 5. Two rabbits, one male and one female, were killed on day 5, three male and three female rabbits were killed on day 8, and the remaining rabbits were killed on day 12. There were no clinical signs of toxicity in any of the rabbits. The only significant changes was a decrease in hemoglobin content compared with both initial values and that of the controls. At necropsy, no evidence of lipid accumulation or any other adverse macroscopic changes was present (BASF, no date, b).

A different batch of PEG-35 Castor Oil was tested using similar procedures. A group of two male and two female rabbits was injected in the ear vein with 4.0 mL/kg of 25% PEG-35 Castor Oil (= 1.0 g/kg) on 5 consecutive days. The animals were observed for signs of toxicity during the study and were killed on day 7 for necropsy. No clinical signs of

toxicity were observed. At necropsy, one rabbit had an enlarged spleen, but no significant pathologic changes were observed during macroscopic or microscopic examination (BASF, no date, b).

PEG-40 Hydrogenated Castor Oil was also tested for short-term toxicity. Groups of 60 Sprague-Dawley rats were administered daily injections of 300, 900, and 2700 mg/kg PEG-40 Hydrogenated Castor Oil via the tail vein for 4 wk. A control group of 60 rats was administered saline. At the end of 4 wk, all except 10 animals from each group were killed for necropsy. The remaining animals were maintained for an additional 6 wk without treatment. At doses of 300 and 900 mg/kg PEG-40 Hydrogenated Castor Oil, no systemic toxicity was observed; however, at a dose of 2700 mg/kg, slight ataxia was observed and body weight was reduced significantly in the males and slightly in the females. Feed intake also was reduced accordingly. At the end of 4 wk, the number of reticulocytes was increased but was not significantly different from control values. Microscopic evaluation produced evidence of a storage process in the splenic reticulum, but these effects apparently did not cause functional disturbance. At necropsy, heart weight was increased and ovary weight was reduced in the females. Hemorrhages and thrombosis were observed at the injection sites of both experimental and control animals, and thrombophlebitis was found during microscopic evaluation. These effects were found to be reversible in the animals that were maintained for an additional 6 wk without treatment. Body weights, feed intake, and reticulocyte numbers normalized, and damage at the injection sites healed. Microscopically, the injection sites had no changes, and only slight accumulation in the splenic reticulum was observed (BASF, 1976).

Intramuscular

Dogs (number not specified) were alternately injected intramuscularly in the right and left flank with 1.0 mL of 50% PEG-35 Castor Oil. Each dog was given a total of 11 injections. Spotty reddening of the skin was observed at the injection sites, but no resorptive toxicity or macroscopic lesions were observed (BASF, no date, c).

In another study, rabbits and guinea pigs (numbers not specified) were alternately injected intramuscularly in the right and left flank with 0.5 mL and 0.1 mL PEG-35 Castor Oil, respectively. Both species were given a total of 10 injections. No irritation of the skin or resorptive poisoning was observed. At microscopic examination of the muscle tissue, nonspecific foreign body reaction of resorptive character was found at the injection sites; however, this lesion was transient (BASF, no date, c).

Subchronic Toxicity

Oral

In a 90-day feeding study, groups of 15 Sherman-Wistar rats were fed diets containing 0.01%, 0.04%, 0.16%, 0.64%, 2.5%, and 5.0% (initially 10.0%) PEG-40 Castor Oil. A control group of 30 rats was fed untreated feed. The animals were weighed at weekly intervals and feed intake was measured. Blood samples were taken from two male and two female rats prior to the study and then periodically during the study. After 8 wk on the diet, the lightest two male and two female rats were killed for necropsy and tissues were removed for microscopic examination. At the end of the study, the lightest two male and two female rats also were killed for necropsy. After 1 wk on the diet, the animals of the 10.0% treatment group stopped eating the feed, so the concentration was reduced to 5.0% PEG-40 Castor Oil. Weight gain, feed intake, and hematology results were comparable between the experimental groups and the control group. No significant gross or microscopic lesions were found at either 8 wk or 90 days (Industrial Biology Research and Testing Laboratories, no date, a).

Dogs also were used in a 90-day feeding study with PEG-40 Castor Oil. One beagle each was fed a diet containing 0.04%, 0.64%, or 5.0% PEG-40 Castor Oil. A control group of three dogs was fed untreated feed. The animals were weighed at weekly intervals and feed intake was measured. Blood samples were taken prior to the study and then periodically during the study. At the end of the 90 days, the dogs were killed and necropsy was performed. No significant difference was observed in weight gain, feed intake, or hematologic values between the dogs fed the PEG-40 Castor Oil diet and the untreated control dogs. At necropsy, perilobular cellular infiltration and parasitic granulomas were observed, but these conditions also were present in the control animals and were attributed to parasitic infection and migration rather than a treatment-related effect (Industrial Biology Research and Testing Laboratories, no date, b).

The subchronic toxicity of PEG-40 Hydrogenated Castor Oil also was investigated. Groups of 20 male and 20 female Sprague-Dawley rats were given feed containing 32,000-ppm or 64,000-ppm PEG-40 Hydrogenated Castor Oil. A group of 25 male and 25 female rats was fed a diet containing 100,000-ppm PEG-40 Hydrogenated Castor Oil and a control group of 20 male and 20 female rats was fed untreated feed. All of the animals survived the study period. During the study, no significant changes in feed intake, body weight gain, or hematologic evaluations were observed. When 20 male and 20 female rats from each group were killed for necropsy after 6 mo, body and organ weights were within the parameters of those of the control group and no significant

changes in gross or microscopic lesions were found. The remaining five male and five female rats fed the 100,000-ppm diet were fed untreated feed for an additional 21 days. No signs of toxicity were observed clinically and no lesions were observed at necropsy in these rats (BASF, no date, d).

A summary of a 6-mo feeding study with dogs reported that groups of three male and three female beagle were fed diets containing 1.0%, 2.5%, and 5.0% PEG-40 Hydrogenated Castor Oil. A control group of dogs was given untreated feed. During the study, no significant changes in behavior, feed intake, or body weight gain were observed. Hematologic and biochemical parameters and urine analyses were similar to those of the control group. One male dog of the low-dose group died before termination of the study, but its death was considered unrelated to treatment. When the remaining animals were killed for necropsy at the end of the study, body and organ weights were within normal limits and no gross changes were observed. No lesions were observed in tissues examined microscopically (BASF, no date, e).

A PEG Castor Oil (number of moles of ethylene oxide was not specified) was tested as a vehicle control in a study with CD-1 mice. Forty mice (20 of each sex) were given 10% PEG Castor Oil in their drinking water for 90 days. A nontreated control group was given deionized water. The animals were observed for signs of toxicity twice a day and body weights were taken at weekly intervals. Necropsy was performed on the animals either when they died during the study or when they were killed at the end of the study. Hematology and clinical chemistry determinations also were performed. All of the mice survived until the end of the study. PEG Castor Oil seemed to make the drinking water less palatable, because the mean fluid consumption was significantly less for the treated animals compared with the untreated control mice. Terminal body weights of the PEG Castor Oil–treated group did not differ significantly from the those of the untreated group. The absolute and relative weights of the kidneys and liver were significantly greater, and the weight of the brain was significantly less in the treated group than in the control group. Significant differences in hematology included greater hematocrit and lower polymorphonuclear values in the male mice. Among the clinical chemistry parameters studied, the percentage of calcium and creatinine was greater and the BUN–creatinine ratio was lower in experimental mice of both sexes. Female mice also had greater cholesterol and albumin values, and male mice had greater plasma alkaline phosphatase values. No significant differences between the PEG Castor Oil group and the groups administered a drug dissolved in PEG Castor Oil were observed (Borzelleca et al., 1985).

In a similar study in which PEG Castor Oil (number of moles of ethylene oxide was not specified) was tested as a vehicle control, 10 male and 10 female Sprague-Dawley rats were administered 0.5% PEG Castor Oil in drinking water for 13 wk. All of the rats survived the study. The PEG Castor Oil–treated rats had slightly lower water consumption than did untreated control animals, but no significant differences in body weight gain were observed. The only change in organ weights occurred with the brain weight, expressed as a percentage of body weight, which was lower than that of the untreated group. No significant changes were observed in the biochemical, hematologic, and histologic parameters investigated (Villeneuve et al., 1985).

Dermal

A formulation containing 0.25% PEG-40 Hydrogenated Castor Oil was applied by gentle inunction to the shaved skin on the backs of 10 male and 10 female Sprague-Dawley rats. Applications were made once daily for 5 days-wk over a 13-wk period. The daily dose, 1640 mg/kg/day of the formulation, was considered to be 100 times the average daily use level of the product by consumers. Behavioral observations were made daily, body weight was measured weekly, and blood and urine samples were evaluated during weeks 7 and 13. Clinical chemistry parameters also were monitored. At the end of the study, all of the rats were killed and necropsy performed. No deaths occurred during the study and no treatment-related changes in body weight gain, behavior, hematology, urinalysis, or clinical chemistry parameters were observed. After five doses, minimal irritation and desquamation were observed and persisted until the end of the study. The mean relative hepatic weight for male rats was significantly greater compared with the untreated controls; however, this finding was not considered toxicologically significant because no significant lesions were observed at microscopic examination (CTFA, 1984).

In a similar study, two groups of 10 female ChR-CD rats were given topical applications of 284 or 2840 mg/kg of a formulation containing 3.0% PEG-60 Hydrogenated Castor Oil. Applications were made five times a week for 13 consecutive weeks. As seen in the previous study, the only treatment-related lesions occurred on the skin. Slight erythema and drying of the skin was observed; however, control animals also exhibited these effects. At necropsy, no gross lesions were observed. The hepatic weights of the rats treated with 2840 mg/kg of the formulation and the renal-to-body weight ratio of the rats treated with 284 mg/kg of the formulation were significant. It was noted, however, that these changes were within the normal accepted range for the laboratory and that no significant lesions were observed during histopathologic examination (CTFA, 1977a).

Nephrotoxicity

The isolated perfused rat kidney model was used to assess the acute nephrotoxic effects of cyclosporine and its vehicle, PEG-35 Castor Oil. In this model, the right kidney from male Sprague-Dawley rats was perfused with 100 mL of a perfusate solution at normothermic temperature. After 50 min of perfusion, cyclosporine dissolved in PEG-35 Castor Oil or 200 µL PEG-35 Castor Oil was added to the perfusate, and perfusion was continued for an additional 130 min. Control experiments were conducted with the perfusate alone. Serial determination of renal hemodynamics and tubular function was made over the 3-h period. Marked vasoconstriction occurred following perfusion with PEG-35 Castor Oil, and renal blood flow and glomerular filtration rate were reduced by 45% and 28%, respectively, after 3 h. A statistically significant increase occurred in renal vascular resistance. The investigators concluded that PEG-35 Castor Oil had a direct toxic effect on the tubular cells. Because similar results were observed in tests with cyclosporine dissolved in PEG-35 Castor Oil, the investigators suggested that PEG-35 Castor Oil is a contributing factor in severe acute nephrotoxicity sometimes observed in patients following prolonged treatment with intravenous cyclosporine (Hirsch et al., 1987; Besarab et al., 1987).

