Safety Assessment of
Styrene and Vinyl-type Styrene Copolymers as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	August 18, 2014
Panel Date:	September 8-9, 2014

The 2014 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst and Bart Heldreth, Ph.D., Chemist.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: August 18, 2014
Subject: Draft Final Report on Styrene and Vinyl-type Styrene Copolymers

A tentative report with a safe as used conclusion was issued at the June 9-10, 2014 CIR Expert Panel meeting. This safety assessment, now a draft final report, is identified as *styren092014_final for posting* in the pdf document. Comments from the Personal Care Products Council (Council) were received during the 60-day comment period, and have been addressed. Additionally, an estrogenic (uterotrophic) assay on polystyrene was received from the National Technical Information Service (NTIS).

Included in this package for your review is the Draft Final Report on Styrene and Vinyl-type Styrene Copolymers, the CIR report history, Literature search strategy, Ingredient Data profile, 2014 FDA VCRP data, Minutes from the June 9-10, 2014 Panel meeting, and Comments from the Council (pcpc1 pdf file). The results (positive) of the uterotrophic assay received from NTIS are summarized in the section on Hormonal Activity in the draft final report.

After reviewing the uterotrophic assay results and other available data, the Panel needs to determine whether a final report with a conclusion stating that the styrene and vinyl-type styrene copolymers are safe in the present practices of use and concentration in cosmetics should be issued.

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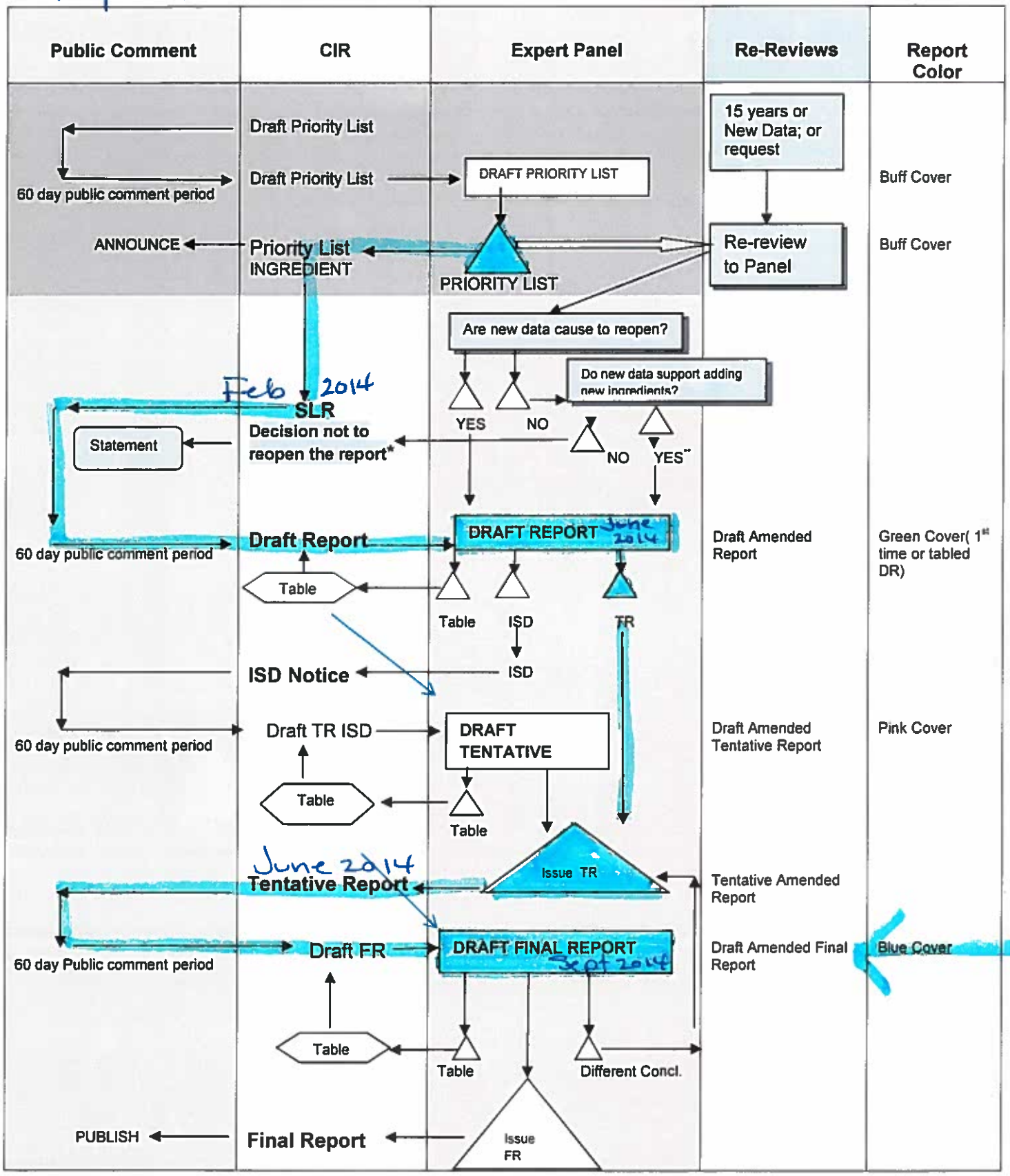
Styrene and Vinyl-type Styrene Copolymers

SAFETY ASSESSMENT FLOW CHART

Sept 2014



*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.

CIR History of:

Styrene and Vinyl-type Styrene Copolymers

A Scientific Literature Review (SLR) Notice was announced on February 21, 2014. Comments and safety test data were received during the 60-day comment period. Use concentration data were received prior to issuance of the SLR.

Draft Report, Belsito and Marks Teams/Panel: June 9-10, 2014

Use concentration data and safety test data received from the Council have been incorporated. Comments received from the Council have been addressed. Additional safety test data received will be included in the wave 2 data submission.

The Panel agreed that percutaneous absorption is not expected, after considering the large sizes of these molecules. It was noted that styrene monomer, a component of all of the copolymers reviewed in this safety assessment, and 1,3-butadiene monomer are classified as carcinogenic in animals and in humans. However, the Panel agreed that any detectable levels of residual styrene or 1,3-butadiene in cosmetic products would be substantially below levels of concern.

The Panel concluded that styrene and vinyl-type styrene copolymers are safe in the present practices of use and concentration in cosmetics, as described in this safety assessment and issued a tentative report.

Draft Final Report, Belsito and Marks Teams/Panel: September 8-9, 2014

Comments on the tentative report received from the Council have been addressed.

Day 1 of the June 9-10, 2014 CIR Expert Panel Meeting – Dr. Belsito's Team

Styrene and Vinyl-type Styrene Copolymers

Anything else? Okay. Well, let's save this puppy -- and styrene. I guess that's why I was thinking of styrene peanuts in ear canals.

DR. LIEBLER: What's that, Don?

DR. KLAASEN: Can't hear you. (Laughter)

DR. BELSITO: Okay, so, new comments. We also got Wave 2 stuff on styrene with --

Thankfully, data on styrene with the highest number of uses: Ethylene/propylene/styrene copolymer, which was nice, something that's so widely used. We got some acute oral; we got ocular irritation, dermal irritation in animals and human sensitization on that one.

And we got a little bit more data on polystyrene, which is used up to 36 percent in rinse-offs; and the styrene/acrylates copolymer that's used 35 percent now in products is the one that was really driving this.

And then we got data on polyacrylates, and that gets back to my point that -- assume that all the data that we got on polyacrylate 18 was with a combination of 18 and 19, but I don't see polyacrylate 19 listed as a cosmetic ingredient. So, I'm wondering why they did these studies on a compound containing a mixture of polyacrylate 18 and 19.

DR. EISENMANN: I'd have to look back, but of the -- these ingredients are, for the most part -- (Microphone problems) Sorry. Some of these ingredients are only sold as mixtures, so if all they're selling is a mixture, then they'll only have data on the mixture; we won't have data on the individual --

MR. JOHNSON: I understand, but if they're selling polyacrylate 18,19 mixture, why is polyacrylate not on the list of things we're reviewing?

DR. EISENMANN: My guess is it's not a styrene-type polymer, that it's a little bit different type of a polymer. I haven't looked it up.

MR. JOHNSON: Okay, I'm just raising the question, because we're looking at data that says polyacrylate 18,19, and I don't see 19 here, and I don't want it to be here next year at this time and someone saying: Oh, we forgot to add polyacrylate 19 and 32.

DR. EISENMANN: Well, my guess is that it doesn't have the styrene in it. That's --

MR. JOHNSON: Okay, I'm just raising the question. If we could make certain of that, though, rather than just guessing?

DR. EISENMANN: Mm-hmm.