Cyclosporine in PEG-35 Castor Oil, diluted in NaCl, was evaluated for nephrotoxicity in a study using male Fisher rats. Three control rats were administered intravenous PEG-35 Castor Oil in NaCl, and six control rats were administered NaCl alone for 15 days (volume of intravenous administration not reported). The rats were killed on day 15, and functional studies (inulin clearance) were performed and microscopic examination of the kidneys conducted. No evidence showed that PEG-35 Castor Oil caused alterations in the glomerular filtration rate. Numerous cytoplasmic dark crystals were observed in the proximal tubules of both groups receiving cyclosporine in PEG-35 Castor Oil and the control group receiving PEG-35 Castor Oil and NaCl. Unlike the rats treated with cyclosporine, the rats administered PEG-35 Castor Oil and NaCl had no vacuolization of the proximal tubules. Because no crystals were observed in the tubules of the rats treated with NaCl alone, the investigators concluded that PEG-35 Castor Oil caused the crystal structures in the proximal tubules (Verani, 1986).

No evidence of nephrotoxic effects were observed with PEG-35 Castor Oil in a study using New Zealand White rabbits. In this study, groups of five rabbits were given daily intravenous injections (1.0 mL) of cyclosporine in PEG-35 Castor Oil diluted in saline for 30 days. One control group of rabbits was administered saline, and another received only PEG-35 Castor Oil. The rabbits were placed in metabolic cages for

24-h urine collections. Serum and whole blood also were collected and analyzed regularly during the study. At the end of the study, cardiac puncture was performed to obtain both heparinized whole blood and serum for creatinine and cyclosporine determinations. Tissue samples were taken from different regions of each kidney and microscopic and ultrastructural evaluations were performed. Reductions in creatinine clearance and the development of leukocyte infiltrates, tubular atrophy, and interstitial fibrosis of the kidneys were observed in rabbits treated with cyclosporine. Structural changes also were observed in specimens examined by light and electron microscopy; however no morphologic or functional changes were observed in the rabbits treated with PEG-35 Castor Oil alone. The investigators concluded that PEG-35 Castor Oil did not contribute to the compromise in renal structure and function observed with cyclosporine administration (Thliveris et al., 1991).

Anaphylactoid Reactions

Twenty-percent PEG-35 Castor Oil was administered intravenously to dogs at a constant 30 mL/h; the infusion was stopped when the systolic arterial pressure decreased by more than 50% of the control. This treatment induced a significant decrease in blood pressure and cardiac output associated with massive increases in plasma histamine and catecholamine. The investigators suggested that the large increase in histamine release was indicative of acute mast cell degranulation. Thoracopulmonary compliance decreased rapidly and was reduced markedly by the end of infusion. A significant reduction in blood volume, which was caused by a decrease in plasma volume, was observed. Hematocrit increased significantly by the end of infusion, whereas platelet and leukocyte counts sharply decreased. It was also noted that 6 of 13 dogs had cutaneous erythema and edema of their paws and muzzle. The investigators concluded that 20% PEG-35 Castor Oil induced cardiovascular collapse, and that PEG-35 Castor Oil–induced shock "is of the anaphylactoid type, and includes cutaneous erythema and edema, hypotension, venous pooling, plasma extravasation, histamine and catecholamine release, and decreases in dynamic thoracopulmonary compliance and leucocyte and platelet counts" (Gaudy et al., 1987).

Dermal Irritation

When undiluted PEG-35 Castor Oil was applied to the shaved backs or to the external ears of albino rabbits for more than 20 h (experimental details not provided), slight transient irritation was reported (BASF, no date, c).

Undiluted PEG-40 Hydrogenated Castor Oil reportedly caused reddening and scaling of the skin when applied to the backs of albino rabbits for 20 h (experimental details not provided). Only slight transient reddening was reported when applications were made to the external ears of rabbits for 20 h (BASF, no date, c).

The primary skin irritation potential of a formulation containing 2.0% PEG-25 Hydrogenated Castor Oil was minimal. Only one of nine rabbits had evidence of erythema 24 h after a single application of the formulation under an occlusive patch (amount not stated). The overall primary irritation index (PII) was 0.11/8 (CTFA, 1982c). For formulations containing either 0.25% PEG-40 Hydrogenated Castor Oil or 3.0% PEG-60 Hydrogenated Castor Oil, the PIIs were 0.22/8 and 0.67/8, respectively (CTFA, 1982d; CTFA, 1976b).

Dermal Sensitization

The flanks of 10 guinea pigs were shaved, degreased with ether, and 50% PEG-35 Castor Oil in acetone was applied to the left flank of each animal (painted three times sequentially with a saturated cotton swab) for 10 consecutive days. The right flanks were left untreated. After a 12-day nontreatment period, 5% PEG-35 Castor Oil in acetone was applied to the right flank (as above, after degreasing with ether). The skin was observed for signs of irritation after 12 h. A control group of three guinea pigs was untreated during the induction phase of the experiment but was given a single application of 5% PEG-35 Castor Oil. Slight reddening of the skin was observed during induction with PEG-35 Castor Oil, but no signs of irritation were observed after the challenge application. When this study was duplicated, the same results were obtained (BASF, no date, f).

In a subcutaneous sensitization study, 10 daily injections with 0.1% PEG-35 Castor Oil (1 $\times$ 0.05 mL; 9 $\times$ 0.1 mL) were administered to guinea pigs (number not specified) in their backs. After a 13-day nontreatment period, a challenge injection of 0.1% PEG-35 Castor Oil (1 $\times$ 0.05 mL) was administered into the neck. Reddening occurred around the injection sites during induction, but no sign of sensitization was present (BASF, no date, f).

Tachon et al. (1983) also assessed the allergenic potential of PEG-35 Castor Oil. Ten consecutive intradermal injections of 0.5 mL PEG-35 Castor Oil were performed to the backs of 10 male and 10 female Dunkin-Hartley guinea pigs, and an occlusive patch was applied for 48 h. After a 12-day nontreatment period, the animals were challenged with 0.5 mL PEG-35 Castor Oil on their abdomens. When macroscopic evaluations were performed 48 h following challenge, 60% of the male and 50% of the female guinea pigs had doubtful reactions; however, no

evidence of sensitization was observed at microscopic examination. The investigators concluded that PEG-35 Castor Oil was not a sensitizing agent.

Adjuvancy

Descotes et al. (1983) conducted three studies to determine the adjuvancy of PEG-35 Castor Oil. In the first study, groups of six female Dunkin-Harley guinea pigs were injected with 100 μg bovine serum albumin (BSA) in 0.05 mL PEG-35 Castor Oil. A positive control groups of animals was injected with BSA in Freund's complete adjuvant (FCA), and a negative control group of animals was treated with BSA in saline. Three weeks later the animals were intradermally injected in the right flank with BSA in saline. Skin evaluations were made at 2, 24, and 48 h. PEG-35 Castor Oil caused erythema and skin induration that was of the same severity as seen with FCA.

In the second study, groups of 10 Swiss mice were injected subcutaneously in the back with 10^8 sheep erythrocytes in either 0.005 or 0.01 mL PEG-35 Castor Oil in saline. A control group of mice was injected with sheep erythrocytes in saline. Five days later, the mice were administered an eliciting dose of 10^8 sheep erythrocytes in the hind footpad. The percent increase in footpad swelling was taken as a measure of delayed hypersensitivity. Both doses of PEG-35 Castor Oil caused significant increases in footpad thickness.

In the third study, 10^9 sheep erythrocytes in 0.01 and 0.05 mL PEG-35 Castor Oil in saline was administered intraperitoneally to 10 Swiss mice. A control group of mice was treated with erythrocytes in saline only. Eight days later, blood samples were taken from the mice to measure hemagglutinin concentrations. PEG-35 Castor Oil had no effect on antibody concentrations. Based on the three studies, the investigators concluded that PEG-35 Castor Oil is "a potent adjuvant of cellular immune response."

Ocular Irritation

A 5% active solution (pH = 6–8) of PEG-5 Hydrogenated Castor Oil (w/w) (0.1 mL) was instilled into the left conjunctival sac of six New Zealand white rabbits. Three of the eyes were rinsed after 30 sec. The rights eyes left untreated served as controls. Scoring according to the method of Draize (1944) was made at 24, 48, and 72 h postinstillation. Slight to mild corneal opacity was observed in two unrinsed eyes at 24 h and persisted until 72 h. None of the other treated eyes had evidence of corneal damage. Slight iridial damage was observed in one unrinsed eye at 24 and 48 h, and in another unrinsed eye at 48 and 72 h. Iridial

damage also was observed in one rinsed eye at 24 h, but it cleared by 72 h. At 24 h, all of the treated eyes had mild to moderate conjunctival irritation manifest as hyperemia, chemosis, and discharge. One rinsed eye and one unrinsed eye cleared by 72 h, whereas the remaining eyes were irritated through 72 h. The 24-h maximum mean total score was 36.3/110 for the unrinsed eyes and 13.7/110 for the rinsed eyes. The investigators concluded that PEG-5 Hydrogenated Castor Oil was severely irritating to unrinsed eyes and mildly irritating to rinsed eyes (Product Safety Labs, 1988).

When 50 mm^3 of 50% aq PEG-35 Castor Oil in acetone was instilled into the conjunctival sac of rabbits (number not specified), lacrimation and mild irritation of the conjunctiva were observed. A 30% aq solution did not cause any signs of irritation (BASF, no date, c).

Undiluted and 50% aq PEG-40 Hydrogenated Castor Oil was instilled (0.05 mL) into the conjunctival sacs of rabbits (number not specified), and observations were made at 24 and 48 h. Slight transient reddening of the conjunctiva was observed with both concentrations (BASF, no date, c).

No irritation was observed when the eyes of six rabbits were instilled (volume not given) with a formulation containing 2.0% PEG-25 Hydrogenated Castor Oil (CTFA, 1982e). In a similar study, a formulation containing 0.25% PEG-40 Hydrogenated Castor Oil caused mild transient irritation. The total irritation scores on days 1 to 3 postinstillation were 1/110. All eyes were clear by day 4 (CTFA, 1982f).

A formulation containing 3.0% PEG-60 Hydrogenated Castor Oil (volume not given) caused minimal irritation to the eyes of 2 of 6 rabbits. The irritation score for both rabbits was 2/110 24 h after instillation. All signs of irritation disappeared by 48 h (CTFA, 1976c).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

PEG-40 Hydrogenated Castor Oil was tested for teratogenic effects in a feeding study with Sprague-Dawley rats. Two groups of pregnant rats, 30 in one group and 27 in the other, were fed diets containing 50,000 ppm or 100,000 ppm PEG-40 Hydrogenated Castor Oil, respectively, on days 0 to 20 of gestation. Two control groups of 26 and 29 rats were fed untreated feed. All of the animals were observed for signs of toxicity during gestation and were killed on day 20 for evaluation of the uteri. No evidence of either maternal or fetal toxicity was present. A slight but not statistically significant increase occurred in the number of resorptions in the group treated with 100,000 ppm. The type and number of malformations and anomalies found in the fetuses of the experimental groups were similar to those found among the fetuses from the control groups. The investigators concluded

that PEG-40 Hydrogenated Castor Oil was not teratogenic (BASF, no date, g).

Negative results were also obtained in a teratogenicity study with NMRI mice. Two groups of pregnant mice, 25 in one group and 31 in the other, were fed diets containing either 5000 ppm or 10,000 ppm PEG-40 Hydrogenated Castor Oil on days 6 to 15 of gestation. Two groups of 26 and 28 mice were given untreated feed. There was no statistically significant evidence of either maternal or fetal toxicity. The few malformations observed among the fetuses of the treated dams were similar to type and number to those found in the control groups (BASF, no date, h).