MR. JOHNSON: So, I thought we could go with all of the new data safe as used, and the discussion points would be the impurities 1,3-butadiene and styrene, and they're below the threshold of toxicologic concern with these products used as cosmetics. And my only question to Dan was: Are you okay with this entire grouping?

DR. LIEBLER: Yes, I am. I have no problem with the grouping.

DR. SNYDER: So, the sensitization (inaudible) to receive is only up to 15 percent for the ethylene, another 2 percent for the butylene, but it's used up to 35 percent (inaudible).

DR. BELSITO: Yes, but, you know, these are huge molecules. They're not going to get past the stratum corneum, and what you would be concerned about with sensitization would be a residual monomer that might get through, and the residual monomer we're restricting, basically, you know? So --

DR. SNYDER: Okay. And then Wilbur, throughout the document, particularly under --

DR. BELSITO: So, that would be a discussion point.

DR. SNYDER: Yes.

DR. BELSITO: Okay.

DR. SNYDER: Throughout the document under the Toxic Kinetics section, I think we're always talking about 1,3-butadiene, so sometimes you just default to butadiene. I

think it's always 1,3, so I think we should specify that it's 1,3 throughout the report.

And then on reference 36 under the Inhalation Study, did they specify those pulmonary nodules? Otherwise, were those -- they just talked about the number of nodules? It's under Inhalation Polyacrylate. We just list those as number of pulmonary nodules, but we don't -- I mean, we're making an assumption that they were transfer particles and are probably going along with it. If we could make sure that's what those are.

MR. JOHNSON: That raises another question about the -- is that NRC report on carcinogenicity -- it's supposed to be out in September of this year? And was that -- what was the basis for them to do that carcinogenicity study? Was there an issue related to carcinogenicity? So, should we --

DR. SNYDER: It was on 1,3-butadiene --

MR. JOHNSON: Yes. No. It's on styrene.

DR. BELSITO: What page are you on, Dr. Snyder?

DR. SNYDER: Active P (inaudible). It's on page 15 of the report.

MR. JOHNSON: This is carcinogenicity (inaudible)?

DR. SNYDER: Yes. Yes.

MR. JOHNSON: You state that there's a -- regarding two preceding studies of the International Agency for Research on Cancer -- or, where's that at?

DR. WEINTRAUB: It's on page 23.

MR. JOHNSON: 23 of the PDF? So, I wonder if we should -- they must have had a reason why they did that. So, should we -- do we have any idea if that's going to be available in September or -- I'd hate to publish this and then have something come out on that that might be relevant. But this is on?

DR. WEINTRAUB: Yes, the first full paragraph.

MR. JOHNSON: And there's the toxicology program --

DR. BELSITO: The final report will be issued at the end of the project in approximately 24 government months. (Laughter)

DR. BERGFELD: And it says that it's looking at reproductive and developmental outcomes from studies of human exposed -- occupational exposure to styrene. That's -- I'm not sure what page it's on. It's on 23.

DR. SNYDER: Yes, pending estrogenic studies, the carcinogenicity studies, and --

DR. BELSITO: So, what were you thinking, Paul, if it's going to be out in September, table it until then?

DR. SNYDER: Well, yes. I understand what you're saying, that, you know, this could be two years out, but if we had some idea -- is it close? -- or if there's a preliminary report that there were issues or not issues or something. I mean, this seems --

DR. BELSITO: Well, I mean, we know that -- I mean, I think if this were the only data that we were relying on, you know, but where clearly in occupational groups that are breathing this stuff it's an issue. But, again, in the discussion we say, you know, among individuals working in manufacturing of styrene and 1,3- butadiene there are questionable carcinogenic effects. However, at the concentrations of use and polymerized, non-restorable forms, we don't see this as an issue. So, I don't see tabling this to get a document that, quite honestly, I don't think probably will be available until September of 2016. I mean, we can -- like everything else we do, we can put out a little reminder on Wilbur's calendar that once a quarter he checks and sees if that report is out. And if it comes out, we will take a look at it and decide whether it makes a change to what we should do with the document.

MR. JOHNSON: Yes. I can communicate with the National Research Council, but the approximate start date was September of 2012 -- so, 24 months later. So, it could conceivably be available this year.

DR. SNYDER: Yes, that's what I thought.

DR. BELSITO: So, conceivable.

MR. JOHNSON: Yes.

DR. BELSITO: Right. I doubt that though.

MR. JOHNSON: If the start date was as anticipated. So -- but, I can communicate with them and see exactly what the status of that is.