Lane et al. (1982) tested PEG-30 Castor Oil as a vehicle control in a multigeneration study that was modified to include a screening for dominant lethal and teratogenic effects. Ten male and 30 female ICR Swiss mice (F/0) were administered 1% PEG-30 Castor Oil in their drinking water continuously throughout the study. After 35 days on the test solution, the mice were randomly mated to produced F/1A litters. Two weeks following the weaning of the F/1A litters, the F/0 mice were rerandomized and mated to produce F/1B litters. Then the F/0 mice were mated randomly again 2 weeks after the weaning of the F/1B litters to produce F/1C litters.

Ten male and 30 female weanling mice from the F/1B litters also were administered 1% solutions of PEG-30 Castor Oil in their drinking water and were mated in nonsibling matches to produce F/2A litters. Body weight and fluid consumption, as well as fertility and gestational indices, were determined regularly for the parental mice. Twenty-one day survival studies were conducted on the litters from the F/1A, F/1B, and F/2A matings.

F/1C and F/2B matings also were produced to screen for dominant lethal and teratology effects. In these studies, female mice were killed during gestation and the number of fetal implants, early and late resorptions, viable fetuses, and dominant lethal factors were determined. Fetuses were removed and individually evaluated for gross defects, and one third of them were examined for skeletal and visceral malformations.

No significant changes in reproductive performance were observed in any of the matings. Mean litter size, postnatal body weights, and survival indices also were unaffected. The only significant change observed in both the dominant lethal and teratology screenings was an increase in the ratio of dead fetuses to live fetuses.

PEG-35 Castor Oil also was tested as a solvent control in a teratogenicity study. Groups of pregnant ICR and C57B1/10Dg mice (numbers not specified) were orally given 0.05 mL/10 g body weight 8% PEG-35 Castor Oil and 10% propylene glycol in water on either day 9, 10, or

11 of gestation. An untreated control group of pregnant mice was used for comparison. All of the mice were killed on day 18 of gestation, and the fetuses and placentas were removed for examination. PEG-35 Castor Oil did not have any significant effects on growth or development in any of the treatment groups (Cusic and Dagg, 1984, 1985).

In the following studies, PEG-30 Castor Oil and PEG-35 Castor Oil were tested as negative vehicle control substances. No untreated control animals were used for comparison.

Burkhalter and Balster (1979) used PEG-30 Castor Oil as a vehicle control in a behavioral development evaluation. Male and female albino ICR mice were given daily oral doses of 10 mL/kg of a solution containing one part PEG-30 Castor Oil and eight parts saline. The mice were mated after 3 wk of treatment with PEG-30 Castor Oil, and the dams continued to receive daily doses of PEG-30 Castor Oil through gestation and lactation. A total of five litters was used. Each of these litters was randomly reduced to eight pups, and oral administration of PEG-30 Castor Oil to the pups was initiated 7 d following birth and continued for the remainder of the study. On days 7 to 21, the pups were weighed, and a battery of tests to determine neurobehavioral development was conducted. These tests included measurement of righting reflex, forepaw grasp, rooting reflex, cliff-drop aversion, auditory startle response, bar-holding ability, eye opening, motor performance and learning measures, and placing and grasping responses. In general, the pups experienced gradual weight gain and progressive neurobehavioral development.

PEG-35 Castor Oil was used as the vehicle control in a study using embryo cultures. Embryos from pregnant Swiss Webster mice were removed on day 8.5 of gestation and grown in culture containing 130 μg/mL PEG-35 Castor Oil for 24 h. At the end of culture, the embryos were evaluated for viability and only viable embryos were examined for malformations. Of the 44 embryos examined, only three had abnormalities, including defect of the neural tube, facial arch, and cranial rotation. The mean somite number was 24.2, mean crown-rump length was 2.25, and mean protein content was 86.5 μg per embryo (Uhing et al., 1993).

MUTAGENICITY

Au et al. (1991) investigated the clastogenic and coclastogenic activity of PEG-35 Castor Oil using male ICR mice. Cytogenetic and metabolite analyses were conducted with groups of five mice given 0.1 mL/g of 0.03%, 0.3%, or 3.0% PEG-35 Castor Oil orally. Other groups of mice were treated with benzene in olive oil or benzene in combination with the various doses of PEG-35 Castor Oil. An untreated control group and

a vehicle control (olive oil) group also were used. The mice in the single-treatment groups were killed at 30 h, and the mice receiving the combined treatment were killed after the first treatment. Bone-marrow samples were harvested at the end of the study and evaluated for micronuclei (MN) frequencies in polychromatic erythrocytes (PCE).

The investigators also tested the effect of PEG-35 Castor Oil in hepatic cytochrome P450 isoenzyme expression in liver. Male Swiss albino CD1 mice were given 0.01 mL/g body weight 3% PEG-35 Castor Oil in water orally. Another group of mice was given benzene followed by 3% PEG-35 Castor Oil 1, 3, and 5 h later. The mice given PEG-35 Castor Oil only were killed 1, 3, 5, 15, or 30 h after treatment, whereas the mice treated with both PEG-35 Castor Oil and benzene were killed after 30 h. The livers were removed from all of the mice for evaluation.

PEG-35 Castor Oil did not cause any significant or dose-dependent increses in MN but did enhance significantly the clastogenicity of benzene. When PEG-35 Castor Oil was administered 1, 3, and 5 h after benzene treatment, an inverse time-dependent change occurred in MN frequencies. The enhancement effects of PEG-35 Castor Oil were attributed to its ability to induce the cytochrome P450I family when it was administered 1 h after benzene treatment. No positive synergistic effect was observed when PEG-35 Castor Oil was administered at later intervals. The investigators also noted an increase in *trans,trans* muconic acid (a genotoxic metabolite of benzene) in the urine following combined treatment.

PEG-30 Castor Oil and PEG-35 Castor Oil also were used as negative vehicle controls in several studies. PEG-30 Castor Oil was used in a chromosomal aberration assay using Chinese hamster ovary (CHO) cells and micronucleus and spermhead abnormality assays with mice (Blazak et al., 1988). Machemer and Lorke (1978) used PEG-35 Castor Oil in dominant lethal tests on male and female mice, micronucleus tests on male and female mice, and a spermatogonial test using Chinese hamsters. PEG-35 Castor Oil also was used in a study to detect sex-linked recessive lethals in *Drosophila* spermatozoa (Kortselius, 1978). In all of these studies, known mutagens were used as positive controls and had significant evidence of mutagenicity compared with the PEG-30 Castor Oil and PEG-35 Castor Oil vehicle controls.

CARCINOGENICITY

In the following studies, the PEG Castor Oils were used as vehicle control substances, and no untreated control groups were used.

In an oral carcinogenicity study of several agents, PEG-30 Castor Oil was used as a vehicle control. Male Sprague-Dawley rats were given 1

mL of 10% PEG-30 Castor Oil by gavage three times a week for 16 wk and then once per week for an additional 10 wk. All of the rats were killed during week 77 and necropsy was performed. No untreated control group of animals was used. Of the 29 rats examined, the following neoplasms (and number of neoplasms) were found: benign liver tumor (1), keratoacanthoma (1), pituitary adenomas (4), prostate carcinoma in situ (1), Leydig cell tumor of the testis (1), ear spindle cell sarcoma (1), pancreatic islet cell adenoma (1), spleen lymphomas (2), mammary fibroma (1), subcutaneous myxolipoma (1), subcutaneous fibromas (2), and adrenal adenoma (1). No comment was made by the investigators regarding the normal range of occurrence of these tumors in their historical data base (Fiala et al., 1987).

In another study, a PEG Castor Oil (number of moles of ethylene oxide was unspecified) was used as a vehicle control in a lung adenoma assay using A/J mice. Two groups of 20 female mice were given either 0.2 mL of 2% PEG Castor Oil three times a week for 8 wk or 0.2 mL of 2% PEG Castor Oil twice each dosing day following the same dosing schedule. A positive control group of 40 mice was given benzo[*a*]pyrene (BaP) in PEG Castor Oil following the first dosing schedule. No untreated control group was used. All of the animals were killed 8 mo after the first dose and were examined for neoplasms. The neoplastic response was not significantly different between the two PEG Castor Oil groups, so the data were pooled. Only two of the mice died during the study. Twenty-nine percent of the mice had lung neoplasms, and the average number of neoplasms per mouse was 0.32. None of the mice had squamous cell papillomas or carcinomas of the nonglandular stomach. Of the BaP-treated group, four mice died, 61% of the mice had lung neoplasms, the average number of neoplasms per mouse was 1.42, and 92% of the mice had squamous cell neoplasms of the nonglandular stomach (Robinson et al., 1987).

In a tumor-promotion study, a 2% solution of PEG Castor Oil (unspecified number of moles of ethylene oxide) was used as a vehicle control. PEG Castor Oil (0.2 mL) was orally administered to 110 female SENCAR mice three times a week for 2 wk. After a nontreatment period of 2 wk, 1.0 µg of TPA in acetone was topically applied to the mice three times per week for 20 wk. No untreated control group of animals was used. At the end of the study, 15% of the mice had neoplasms. A total of 20 neoplasms was present, and the neoplasms–animal ratio was 0.18. The investigators also reported the result of 90 mice treated with dimethylsulfoxide followed by TPA treatment: 6% of the mice had neoplasms, there were a total of 5 neoplasms, and the neoplasm–animal ratio was 0.06 (Robinson et al., 1989).

CLINICAL STUDIES

Hemodynamics

Eight men who were previously tested intravenously with a drug dissolved in 20% PEG-35 Castor Oil were given 0.15 mL/kg PEG-35 Castor Oil intravenously over a 10-sec infusion period. Blood samples were taken 1, 5, 10, 20, and 30 min postinjection for histamine analysis, and blood pressure and heart rate was monitored. No increase in plasma histamine concentrations or effects on blood pressure and heart rate were detected (Doenicke et al., 1973).

Dermal Irritation

Twenty subjects were patch tested with 30% PEG-35 Castor Oil in water and 100% PEG-40 Hydrogenated Castor Oil on the skin of their backs. Observations were made after 24 and 48 h. No signs of irritation were observed (University Clinic Eppendorf, 1951–1954).

A 24-h single insult patch test of a formulation containing 2% PEG-25 Hydrogenated Castor Oil was conducted using 20 subjects. One subject developed mild erythema and two subjects had barely perceptible reactions (CTFA, 1982g). In a similar study, a formulation containing 0.25% PEG-40 Hydrogenated Castor Oil caused 1 of 20 subjects to develop a mild reaction to the formulation (CTFA, 1981).

The cumulative irritation potential of a formulation containing 3% PEG-60 Hydrogenated Castor Oil was conducted using 12 volunteers. Occlusive patches of 0.2 mL of the formulation were applied to the backs of each subject for 23 h for 21 consecutive days. Test sites were scored 24 h after each application. The composite total score was 22/756. The investigators concluded that this formulation was essentially nonirritating (Hill Top Research, 1976).

Dermal Irritation and Sensitization

A formulation containing 0.05% PEG-40 Hydrogenated Castor Oil was tested in a repeated insult patch test using 120 volunteers. The formulation (0.10 mL) was applied under occlusive patches to the backs of each subject for 24 h on Mondays, Wednesdays, and Fridays for 3 wk. After a 2-wk nontreatment period, challenge patches of the formulation were applied to previously untreated sites.

Five subjects had one incidence each of barely perceptible erythema during the induction phase of the study. One of these subjects also had a mild reaction to the challenge application at both the 24-h and 48-h readings. One subject, who showed no reaction during the induction phase, had a barely perceptible reaction at the 48-h challenge reading.