DR. BELSITO: But I don't see the need to hold up this report for that. I mean, I'm not sure why you do, because, I mean, because there's conflicting data, and the data -- I mean, it's just like the hair dye epidemiology, you know? Among hairdressers, there is some data to suggest that there may be a risk, but among consumers there's none.

DR. LIEBLER: So, I approach this a little differently, and I knew, going into this, that styrene would be the dying -- there's plenty of evidence on literature that these are carcinogens in the right circumstances.

MR. JOHNSON: Butadiene for sure.

DR. LIEBLER: Yes, and so what I looked at first was the specification for the monomer impurities of the residual monomers.

DR. BELSITO: Right.

DR. LIEBLER: And there the documentation was actually quite good, and we got a lot of product spec sheets and other -- and it summarized very nicely in the report that these are typically very low. And so I think that that means -- my assessment is that in the products that will be formulated with these polymeric ingredients the levels of these monomers are not significant, and we can handle that in discussion. And in fact I even suggested that the section on carcinogenicity and the monomers be condensed and the main studies that are cited summarized in a table just we talked about with the last document. And you can refer to the ongoing assessment by NRC and the other NTP reports in a paragraph that just summarizes that these are -- you know, that the monomers have been extensively studied and continue to be the subject of study. But that -- so, we recognize that the monomers are of potential concern, but the levels in the finished products or the levels of the ingredients supplied are very low. So, I wouldn't think that even if the NRC comes out with a study that says styrene is surprisingly carcinogenic, I'm not sure that that would cause us to reopen the door in 2016 or whatever would come down the pike.

DR. SNYDER: I mean, it would be nice to know what doses they're testing at, I mean -- because it says -- while I agree we have data on the monomer content, but we state that -- all we do is state that 500 parts per million residuals styrene have been developed, but we don't know what it actually is in some of these compositions. And so, again, if -- well, it depends on what doses they were testing, all concentrations they were testing.

DR. EISENMANN: The NRC is just a relook at data. It's not -- they're not perusing any new information.

DR. SNYDER: True.

DR. BELSITO: Okay, so are we comfortable going with a tentative final safe as used, the butadiene, the styrene below the level of threshold toxicologic concern, the sensitization really not an issue, large molecules not getting passed the stratum corneum, and just having Wilbur put on his reminder list once or twice a year to see if that study has actually been published and bring it back to us so we can look and see if it makes -- give us any reason to reopen that document?

DR. LIEBLER: I'm fine with that.

Day 1 of the June 9-10, 2014 CIR Expert Panel Meeting – Dr. Marks' Team

Styrene and Vinyl-type Styrene Copolymers

So, I will move tomorrow that a final report be issued with a safe conclusion for these peptides. So, we're down -- next ingredient is styrene. And this is the first time we've seen these ingredients.

DR. HILL: Sort of.

DR. MARKS: Okay. Let me see my -- so, this is the first review. I had that there are 35 ingredients and on page five we have the list of them. Do they -- the first thing, obviously, is Tom and Rons, are those 35 okay to be included in this group? And then, obviously, the second is, what do we need? So, let's go to page -- I think page five may be the easiest, and does anybody have a problem with these -- all these ingredients? Should any be deleted?

DR. SLAGA: They seemed okay to me.

DR. MARKS: Or are they close enough chemically to be -- we can read across, because obviously there are the --

DR. SLAGA: There is no data.

DR. MARKS: Yeah, the one where we have the most data looks like the styrene acrylic copolymer, and that's about it. That's -- there's a little scattering data on one or two other ingredients.

DR. HILL: So, I had a problem with mixing styrene and olefin polymers with styrene and acrylate type copolymers because the vinyl group, even though you can't argue that there's a biadnial moiety and acrylates, that's chemically extremely different from the vinyl group and olefins that are used in styrene olefin copolymers. So, I got to thinking when I'm looking at this, well, then, if it's just polymers we're talking about and anything with styrene, that would be like reviewing all the proteins and any of them would have tyrosine in it, you'll combine, which I'm being facetious, I realize, but -- and I guess the other way of looking at it as well, they're polymers, they're not going to be bio-available, so why not put every polymer that there is with molecular weight of, say, 10,000 or above and not nano-size, and review all their safety together, so we had one big document of 2,000 polymers and we're done.