Follow-up testing of these two subjects was conducted using the formulation "as is" and at a 1:3 dilution in water. Reactivity was not confirmed in one subject, but the other subject had a very weak reaction to the "as-is" formulation at the 24-h grading period. The investigators noted that this reactivity was much less than at challenge and was of questionable clinical significance. They concluded that this formulation was not an allergic sensitizer (CTFA, 1977b).

Using the same procedures, a formulation containing 0.25% PEG-40 Hydrogenated Castor Oil was tested for allergic contact sensitization potential on 86 subjects. Two subjects had minimal irritation during the induction phase of the study, but neither reacted to the challenge patch. One subject, who had no signs of irritation during induction, had faint erythema at the 24-h grading period only. The investigators concluded that this formulation was not a sensitizer (CTFA, 1982h).

A formulation containing 3.0% PEG-60 Hydrogenated Castor Oil also was tested using the same repeated insult patch procedures with 102 subjects. No signs of irritation were observed in any of the subjects durng induction. Only one doubtful reaction was observed at the 48-h reading after challenge. Follow-up testing of this subject with the formulation and a 1:3 dilution of the formulation was negative (CTFA, 1976d).

Jones and Kennedy (1988) reported two cases of eczema from a topical medicament used to treat leg ulcers. Patch tests with the constituents of this cream implicated PEG-40 Castor Oil (0.1% and 1% pet.) as the sensitizing agent. This ingredient induced severe grade-3 reactions at 48 and 96 h in both patients. The allergenicity of these reactions was supported by tests with 10 control patients, who had negative reactions to 0.1% and 1% PEG-40 Castor Oil.

Anaphylactoid Reactions

Several case studies of anaphylactoid reactions associated with intravenous administration of drugs dissolved in PEG-35 Castor Oil have been reported. In all of these cases, PEG-35 Castor Oil could not be diretly implicated as the cause for the adverse reaction; however, such factors as tolerance of the drugs alone when administered orally, treatment with drugs from the same family not dissolved in PEG-35 Castor Oil, and similar in several types of drugs in which PEG-35 Castor Oil was the solvent strongly suggest that PEG-35 Castor Oil was the cause of the anaphylaxis.

Most of the case reports are of intravenous treatment with cyclosporine dissolved in PEG-35 Castor Oil (Van Hooff et al., 1987; Magalini et al., 1986; Ptachcinski et al., 1985; Howrie et al., 1985; Chapuis et al., 1985; Leunissen et al., 1985; Friedman et al., 1985;

Kahan et al., 1984). In general, subjects experienced flushing, bronchospasm, dyspnea, chest pains, pruritus, urticaria, and hypotension within minutes of injection. Reactions were documented occurring both after the first dose and after multiple doses. In some instances, the researchers were able to determine that the subjects had previous exposure to other drugs dissolved in PEG-35 Castor Oil.

Intravenous treatment with vitamin K_1 (phytonadione) also has been linked with anaphylactoid reactions (de la Rubia et al., 1989; Lefrere and Girot, 1987; Rich and Drage, 1982; Barash et al., 1976). Within minutes of a bolus injection, patients developed facial flushing, hypotension, chest pain, dyspnea, and abdominal pain. In the five cases reported, four subjects were administered the drug an undiluted and one was administered a diluted form. In one case, anaphylactoid reactions were prevented in a subsequent injection by using a diluted form of the drug and administering it at a slower infusion rate. Three of the cases occurred on the first injection, and two occurred after a second injection, which resulted in one death.

The anesthetic drug, Althesin, which was a combination of alphaxalone and alphadolone, was withdrawn from the market in 1983 because of the high incidence of anaphylactic reactions to the solvent, PEG-35 Castor Oil (Smolinske, 1992).

Anaphylactic reaction also have been associated with intravenous treatments with diazepam (Hüttel et al., 1980), teniposide (Siddal et al., 1989), and disoprofol (Briggs et al., 1982).

The mechanism behind these types of reactions is not clear. Doenicke et al. (1973) reported that although histamine release occurs in patients treated with drugs dissolved in PEG-35 Castor Oil, this vehicle alone did not induce histamine release. It is believed that this compound causes histamine release when administered in combination with certain anaesthetic drugs (Lorenz, 1975). Watkins et al. (1976) also proposed that the surfactant properties of PEG-35 Castor Oil enhance the immunogenicity of concurrently administered drugs.

In a study by Radford et al. (1982), activation of the alternative complement pathway was associated with subjects reacting to first exposure to Althesin, whereas the activation of the classic complement pathway was associated with reactions to a repeat exposure to the drug. In general, patients reacting to a repeat exposure to the drug have more severe clinical reactions, which are immunologically related.

In a 10-year survey of 118 patients with Althesin-related hypersensitivity, 1% of the cases were classified as immunoglobin E–mediated type I hypersensitivity, 36% to immune complement-mediated reactions involving other antibodies, 40% to alternate pathway complement C3 activation, and 23% to mixed reactions (Watkins, 1986).

SUMMARY

PEG-30, -33, -35, -36, and -40 Castor Oil and PEG-30 and -40 Hydrogenated Castor Oil are polyethylene glycol derivatives of castor oil and hydrogenated castor oil that are used in a variety of cosmetic products as emulsifiers or solubilizing agents. Formulation data submitted to the FDA in 1995 reported a total of 540 cosmetic formulations containing these ingredients.

At the cellular level, PEG-35 Castor Oil affects a variety of cellular functions, including ATP production, PKC activation, renal proximal tubule cell function, and neurite outgrowth. PEG-40 Hydrogenated Castor Oil affected the integrity of human epithelial cells.

In the pharmaceutical industry, PEG-35 Castor Oil and PEG-40 Castor Oil are commonly used as solvents for intravenous drugs. Therefore, much of the toxicity data available on this family of ingredients are specifically on intravenous use.

Hemodynamic studies indicate that intravenous exposure to PEG-35 Castor Oil causes alterations in cardiac output, blood pressure, blood flow to various organs, and histamine release. Endothelial dysfunction of isolated rat hearts also was altered by exposure to PEG-35 Castor Oil.

The oral LD_{50} of two cosmetic formulations containing either 2.0% PEG-25 Hydrogenated Castor Oil or 0.25% PEG-40 Hydrogenated Castor Oil was reported to be more than 15.0 g/kg for rats. For a formulation containing 3.0% PEG-60 Hydrogenated Castor Oil, the LD_{50} for rats was more than 5.0 g/kg.

PEG-35 Castor Oil causes acute nephrotoxicity in rats. In the isolated perfused rat kidney model, this ingredient induced vasoconstriction and reduced renal blood flow and glomerular filtration rate in rats. Another study reported that PEG-35 Castor Oil caused the development of crystals in the proximal tubules of rats; however, no nephrotoxic effects were observed in a study using rabbits.

Impairment of renal function also was observed in acute intravenous studies of PEG-35 Castor Oil using rats.

In short-term studies, the toxicity of PEG-35 Castor Oil to dogs following intravenous exposure was greater than that of PEG-30 Castor Oil. Changes in lipid and lipoprotein values and accumulation of lipid in the spleen, lymph nodes, liver, and kidneys were observed; however, no toxicity or any adverse macroscopic or microscopic changes were observed in two studies using rabbits. A study of PEG-40 Hydrogenated Castor Oil produced some evidence of toxicity as well as a storage process in the splenic reticulum, but no functional disturbance occurred.

Following repeated intramuscular injections with 50% PEG-35 Castor Oil, no significant signs of toxicity were observed in dogs. Negative results also were obtained in studies with rabbits and guinea pigs.

No significant signs of toxicity were observed in subchronic oral studies of 5% PEG-40 Castor Oil using rats and dogs, 100,000-ppm PEG-40 Hydrogenated Castor Oil using rats, and 5% PEG-40 Hydrogenated Castor Oil using dogs. Results were also negative in subchronic dermal studies using rats for formulations containing 0.25% PEG-40 Hydrogenated Castor Oil or 3.0% PEG-60 Hydrogenated Castor Oil.

Undiluted PEG-35 Castor Oil and PEG-40 Hydrogenated Castor Oil caused mild transient dermal irritation when applied to the skin of rabbits. Primary irritation studies of formulations containing either 2.0% PEG-25 Hydrogenated Castor Oil or 0.25% PEG-40 Hydrogenated Castor Oil produced minimal signs of irritation.

In a sensitization study with guinea pigs, 50% PEG-35 Castor Oil caused irritation during the induction phase of the experiment, but no sensitization was observed following a challenge application of 5% PEG-35 Castor Oil. Similar results were obtained in intradermal studies.

Some evidence showed that PEG-35 Castor Oil was a potent adjuvant of cellular immune response in studies using guinea pigs and mice.

No ocular irritation was observed in rabbits with either 30% aq PEG-35 Castor Oil or a formulation containing 2.0% PEG-25 Hydrogenated Castor Oil. Slight, transient ocular irritation was observed with undiluted and 50% aq PEG-40 Hydrogenated Castor Oil and with formulations containing either 0.25% PEG-40 Hydrogenated Castor Oil or 3% PEG-60 Hydrogenated Castor Oil.

A diet of 100,000-ppm PEG-40 Hydrogenated Castor Oil fed to pregnant rats through 20 days of gestation did not cause teratogenic effects to the fetuses. Similarly, no teratogenic effects were observed when pregnant mice were fed 10,000-ppm PEG-40 Hydrogenated Castor Oil.

In reproductive and developmental toxicity studies in which 1% PEG-30 and 8% PEG-35 Castor Oil were used as vehicle controls, adverse effects on fertility or development following oral administration were not observed.

PEG-35 Castor Oil did not cause any significant clastogenic effects in mice but did produce coclastogenic effects when administered in combination with benzene. PEG-30 and PEG-35 Castor Oil were used as negative vehicle controls in a variety of mutagenicity assays. In these studies, known mutagens had significant evidence of mutagenicity compared with these vehicles.

The only available data on the carcinogenic potential of the PEG Castor Oils were from studies in which these ingredients were used as vehicle controls. In clinical studies, PEG-35 Castor Oil had no effect on the plasma histamine concentration of men following intravenous administration.

A 30% solution of PEG-35 Castor Oil and 100% PEG-40 Hydrogenated Castor Oil were not irritating to the skin of 20 subjects. Negative results also were obtained in single 24-h insult patch tests with formulations containing either 2.0% PEG-25 Hydrogenated Castor Oil or 0.25% PEG-40 Hydrogenated Castor Oil. In a cumulative irritation study, a formulation containing 3% PEG-60 Hydrogenated Castor Oil was nonirritating.

No evidence of sensitization was shown in clinical studies with formulations containing either 0.05% or 0.25% PEG-40 Hydrogenated Castor Oil, or 3.0% PEG-60 Hydrogenated Castor Oil.

PEG-35 Castor Oil has been associated with case reports of anaphylactoid reactions following intravenous administration of drugs dissolved in this vehicle. Although PEG-35 Castor Oil has not been directly implicated as the cause for these types of reactions, factors such as tolerance of the drugs alone when administered orally, treatment with drugs from the same family not dissolved in PEG-35 Castor Oil, and similar reactions observed in several types of drugs in which PEG-35 Castor Oil was the solvent strongly suggest that PEG-35 Castor Oil was the cause of the anaphylactic reactions.