So, the way I would look at it is that any potential sensitization -- and that would be the major issue here -- would be driven by any releasable acrylate type moieties in the ones that have acrylates or acrylimide or acrolein -- not acrolein, the one with the nitryl group, and then the ones that are simple olefin styrene polymers, they have a totally different set of issues, which is probably practically nothing other than styrene toxicology itself and the olefin toxicology. So, I didn't like combining those two groups and I realize that means we don't have a read- across for the styrene olefin polymers and, as far as I'm concerned on that, so be it, and somebody can produce some data.

DR. MARKS: Ron Shank?

DR. SHANK: I can't argue with the chemistry.

DR. HILL: Yeah, you can. But olefins are olefins.

DR. SHANK: The polymers themselves (inaudible), they might be unreactive monomers or --

DR. MARKS: Right, and that's --

DR. SHANK: -- other things.

DR. SLAGA: We already reviewed the acrylate copolymer and said it was safe.

DR. HILL: Did any of those have styrenes in them?

DR. SLAGA: -- but they're not irritating.

DR. HILL: Did any of those have styrene as one of the monomers?

DR. SLAGA: I don't think they have styrene.

DR. HILL: No, I don't think so.

DR. MARKS: So, Bart, do you want to -- so, yeah, these -- we've got a lot of weight to data. Low residual monomers. Yeah, and as you mentioned, Tom, that PVPVA copolymer, we have a conclusion as safe. So, Bart, what do you think about the chemistry of all this business? You put this together, didn't you?

DR. HELDRETH: Yeah, I mean, if -- if there's evidence that these polymers are

smaller, like Dr. Hill was mentioning, than you would expect from styrene or vinyl-type polymers, then that would certainly be a concern, but if these are traditional polymer vinyl-type materials, then it comes down to impurities that are either residuals or they --

DR. SLAGA: The monomers.

DR. HELDRETH: -- non-reactive monomer or if a (inaudible) is used in some large amount and it's getting trapped in there, those types of things would be what we would worry that could potentially (inaudible). I mean, even if (inaudible), they may not be (inaudible). So, those types of things, I think, are the main thing here and that's why --

DR. SLAGA: It's the impurities.

DR. HELDRETH: That's why Wilbur brought in some of the other reports that had acrylates, EVP, so that you could see how he addressed those potential residual monomers, not that there was technically any read across between the acrylates polymers that we looked at before and these polymers, but they had the same -- some of the same monomer overlap concerns.

DR. SLAGA: And the impurities section really emphasized the number of the products, the level of impurities that the styrene and 1,3 (inaudible).

DR. HELDRETH: Right.

DR. SLAGA: I think the maximum was like 500 parts per million on average maybe 100.

DR. HELDRETH: Right. So, I mean, if there's a size concern, I mean, you could certainly have some sort of conclusion that says, well, these are safe or unsafe or whatever as long as the polymer is at least such and such molecular weight or number of repeat units.

DR. HILL: It's not a size concern with the polymer itself. There isn't any of that in this case. At least I don't see anything that suggests to me that there should be. It was just I had problems because I don't know why we're reviewing the ones that are polymers or simple olefins together with the ones that are acrylate based because any concerns that would relate to the ones that are acrylate based probably much more to do with any of the acrylates, and again, any residuals from the chemistry used to make them, which would be different than the chemistry used to make the olefin polymers. The chemistry won't be the same. We don't have a good capsulation of exactly how the polymerization is done, so is it always peroxides that are initiating whether it's acrylate or whether it's olefins? I can't totally get a firm picture because we don't have that across all of these ingredients.

So, I just -- to me, it's muddying the water and I realize if we were to split them into two different groups, which is what I would do, then we have nothing to read across from and the ones that are simple olefin styrene polymers but to me there shouldn't be because it's two sets of issues.

Now, I guess if the acrylate polymers are clean and we can establish that there's no levels of these olefins, like butadiene in particular, that are going to be a problem and I think there's vinyltoluene that's mentioned, we don't have that toxicity -- toxicology captured, but there's probably no significant amount of vinyltoluene in the polymers, then sure we could kind of read across here, but it just bothered me that those were so chemically different that by putting them together and reviewing them we're muddying water that didn't need to be muddied. But I can live with it.

DR. HELDRETH: So, if we had details on manufacturing or residual materials --

DR. HILL: We're not going to get them. We never get them because those processes are proprietary. I think we should be doing a better job beating the bushes for residuals, but the problem is, if you say there's a residual this, then that tells the world how you're -- really, it tells the world how you're making it. So, that's --

MR. JOHNSON: Well, some of the composition data from industry do in fact include the levels of residual monomer --

DR. HILL: Yes.