DISCUSSION

The Cosmetic Ingredient Review (CIR) Expert Panel reviewed the available safety data on the PEG Castor Oils and the PEG Hydrogenated Castor Oils and agreed that these ingredients seem to have little toxicity. The only adverse reactions observed were anaphylactoid reactions in intravenous studies. Because this route of exposure does not occur from cosmetic use, the Panel was not concerned about this type of risk. The Panel did express concern over the lack of current concentration of use data. It was agreed that concentration limits should be based on the available test data on irritation and sensitization. The highest concentration tested yielding negative results for the PEG Castor Oil family was 50% PEG-35 Castor Oil in a sensitization study with guinea pigs. For the PEG Hydrogenated Castor Oil family, undiluted PEG-40 Hydrogenated Castor Oil was negative in animal and clinical irritation studies. The Panel agreed that the chemical similarity of these two ingredients to the other ingredients in their respective families allows for extrapolation of the concentration limits to these other ingredients.

CONCLUSION

Based on the irritation and sensitization data presented in this report, the CIR Expert Panel concludes that PEG-30, -33, -35, -36, and -40 Castor Oil are safe for use in cosmetics at concentrations up to 50% and that PEG-30 and -40 Hydrogenated Castor Oil are safe for use at concentrations of up to 100%.

REFERENCES

Anderberg, E. K., Nyström, C., and Artursson, P. 1992. Epithelial transport of drugs in cell culture. VII: Effects of pharmaceutical surfactant excipients and bile acids on transepithelial permeability in monolayers of human intestinal epithelial (Caco-2) cells. *J. Pharm. Sci.* 81:879–887.

Au, W. W., Anwar, W., Paolini, M., et al. 1991. Mechanism of clastogenic and co-clastogenic activity of cremophore and benzene in mice. *Carcinogenesis* 12:53–57.

Barash, P., Kitahata, L. M., and Mandel, S. 1976. Acute cardiovascular collapse after intravenous phytonadione. *Anesth. Analg.* 55:304–306.

BASF. No date, a. The action of Cremophor EL and polyoxyethylene sorbitan monooleate (PSM) on the blood pressure of animals. (Submitted by FDA in response to FOI request.)*

BASF. No date, b. Report on comparison tests made on the intravenous toxicity of two different batches of Cremophor EL to rabbits. (Submitted by FDA in response to FOI request.)*

BASF. No date, c. Cremophor EL. (Submitted by FDA in response to FOI request.)*

BASF. No date, d. Report on a six-months rat-feeding test with Cremophor RH 40. (Submitted by FDA in response to FOI request.)*

BASF. No date, e. Summary of a report on a six month feeding study in dogs with Cremophor RH 40. (Submitted by FDA in response to FOI request.)*

BASF. No date, f. Report on the testing of Cremophor EL for skin sensitizing effects on guinea pigs. (Submitted by FDA in response to FOI request.)*

BASF. No date, g. Feeding study with Cremophor RH 40 to ascertain any possible teratogenic effects in rats. (Submitted by FDA in response to FOI request.)*

BASF. No date, h. Study with Cremophor RH 40 to ascertain any possible teratogenic effects in mice when applied preorally. (Submitted by FDA in response to FOI request.)*

BASF. 1976. Summary of a 4-week toxicity report of Cremophor RH 40 on rats after intravenous application. (Submitted by FDA in response to FOI request.)*

Besarab, A., Jarrell, B. E., Hirsch, S., et al. 1987. Use of the isolated perfused kidney model to assess the acute pharmacologic effects of cyclosporine and its vehicle, Cremophor EL. *Transplantation* 44:195–201.

Blazak, W. F., Meier, J. R., Stewart, B. E., et al. 1988. Activity of 1,1,1-and 1,1,3-trichloroacetones in chromosomal aberration assay in CHO cells and the micronucleus and spermhead abnormality assays in mice. *Mutat. Res.* 206:431–438.

Board, P. G. 1993. Inhibition of erythrocyte glutathione conjugate transport by polyethoxylated surfactants. *FEBS Lett.* 315:298–300.

Borzelleca, J. F., Hayes, J. R., Condie, L. W., et al. 1985. Acute and subchronic toxicity of 2,4-dicholorophenol in CD-1 mice. *Fund. Appl. Toxicol.* 5:478–486.

Bowers, V. D., Locker, S., Ames, S., et al. 1991. The hemodynamic effects of Cremophor EL. *Transplantation* 51:847–850.

Brat, D. J., Windebank, A. J., and Brimjoin, S. 1992. Emulsifier for intravenous cyclosporin inhibits neurite outgrowth, causes deficits in rapid axonal transport and leads to structural abnormalities in differentiating N1E.115 neuroblastoma. *J. Pharm. Exp. Ther.* 261:803–810.

Briggs, L. P., Clarke, R. S. J., and Watkins, J. 1982. An adverse reaction to the administration of disoprofol (Diprivan). *Anaesthesia* 37:1099–1101.

Budavari, S. 1989. *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals*, 11th ed. 290. Rahway, NJ: Merck & Co.

Burkhalter, J. E., and Balster R. L. 1979. Behavioral teratology evaluation of trichloromethane in mice. *Neurobehav. Toxicol.* 1:199–205.

Chapuis, B., Helg, C., Jeannet, M., et al. 1985. Anaphylactic reaction to intravenous cyclosporine. *N. Engl. J. Med.* 312:1259.

Chuang, L. F., Israel, M., and Chuang, R. Y. 1991. Cremophor EL inhibits 12-*o*-tetradecanolyphorbol-13-acetate (TPA)-induced protein phosphorylation in human myeloblastic leukemia ML-1 cells. *Anticancer Res.* 11:1517–1522.

Constantine, J. W., and Lebel, W. S. 1979. Histamine release in dogs by Emulphor EL620. *Experentia* 35:338–339.

Coppi, G., Bornardi, G., and Casadio, S. 1971. Antidiuretic effects of Cremorphor EL in rats. *Toxicol. Appl. Pharmacol.* 19:721–722.

Cosmetic, Toiletry, And Fragrance Association (CTFA). 1976a. Acute oral toxicity of 3.0% PEG-60 Hydrogenated Castor Oil (RI 0547), Test No. 16-072. Unpublished data submitted by CTFA (1 page).*

CTFA. 1976b. Primary skin irritation of 3.0% PEG-60 Hydrogenated Castor Oil (RI 0547), Test No. 08-179. Unpublished data submitted by CTFA (1 page).*

CTFA. 1976c. Eye irritation of 3.0% PEG-60 Hydrogenated Castor Oil (RI 0547), Test No. 28-035. Unpublished data submitted by CTFA (1 page).*

CTFA. 1976d. Allergic contact sensitization test of 12G/66171-04 containing 3.0% PEG-60 Hydrogenated Castor Oil. Unpublished data submitted by CTFA (9 pages).*

CTFA. 1977a. Thirteen week subacute dermal toxicity study in female ChR-CD rats, night cream containing 3.0% PEG-60 Hydrogenated Castor Oil. Unpublished data submitted by CTFA (9 pages).*

CTFA. 1977b. Allergic contact sensitization test of 10767-11 containing 0.05% PEG-40 Hydrogenated Castor Oil. Unpublished data submitted by CTFA (9 pages).*

CTFA. 1981. Clinical evaluation report: Human patch test of roll-on deodorant 20851-34 containing 0.25% PEG-40 Hydrogenated Castor Oil. Unpublished data submitted by CTFA (1 page).*

CTFA. 1982a. Acute oral toxicity of 2.0% PEG-25 Hydrogenated Castor Oil (RI 0562), Test No. 34-123. Unpublished data submitted by CTFA (1 page).*

CTFA. 1982b. Acute oral toxicity of 2.5% PEG-40 Hydrogenated Castor Oil (RI 0538), Test No. 34-054. Unpublished data submitted by CTFA (1 page).*

CTFA. 1982c. Primary skin irritation of 2.0% PEG-25 Hydrogenated Castor Oil (RI 0562), Test No. 14-001. Unpublished data submitted by CTFA (1 page).*

CTFA. 1982d. Primary skin irritation of 0.25% PEG-40 Hydrogenated Castor Oil (RI 0538), Test No. 13-178. Unpublished data submitted by CTFA (1 page).*

CTFA. 1982e. Eye irritation of 2.0% PEG-25 Hydrogenated Castor Oil (RI 0562), Test No. 53-001. Unpublished data submitted by CTFA (1 page).*

CTFA. 1982f. Eye irritation of 0.25% PEG-40 Hydrogenated Castor Oil (RI 0538), Test No. 53-014. Unpublished data submitted by CTFA (1 page).*

CTFA. 1982g. Clinical evaluation report: Human patch test of toner containing 2.0% PEG-25 Hydrogenated Castor Oil. Unpublished data submitted by CTFA (1 page).*

CTFA. 1982h. Allergic contact sensitization test of 14A/Roll-on deodorant 20851-34 containing 0.25% PEG-40 Hydrogenated Castor Oil (RI 0538). Unpublished data submitted by CTFA (7 pages).*

CTFA. 1984. 13 week subchronic dermal toxicity study of formula 20851-34 containing 0.25% PEG-40 Hydrogenated Castor Oil (RI 0538). Unpublished data submitted by CTFA (19 pages).*

Cusic, A. M., and Dagg, C. P. 1984. Teratogenesis of retinoic acid in two strains of mice. *J. Alabama Acad. Sci.* 55:106–118.

Cusic, A. M., and Dagg, C. P. 1985. Spontaneous and retinoic acid-induced postaxial polydactyly in mice. *Teratology* 31:49–59.

de la Rubia, J., Grau, E., Montserrat, I., et al. 1989. Anaphylactic shock and vitamin K_1. *Ann. Intern. Med.* 110:943.

Descotes, J., Tachon, P., Laschi-Locquerie, A., et al. 1983. Adjuvancy of Cremophor EL in rodents. *Int. Arch. Allergy Appl. Immun.* 72:287–288.

Doenicke, A., Lorenz, W., Beigl, R., et al. 1973. Histamine release after intravenous application of short-acting hypnotics. *Brit. J. Anaesth.* 45:1097–1104.

Draize, J. H., Woodard, G., Calvery, H. O. 1944. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. *J. Pharmacol. Exp. Ther.* 82:377–390.

Ennis, M., Lorenz, W., and Gerland, W. 1986. Modulation of histamine release from rat peritoneal mast cells by noncytotoxic concentrations of the detergents Cremophor EL (oxethylated castor oil) and Triton X100. A possible explanation for unexpected adverse drug reactions. *Agents Actions* 18:235–238.

Ennis, M., Lorenz, W., Kapp, B., et al. 1985. Comparison of the histamine-releasing activity of cremophor EL and some of its derivatives in two experimental models: The in vivo anaesthetized dog and in vitro rat peritoneal mast cells. *Agents Actions* 16:265–268.

Federal Register. January 28, 1992. Modification in voluntary filing of cosmetic product ingredient and cosmetic raw material composition statements. Final rule. 57:3128–3130.

Fiala, E. S., Czerniak, R., Castonguay, A., et al. 1987. Assay of 1-nitropropane, 2-nitropropane, 1-azoxypropane and 2-azoxypropane for carcinogenicity by gavage in Sprague-Dawley rats. *Carcinogenesis* 8:1947–1949.

Food and Drug Administration (FDA). 1984. Cosmetic product formulation and frequency of use data. *FDA database.* Washington, D.C.: FDA.

FDA. 1995. Frequency of use of cosmetic ingredients. *FDA database.* Washington, D.C.: FDA.

Friche, E., Jensen, P. B., Sehested, M., et al. 1990. The solvents Cremophor EL and Tween 80 modulate daunorubicin resistance in the multidrug resistant Ehrlich ascites tumor. *Cancer Comm.* 2:297–303.

Friedman, L. S., Dienstag, J. L., Nelson, P. W., et al. 1985. Anaphylactic reaction and cardiopulmonary arrest following intravenous cyclosporine. *Am. J. Med.* 78:343–345.

Gaudy, J. H., Sicard, J. F., Lhoste, F., et al. 1987. The effects of Cremophor EL in the anaesthetized dog. *Can. J. Anaesth.* 34;122–129.

Glen, J. B., Davies, G. E., Thomson, D. S., et al. 1979. An animal model for the investigation of adverse responses to i.v. anaesthetic agents and their solvents. *Br. J. Anaesth.* 51:819–827.

Hacker, M., Koeferl, M., Hong, C. B., et al. 1981. Cremophor and Emulphor induced alterations of serum lipids and lipoprotein electrophoretic patterns of dogs. *Res. Comm. Chem. Pathol. Pharmacol.* 31:119–128.

Hill Top Research. 1976. The study of cumulative irritant properties of a series of test materials, 12G/66171-04, containing 3.0% PEG-60 Hydrogenated Castor Oil (0547). Unpublished data submitted by CTFA (6 pages).*

Hirsch, S., Besarab, A., Jarrell, B. E., et al. 1987. Acute nephrotoxicity following intravenous cyclosporine. *Transplant. Proc.* 19:1387–1390.

Howrie, D. L., Ptachcinski, R. J., Griffith, B. P., et al. 1985. Anaphylactoid reactions associated with parenteral cyclosporine use: Possible role of Cremophor EL. *Drug Intell. Clin. Pharm.* 19:425–427.

Hüttel, M. S., Olessen, A. A., Stoffersen, E. 1980. Complement-mediated reactions to diazepam with cremophore as solvent (Stesolid MR). *Br. J. Anaesthe.* 52:77–79.

Industrial Biology and Research Testing Laboratories. No date, a. Ninety day feeding study in rats with General Aniline and Film Corporation—Emulphor EL-719. (Submitted by FDA in response to FOI request.)*

Industrial Biology and Research Testing Laboratories. No date, b. Ninety day feeding study in dogs with General Aniline and Film Corporation—Emulphor EL-719. (Submitted by FDA in response to FOI request.)*

Jones, S. K., and Kennedy, C. T. C. 1988. Contact dermatitis from Eumulgin RO/40, an emulsifier in Hioxyl cream. *Contact Derm.* 18:108–110.

Kahan, B. D., Wideman, C. A., Flechner, S., et al. 1984. Anaphylactic reaction to intravenous cyclosporin. Lancet 1:52.

Kongshaug, M., Cheng, L. S., Moan, J., et al. 1991. Interaction of Cremophor EL with human plasma. *Int. J. Biochem.* 23:473–478.

Kortselius, M. J. H. 1978. Mutagenicity of BCNU and related chloroethylnitrosoureas in *Drosophila. Mutat. Res.* 57:297–305.

Lane, R. W., Riddle, B. L., and Borzelleca, J. F. 1982. Effects of 1,2-dichloroethane and 1,1,1-trichloroethane in drinking water on reproduction and development in mice. *Toxicol. Appl. Pharmacol.* 63:409–421.

Langendorf, O. 1935. Untersuchungen am uberlebender Saugertierherzen. *Pfluger's Archiv.* 61:291–332.

Lefrere, J. J., and Girot, R. 1987. Acute cardiovascular collapse during intravenous vitamin K_1 injection. *Thromb. Haemostasis* 58:790.

Leunissen, K. M. L., Waterval, P. W. G., and Van Hooff, J. P. 1985. Anaphylactic reaction to intravenous cyclosporine. *Lancet* 1:636.

Lorenz, W. 1975. Histamine release in man. *Agents Actions* 5:402–416.

Lorenz, W., Reimann, H. J., Schmal, A., et al. 1977. Histamine release in dogs by Cremophor EL and its derivatives: Oxethylated oleic acid is the most effective constituent. *Agents Actions* 7:63–67.

Lorenz, W., Schmal, A., Schult, H., et al. 1982. Histamine release and hypotensive reactions in dogs by solubilizing agents and fatty acids: Analysis of various components in cremophor EL and development of a compound with reduced toxicity. *Agents Actions* 12:64–80.

Machemer, L., and Lorke, D. 1978. Mutagenicity studies with praziquantel, a new anthelmintic drug, in mammalian systems. *Arch. Toxicol.* 39:187–197.

Magalini, S. C., Nanni, G., Agnes, S., et al. 1986. Anaphylactic reaction to first exposure to cyclosporine. *Transplantation* 42:443–444.

Mankad, P., Spatenka, J., Slavik, Z., et al. 1992. Acute effects of cyclosporin and Cremophor EL on endothelial function and vascular smooth msucle in the isolated rat heart. *Cardiovasc Drugs Ther.* 6:77–83.

Nässberger, L. 1990. Effect of cyclosporin A and different vehicles on ATP production and mitochondria isolated from the rat kidney cortex. *Pharm. Toxicol.* 67:147–150.

Nässberger, L., Bergstrand, A., Depierre, J. W. 1991. An electron and fluorescence microscopic study of LLC-PK_1 cells, a kidney epithelial cell line: Normal morphology and cyclosporin A- and cremophor-induced alterations. *Int. J. Exp. Path.* 72:365–378.

Nikitakis, J. M., and McEwen, G. N., Jr., 1990. PEG Castor Oil entry in *CTFA Compendium of Cosmetic Ingredient Composition. Descriptions I.* Washington: The Cosmetic, Toiletry, and Fragrance Association.

O'Hara, T. M., Borzelleca, J. F., Clarke, E. C., et al. 1989. A $CCl_4/CHCl_3$ interaction study in isolated hepatocytes: Selection of a vehicle. *Fund. Appl. Toxicol.* 13:605–615.

Product Safety Labs. 1988. FHSA Primary eye irritation test with polyoxyethylene (5) hydrogenated castor oil in rabbits. NTIS Report No. OTS0539986.

Ptachcinski, R. J., Gray, J., Venkataramanan, R., et al. 1985. Anaphylactic reaction to intravenous cyclosporin. *Lancet* 1:636–637.

Radford, S. G., Lockyer, J. A., and Simpson, P. J. 1982. Immunological aspects of adverse reactions to Altheisn. *Br. J. Anaesth.* 54:859–864.

Rich, E. C., and Drage, C. W. 1982. Severe complications of intravenous phytonadione therapy. *Postgrad. Med.* 72:303–306.

Robinson, M., Bull, R. J., Olson, G. R., et al. 1989. Carcinogenic activity associated with halogenated acetones and acroleins in the mouse skin assay. *Cancer Lett.* 48:197–203.

Robinson, M., Laurie, R. D., Bull, R. J., et al. 1987. Carcinogenic effects on A/J mice of particulate of a coal tar paint used in potable water systems. *Cancer Lett.* 34:49–54.

Roman, I. D., Monte, M. J., Esteller, A., et al. 1989. Cholestasis in the rat by means of intravenous administration of cyclosporine vehicle, Cremophor EL. *Transplantation* 48:554–558.

Schuurhuis, G. J., Broxterman, H. J., Pinedo, H. M., et al. 1990. The polyoxyethylene castor oil Cremophor EL modifies multidrug resistance. *Br. J. Cancer* 62:591–594.

Siddal, S. J., Martin, J., Nunn, A. J. 1989. Anaphylactic reactions to teniposide. *Lancet* 1:394.

Smolinske, S. C. 1992. *Handbook of Food, Drug, and Cosmetic Excipients.* 279–293. Boca Raton, FL: CRC Press.

Sokol, P. P., Capodagli, L. C., Dixon, M., et al. 1990. Cyclosporin A and vehicle toxicity in primary cultures of rabbit renal proximal tubule cells. *Am. J. Physiol.* 259:C879–903.

Tachon, P., Descotes, J., Laschi-Loquerie, A., et al. 1983. Assessment of the allergenic potential of althesin and its constituents. *Br. J. Anaesth.* 55:715–717.

Thiel, G., Hermle, M., and Brunner, F. P. 1986. Acutely impaired renal function during intravenous administration of cyclosporine A: A cremophore side-effect. *Clin. Nephrol.* 25:S40–42.

Thliveris, J. A., Yatscoff, R. W., Lukowski, M. P., et al. 1991. Chronic cyclosporin nephrotoxicity: A rabbit model. *Nephron.* 57:470–476.

Uhing, M. R., Goldman, A. S., and Goto, M. P. 1993. Cyclosporin A-induced embryopathy in embryo culture is mediated through inhibition of the arachidonic acid pathway. *Proc. Soc. Exp. Biol. Med.* 202:307–312.

University Clinic Eppendorf. 1951–1954. Testing for skin compatibility. (Submitted by FDA in response to FOI request.)*

Van Hooff, J. P., Bessems, P., Beuman, G. H., et al. 1987. Absence of allergic reaction to cyclosporin capsules in patient allergic to standard oral and intravenous solution of cyclosporin. *Lancet* 2:1456.

Verani, R. 1986. Cyclosporine nephrotoxicity in the Fischer rat. *Clin. Nephrol.* 25:S9–13.

Villeneuve, D. C., Chu, I., Secours, V. E., et al. 1985. Results of a 90-day toxicity study on 1,2,3- and 1,1,2-Trichloropropane administered via the drinking water. *Sci. Total Environ.* 47:421–426.

Watkins, J. 1986. The allergic reaction to intravenous induction agents. *Br. J. Hosp. Med.* 36:45–48.

Watkins, J., Clark, A., Appleyard, T. N., et al. 1976. Immune-mediated reactions to Althesin (alphaxalone). *Br. J. Anaesth.* 48:881–886.

Wenninger, J. A., and McEwen, G. N., Jr., 1995a. *International Cosmetic Ingredient Dictionary*, 6th ed. vol. 1. 479–481, 684–685, 703. Washington: The Cosmetic, Toiletry, and Fragrance Association.

Wenninger, J. A., and McEwen, G. N., Jr., 1995b. *CTFA Cosmetic Ingredient Handbook*, 3rd ed. 279–280, 493–494, 507. Washington, D.C., The Cosmetic, Toiletry, and Fragrance Association.

Woodcock, D. M., Jefferson, S., Linsenmeyer, M. E., et al. 1990. Reversal of the multidrug resistance phenotype with Cremophor EL, a common vehicle for water-insoluble vitamins and drugs. *Cancer Res.* 50:4199–4203.

Woodcock, D. M., Linsenmeyer, M. E., Chojnowski, G., et al. 1992. Reversal of multidrug resistance by surfactants. *Br. J. Cancer* 66:62–68.

Yalabik-Kas, H. S., Bulut, F., and Hincal, A. A. 1982. Some properties of an ethoxylated caster oil and ethoxylated oleyl alcohol. *Drug Dev. Ind. Pharm.* 8:383–396.

Zhao, F. K., Chuang, L. F., Israel, M., et al., 1989. Cremophor EL, a widely used parenteral vehicle, is a potent inhibitor of protein kinase C. *Biochem. Biophys. Res. Comm.* 159:1359–1367.

* Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Washington, DC 20036.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: April 24, 2012

SUBJECT: Concentration of Use by FDA Product Category: PEGylated Castor Oil Ingredients

Concentration of use by FDA product category for PEGylated oil ingredients included in the January 2012 concentration of use survey.

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Concentration of Use By FDA Product Category*

PEG-30 Castor Oil
PEG-33 Castor Oil
PEG-35 Castor Oil
PEG-36 Castor Oil
PEG-40 Castor Oil
PEG-40 Hydrogenated Castor Oil
PEG-30 Hydrogenated Castor Oil
PEG-2 Castor Oil
PEG-3 Castor Oil
PEG-4 Castor Oil
PEG-5 Castor Oil
PEG-8 Castor Oil
PEG-9 Castor Oil
PEG-10 Castor Oil
PEG-11 Castor Oil
PEG-15 Castor Oil
PEG-16 Castor Oil
PEG-20 Castor Oil
PEG-25 Castor Oil
PEG-26 Castor Oil
PEG-29 Castor Oil
PEG-44 Castor Oil
PEG-50 Castor Oil
PEG-54 Castor Oil
PEG-55 Castor Oil
PEG-60 Castor Oil
PEG-75 Castor Oil
PEG-80 Castor Oil
PEG-100 Castor Oil
PEG-200 Castor Oil
PEG-2 Hydrogenated Castor Oil
PEG-5 Hydrogenated Castor Oil
PEG-6 Hydrogenated Castor Oil
PEG-7 Hydrogenated Castor Oil
PEG-8 Hydrogenated Castor Oil
PEG-10 Hydrogenated Castor Oil
PEG-16 Hydrogenated Castor Oil
PEG-20 Hydrogenated Castor Oil
PEG-25 Hydrogenated Castor Oil
PEG-35 Hydrogenated Castor Oil
PEG-45 Hydrogenated Castor Oil
PEG-50 Hydrogenated Castor Oil
PEG-54 Hydrogenated Castor Oil
PEG-55 Hydrogenated Castor Oil
PEG-60 Hydrogenated Castor Oil
PEG-65 Hydrogenated Castor Oil
PEG-80 Hydrogenated Castor Oil
PEG-100 Hydrogenated Castor Oil
PEG-200 Hydrogenated Castor Oil
Hydrogenated Castor Oil PEG-8 Esters

Ingredient	Product Category	Maximum Concentration of Use
PEG-30 Castor Oil	Shampoos (noncoloring)	0.1%
PEG-35 Castor Oil	Hair conditioners	0.001-0.4%
PEG-35 Castor Oil	Permanent waves	1%
PEG-35 Castor Oil	Shampoos (noncoloring)	0.004-0.4%
PEG-35 Castor Oil	Tonics, dressings and other hair grooming aids	0.2%
PEG-35 Castor Oil	Wave sets	0.2-1%
PEG-35 Castor Oil	Other hair preparations (noncoloring)	1%
PEG-35 Castor Oil	Other hair coloring preparations	0.2-0.4%
PEG-35 Castor Oil	Other personal cleanliness products	0.005%
PEG-35 Castor Oil	Skin cleansing (cold creams, cleansing lotions, liquids and pads_	0.005%
PEG-35 Castor Oil	Face and neck creams, lotions and powders not spray	0.005%
PEG-40 Hydrogenated Castor Oil	Baby lotions, oils and creams (not powder)	2%

PEG-40 Hydrogenated Castor Oil	Other baby products not spray detangling spray	 4% 0.5%
PEG-40 Hydrogenated Castor Oil	Bath oils, tablets and salts	0.001-0.2%
PEG-40 Hydrogenated Castor Oil	Bubble baths	2-5%
PEG-40 Hydrogenated Castor Oil	Other bath preparations	5%
PEG-40 Hydrogenated Castor Oil	Eye liner	0.05-3%
PEG-40 Hydrogenated Castor Oil	Eye shadow	0.7-2%
PEG-40 Hydrogenated Castor Oil	Eye makeup remover	2%
PEG-40 Hydrogenated Castor Oil	Mascara	0.002-15%
PEG-40 Hydrogenated Castor Oil	Other eye makeup preparations	0.2%
PEG-40 Hydrogenated Castor Oil	Colognes and toilet waters	0.07-10%
PEG-40 Hydrogenated Castor Oil	Perfumes	0.03-6%
PEG-40 Hydrogenated Castor Oil	Powders (dusting and talcum)	0.002%
PEG-40 Hydrogenated Castor Oil	Other fragrance preparations spray pump spray	2% 0.003% 6%
PEG-40 Hydrogenated Castor Oil	Hair conditioners	0.008-2%
PEG-40 Hydrogenated Castor Oil	Hair sprays aerosols pump sprays	 0.02-0.4% 0.2-0.7%
PEG-40 Hydrogenated Castor Oil	Hair straighteners	0.3-2%
PEG-40 Hydrogenated Castor Oil	Rinses (noncoloring)	1%
PEG-40 Hydrogenated Castor Oil	Shampoos (noncoloring)	0.008-3%
PEG-40 Hydrogenated Castor Oil	Tonics, dressings and other hair grooming aids not spray spray	0.5-22% 0.02-0.6% 0.5%
PEG-40 Hydrogenated Castor Oil	Other hair preparations (noncoloring)	0.2-2%
PEG-40 Hydrogenated Castor Oil	Hair dyes and colors (all types requiring caution statement and patch test)	0.06-3%
PEG-40 Hydrogenated Castor Oil	Hair rinses (coloring)	2%
PEG-40 Hydrogenated Castor Oil	Other hair coloring preparation	14%
PEG-40 Hydrogenated Castor Oil	Foundations	0.3-2%
PEG-40 Hydrogenated Castor Oil	Lipstick	2%

PEG-40 Hydrogenated Castor Oil	Basecoats and undercoats (manicuring preparations)	0.8%
PEG-40 Hydrogenated Castor Oil	Dentifrices (aerosol, liquid, pastes and powders)	3%
PEG-40 Hydrogenated Castor Oil	Mouthwashes and breath fresheners (liquids and sprays)	0.9-4%
PEG-40 Hydrogenated Castor Oil	Bath soaps and detergents	0.008-9%
PEG-40 Hydrogenated Castor Oil	Deodorants not spray aerosol	 0.02-1% 4%
PEG-40 Hydrogenated Castor Oil	Feminine hygiene deodorants	0.1%
PEG-40 Hydrogenated Castor Oil	Other personal cleanliness products	0.002-10%
PEG-40 Hydrogenated Castor Oil	Aftershave lotions	0.6-3%
PEG-40 Hydrogenated Castor Oil	Shaving cream (aerosol, brushless and lather)	0.002-2%
PEG-40 Hydrogenated Castor Oil	Shaving soap (cakes, sticks, etc.)	0.001%
PEG-40 Hydrogenated Castor Oil	Other shaving preparations	2%
PEG-40 Hydrogenated Castor Oil	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.00007-2%
PEG-40 Hydrogenated Castor Oil	Depilatories	4%
PEG-40 Hydrogenated Castor Oil	Face and neck creams, lotions and powders not spray	 0.1-3%
PEG-40 Hydrogenated Castor Oil	Body and hand creams, lotions and powders not spray spray	 0.03-10% 3%
PEG-40 Hydrogenated Castor Oil	Foot powders and sprays sprays	 3%
PEG-40 Hydrogenated Castor Oil	Moisturizing creams, lotions and powders not spray	 0.0007-2%
PEG-40 Hydrogenated Castor Oil	Night creams, lotions and powders not spray	 0.0007%
PEG-40 Hydrogenated Castor Oil	Paste masks and mud packs	0.5-2%
PEG-40 Hydrogenated Castor Oil	Skin fresheners spray	0.03-2% 2%
PEG-40 Hydrogenated Castor Oil	Other skin care preparations	0.3-8%
PEG-40 Hydrogenated Castor Oil	Suntan gels, creams and liquids not spray	 0.2%

PEG-40 Hydrogenated Castor Oil	Indoor tanning preparations	0.1%
PEG-40 Hydrogenated Castor Oil	Other suntan preparations	1%
PEG-30 Hydrogenated Castor Oil	Nail polish and enamel	0.06%
PEG-30 Hydrogenated Castor Oil	Bath soaps and detergents	10%
PEG-30 Hydrogenated Castor Oil	Shaving cream (aerosol, brushless and lather)	2%
PEG-30 Hydrogenated Castor Oil	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	6%
PEG-30 Hydrogenated Castor Oil	Face and neck creams, lotions and powders not spray	 2%
PEG-9 Castor Oil	Tonics, dressings and other hair grooming aids	0.3%
PEG-25 Castor Oil	Hair spray pump spray	 3%
PEG-25 Castor Oil	Tonics, dressings and other hair grooming aids	17%
PEG-60 Castor Oil	Bath oils, tablets and salts	6%
PEG-60 Castor Oil	Eye lotion	0.08-1%
PEG-60 Castor Oil	Mascara	0.4%
PEG-60 Castor Oil	Perfumes	4%
PEG-60 Castor Oil	Powders (dusting and talcum)	0.2%
PEG-60 Castor Oil	Other fragrance preparations	4%
PEG-60 Castor Oil	Hair conditioners	1-9%
PEG-60 Castor Oil	Hair sprays aerosol pump spray	 16% 0.5%
PEG-60 Castor Oil	Hair straighteners	8%
PEG-60 Castor Oil	Permanent waves	9%
PEG-60 Castor Oil	Rinses (noncoloring)	2%
PEG-60 Castor Oil	Shampoos (noncoloring)	4-9%
PEG-60 Castor Oil	Tonics, dressings and other hair grooming aids	0.6-23%
PEG-60 Castor Oil	Wave sets	0.5%
PEG-60 Castor Oil	Hair dyes and colors (all types requiring caution statement and patch test)	8%
PEG-60 Castor Oil	Hair tints	0.6%

PEG-60 Castor Oil	Blushers (all types)	0.1%
PEG-60 Castor Oil	Face powders	0.2%
PEG-60 Castor Oil	Foundations	0.2-2%
PEG-60 Castor Oil	Lipstick	0.06-0.3%
PEG-60 Castor Oil	Makeup bases	1%
PEG-60 Castor Oil	Mouthwashes and breath fresheners	2%
PEG-60 Castor Oil	Deodorants not spray aerosol	 0.5% 0.04%
PEG-60 Castor Oil	Aftershave lotions	1%
PEG-60 Castor Oil	Shaving cream (aerosol, brushless and lather)	0.6%
PEG-60 Castor Oil	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.002-11%
PEG-60 Castor Oil	Face and neck creams, lotions and powders not spray spray	 1-4% 0.4%
PEG-60 Castor Oil	Body and hand creams, lotions and powders not spray	 4%
PEG-60 Castor Oil	Moisturizing creams, lotions and powders not spray	 0.8%
PEG-60 Castor Oil	Paste masks and mud packs	1%
PEG-7 Hydrogenated Castor Oil	Eye liner	5%
PEG-7 Hydrogenated Castor Oil	Other hair preparations (noncoloring)	0.05%
PEG-7 Hydrogenated Castor Oil	Lipstick	8%
PEG-7 Hydrogenated Castor Oil	Aftershave lotions	2%
PEG-7 Hydrogenated Castor Oil	Night creams, lotions and powders not spray	 0.6%
PEG-10 Hydrogenated Castor Oil	Face and neck creams, lotions and powders not spray	 3%
PEG-20 Hydrogenated Castor Oil	Makeup bases	0.1%
PEG-20 Hydrogenated Castor Oil	Face and neck cream, lotions and powders not spray	 0.05-0.5%
PEG-20 Hydrogenated Castor Oil	Body and hand creams, lotions and powders not spray	 0.1%

PEG-20 Hydrogenated Castor Oil	Moisturizing creams, lotions and powders not spray	 0.5%
PEG-25 Hydrogenated Castor Oil	Tonics, dressings and other hair grooming aids	3-23%
PEG-25 Hydrogenated Castor Oil	Aftershave lotions	2%
PEG-25 Hydrogenated Castor Oil	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.3%
PEG-25 Hydrogenated Castor Oil	Face and neck creams, lotions and powders not spray	 0.01-1%
PEG-25 Hydrogenated Castor Oil	Body and hand creams, lotions and powders not spray	 0.01%
PEG-50 Hydrogenated Castor Oil	Other hair preparations (noncoloring)	0.2%
PEG-60 Hydrogenated Castor Oil	Eyebrow pencil	3%
PEG-60 Hydrogenated Castor Oil	Eyeliner	5%
PEG-60 Hydrogenated Castor Oil	Mascara	3%
PEG-60 Hydrogenated Castor Oil	Other eye makeup preparations	3%
PEG-60 Hydrogenated Castor Oil	Hair conditioners	0.5%
PEG-60 Hydrogenated Castor Oil	Hair sprays aerosol pump	 0.3% 0.9%
PEG-60 Hydrogenated Castor Oil	Tonics, dressings and other hair grooming aids	0.4-18%
PEG-60 Hydrogenated Castor Oil	Other hair preparations (noncoloring)	0.5-1%
PEG-60 Hydrogenated Castor Oil	Foundations	2%
PEG-60 Hydrogenated Castor Oil	Lipstick	6%
PEG-60 Hydrogenated Castor Oil	Makeup bases	0.4%
PEG-60 Hydrogenated Castor Oil	Nail creams and lotions	3%
PEG-60 Hydrogenated Castor Oil	Bath soaps and detergents	0.5%
PEG-60 Hydrogenated Castor Oil	Other personal cleanliness products	0.004%
PEG-60 Hydrogenated Castor Oil	Aftershave lotions	0.4-3%
PEG-60 Hydrogenated Castor Oil	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.00004-0.3%
PEG-60 Hydrogenated Castor Oil	Face and neck creams, lotions and powders not spray spray	 0.3-3% 1%
PEG-60 Hydrogenated Castor Oil	Body and hand creams, lotions and powders	

	not spray	0.004-2%
PEG-60 Hydrogenated Castor Oil	Moisturizing creams, lotions and powders not spray	0.00004-1%
PEG-60 Hydrogenated Castor Oil	Night creams, lotions and powders not spray	0.04%
PEG-100 Hydrogenated Castor Oil	Bath oils, tablets and salts	4%
PEG-100 Hydrogenated Castor Oil	Other fragrance preparations aerosol	0.3%
PEG-100 Hydrogenated Castor Oil	Tonics, dressings and other hair grooming aids	0.2-3%
PEG-100 Hydrogenated Castor Oil	Lipstick	0.5%
PEG-100 Hydrogenated Castor Oil	Makeup bases	1%
PEG-100 Hydrogenated Castor Oil	Bath soaps and detergents	2%
PEG-100 Hydrogenated Castor Oil	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	1%
PEG-100 Hydrogenated Castor Oil	Face and neck creams, lotions and powders not spray	0.6-1%
PEG-100 Hydrogenated Castor Oil	Body and hand creams, lotions and powders not spray	0.3%
PEG-100 Hydrogenated Castor Oil	Night creams, lotions and powders not spray	0.02%
PEG-100 Hydrogenated Castor Oil	Other skin care preparations	0.2%

*Ingredients found in the title of the table but not in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2012
Table prepared April 24, 2012

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: August 1, 2012

SUBJECT: Concentration of Use by FDA Product Category: PEGylated Oils, April 2012 Survey

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Concentration of Use by FDA Product Cagetogry
PEGylated Oils*

Adansonia Digitata Seed Oil PEG-8 Esters
Almond Oil PEG-6 Esters
Almond Oil PEG-8 Esters
Apricot Kernel Oil PEG-40 Esters
Apricot Kernel Oil PEG-6 Esters
Apricot Kernel Oil PEG-8 Esters
Argan Oil PEG-8 Esters
Avocado Oil PEG-11 Esters
Avocado Oil PEG-8 Esters
Bertholletia Excelsa Seed Oil PEG-8 Esters
Borage Seed Oil PEG-8 Esters
Coconut Oil PEG-10 Esters
Corn Oil PEG-6 Esters
Corn Oil PEG-8 Esters
Grape Seed Oil PEG-8 Esters
Hazel Seed Oil PEG-8 Esters
Hydrogenated Palm/Palm Kernel Oil PEG-6 Esters
Jojoba Oil PEG-150 Esters
Jojoba Oil PEG-8 Esters
Linseed Oil PEG-8 Esters
Macadamia Ternifolia Seed Oil PEG-8 Esters
Mango Seed Oil PEG-70 Esters
Mink Oil PEG-13 Esters
Olive Oil PEG-10 Esters
Olive Oil PEG-6 Esters
Olive Oil PEG-7 Esters
Olive Oil PEG-8 Esters
Orbignya Oleifera Seed Oil PEG-8 Esters
Palm Oil PEG-8 Esters
Passiflora Edulis/Passiflora Incarnata Seed Oils PEG-8 Esters
Peanut Oil PEG-6 Esters
PEG-10 Hydrogenated Castor Oil Isostearate
PEG-10 Hydrogenated Castor Oil Triisostearate
PEG-15 Hydrogenated Castor Oil Isostearate
PEG-15 Hydrogenated Castor Oil Triisostearate
PEG-18 Castor Oil Dioloeate
PEG-20 Hydrogenated Castor Oil Isostearate
PEG-20 Hydrogenated Castor Oil Laurate
PEG-20 Hydrogenated Castor Oil PCA Isostearate
PEG-20 Hydrogenated Castor Oil Triisostearate
PEG-30 Hydrogenated Castor Oil Isostearate
PEG-30 Hydrogenated Castor Oil Laurate
PEG-30 Hydrogenated Castor Oil PCA Isostearate
PEG-30 Hydrogenated Castor Oil Triisostearate
PEG-40 Hydrogenated Castor Oil Isostearate
PEG-40 Hydrogenated Castor Oil Laurate
PEG-40 Hydrogenated Castor Oil PCA Isostearate
PEG-40 Hydrogenated Castor Oil Triisostearate
PEG-5 Hydrogenated Castor Oil Isostearate
PEG-5 Hydrogenated Castor Oil Triisostearate
PEG-50 Hydrogenated Castor Oil Isostearate
PEG-50 Hydrogenated Castor Oil Laurate
PEG-50 Hydrogenated Castor Oil Succinate
PEG-50 Hydrogenated Castor Oil Triisostearate
PEG-58 Hydrogenated Castor Oil Isostearate
PEG-60 Castor Oil Isostearate
PEG-60 Hydrogenated Castor Oil Laurate
PEG-60 Hydrogenated Castor Oil PCA Isostearate
PEG-60 Hydrogenated Castor Oil Triisostearate
PEG-75 Crambe Abyssinica Seed Oil
PEG-75 Meadowfoam Oil
Potassium PEG-50 Hydrogenated Castor Oil Succinate
Pumpkin Seed Oil PEG-8 Esters
Rapeseed Oil PEG-20 Esters
Rapeseed Oil PEG-3 Esters
Raspberry Seed Oil PEG-8 Esters
Safflower Seed Oil PEG-8 Esters
Schinziophyton Rautanenii Kernel Oil PEG-8 Esters
Sclerocarya Birrea Seed Oil PEG-8 Esters
Sesame Seed Oil PEG-8 Esters
Sodium PEG-50 Hydrogenated Castor Oil Succinate
Soybean Oil PEG-20 Esters
Soybean Oil PEG-36 Esters
Soybean Oil PEG-8 Esters
Sunflower Seed Oil PEG-32 Esters
Sunflower Seed Oil PEG-8 Esters
Sweet Almond Oil PEG-8 Esters
Watermelon Seed Oil PEG-8 Esters
Wheat Germ Oil PEG-40 Butyloctanol Esters
Wheat Germ Oil PEG-8 Esters

Ingredient	Product Category	Maximum Concentration of Use
Apricot Kernel Oil PEG-6 Esters	Eye lotion	1%
Apricot Kernel Oil PEG-6 Esters	Face and neck creams, lotions and powders not spray	0.8-1%
Avocado Oil PEG-11 Esters	Tonics, dressings and other hair grooming aids	0.1%
Hydrogenated Palm/Palm Kernel Oil PEG-6 Esters	Eye liner	9-10%
Hydrogenated Palm/Palm Kernel Oil PEG-6 Esters	Eye shadow	24%
Hydrogenated Palm/Palm Kernel Oil PEG-6 Esters	Other eye makeup preparations	11%
Hydrogenated Palm/Palm Kernel Oil PEG-6 Esters	Blushers (all types)	16%
Hydrogenated Palm/Palm Kernel Oil PEG-6 Esters	Face powders	16%
Hydrogenated Palm/Palm Kernel Oil PEG-6 Esters	Suntan gels, creams and liquids not spray	0.6%
Jojoba Oil PEG-8 Esters	Shampoos (noncoloring)	0.5%
Olive Oil PEG-7 Esters	Hair spray pump spray	1%
Olive Oil PEG-7 Esters	Shampoos	0.05-0.4%
Olive Oil PEG-7 Esters	Lipstick	0.9%
Olive Oil PEG-7 Esters	Bath soap and detergents	0.1%
Olive Oil PEG-7 Esters	Other shaving preparations	97%
Olive Oil PEG-7 Esters	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	1-3%
Olive Oil PEG-7 Esters	Body and hand creams, lotions and powders not spray	12%
Olive Oil PEG-7 Esters	Other skin care preparations	3%
Olive Oil PEG-10 Esters	Bath soaps and detergents	0.003-0.009%

Olive Oil PEG-10 Esters	Moisturizing creams, lotions and powders not spray	 0.002%
PEG-40 Hydrogenated Castor Oil Triisostearate	Shampoos (noncoloring)	0.003%
PEG-40 Hydrogenated Castor Oil Triisostearate	Bath soaps and detergents	0.002-0.003%
PEG-50 Hydrogenated Castor Oil Succinate	Eye makeup remover	1%
PEG-50 Hydrogenated Castor Oil Succinate	Tonics, dressings and other hair grooming aids	40%
PEG-75 Meadowfoam Oil	Hair sprays pump spray	 0.08%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2012
Table prepared July 31, 2012

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: March 1, 2012

SUBJECT: Comments on the Draft Report on PEGylated Oils as Used in Cosmetics Prepared for the March 5-6, 2012 CIR Expert Panel Meeting

Chemistry section - There should be an Impurities subsection in the Chemistry section that discusses the potential for 1,4-dioxane to be a contaminant of these ingredients. Please check the USP National Formulary (NF) for PEG-40 Hydrogenated Castor Oil (perhaps others), and include the NF specifications in the Chemistry section.

p.3 - In the last sentence of the Absorption, Distribution, Metabolism, Excretion section, please change "rats of elimination" to "rates of elimination"

p.3 - What was the compound studied in the penetration enhancement study? Currently it states "PEG-40 hydrogenated". Was there any indication about the extent of penetration enhancement by PEG-40 hydrogenated x?

p.4 - As it states that guinea pigs were tested in the skin irritation study, please change "species not specified" to "strain not specified".

p.4 - Please include the route of exposure in the case report.

p.7-12, Table 3 - Please add references to this Table to make it clear which definitions came from the *International Cosmetic Ingredient Dictionary and Handbook.*

Please add a table (or list) of ingredients with no uses reported to the VCRP (or Council concentration of use survey when that information is available).

p.17, reference 8 - Please correct the spelling of "isotertinoin" to "isotretinoin"

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