MR. JOHNSON: -- and trade name materials.

DR. HILL: Yes, but we don't have it for every single one.

MR. JOHNSON: That's true.

DR. HILL: So, our idea is we're trying to read across for things like sensitization, which should -- unless we had something akin to silicosis from inhalation of these

things, which I don't think is the case, then the only issue I could see is any sensitization resulting from release of (inaudible) monomers or reactants in the (inaudible) process.

DR. MARKS: So, let's get back to the -- I hear the olefins you have problems, including grouping that with the acrylates --

DR. HILL: I do.

DR. MARKS: So --

DR. HILL: I might be the only one.

DR. MARKS: Bart, why did you put them together?

DR. HILL: Because they both have (inaudible) moiety (inaudible).

DR. HELDRETH: I mean, as monomers, certainly, I agree with Dr. Hill that we're talking about different materials, but once we're talking about an end product and we're no longer looking at a vinyl type whether it's an olefin or literally a three carbon vinyl group, a lot of those differences disappear in the end product, the intended product.

So, yes, the potential monomers that we need to worry about are different, but there's also a thread -- a similarity through here that they're all styrene monomers that we're going to need to worry about. We're going to need to worry about acrylates in some of those cases and we have previous reports that attend to that. If there's ones in here where there are monomers that we are concerned about and we don't have any previous conclusions or data on, then we could address those as either insufficient data or unsafe or we just don't know.

DR. HILL: So, my objection to the grouping was as much philosophical as it was practical because, again, I could be facetious and say, you know, okay, I realize there's a commonality with styrene. That's like saying we'll review all the proteins that have tyrosine in it. Or we just take the other approach and say, every polymer that has a molecular weight above 10,000 and has no -- actually, it doesn't even have to be that high -- molecular weight above 2,000 and doesn't have nano particulates, we review them all together as one big document, polymers, and be done with it.

DR. MARKS: Ron and Tom?

DR. HILL: Or high molecular weight.

DR. SLAGA: I didn't have any problem. I mean, we're dealing with the final product of a very high molecular weight and the monomers, you know, as long as we deal with the impurities related to the monomers, I think we're all right, be it acrylate or, you know, any of the ones here, the 1,3 butadiene or the styrene.

DR. MARKS: So, why don't we do this? I'm going to be the one presenting this tomorrow. What I'm going to do when it comes to the discussion, Ron Hill, do you want to bring that up?

DR. HILL: I may decide by tomorrow I don't.

DR. MARKS: Okay, but if you do --

DR. HILL: All right, thank you.

DR. MARKS: -- you know, tomorrow's the time to bring it up, early, rather than when we get to the draft final report, and then let's not go back and revisit the olefins and the acrylates at that point. I think we need to commit whether we're going to have all -- is it 30 -- yeah, 30 ingredients. Okay. So, I'm going to put okay at this point and, Ron Hill, you're obviously -- we'll see what the Belsito team thinks. They may be similar, but for this point we're going to consider all.

Now, what needs do we have? We talked a lot about impurities and monomers here. I had the styrene acrylate copolymer irritation sensitization was good, except we didn't know the concentration tested in the sun smears and (inaudible) but then (inaudible) to that, we have irritation sensitization, that was one of the big thing with the sun tran, 100 percent, as well as other polyacrylates with (inaudible) that that was okay. So, I think from an irritation sensitization that it looks okay.

DR. SLAGA: Safe.

DR. MARKS: Safe, well that's -- I have safe with a question mark because I wanted, obviously, your input from --

DR. SLAGA: You have all the impurities, styrene monomer and the one --

DR. MARKS: All the other toxicology, which I look at, but I'm not the expert in that, obviously.

DR. SLAGA: Those generally have to be given in reasonably high concentration to --

DR. MARKS: (Inaudible) it's said there was low residual monomer, that's five parts of (inaudible) in the one, so, yeah, I -- so, safe?

DR. SLAGA: Yes.

MR. JOHNSON: One question that I had beside just giving the composition data, you know, provided, I guess the concentration of the ingredient in question can range anywhere from 26 percent to 90 percent. So, you know, given the composition data provided, are the data on these trade name materials -- can those data be used to evaluate the safety of the individual, INCI name ingredient? And I know that in some cases composition data are provided whereas in other cases, they are not.

DR. SHANK: When we know the concentration, we can use that. If we don't know the concentration, it's not (inaudible).

MR. JOHNSON: Okay.

DR. HILL: Well, you know, that's why -- one of the reasons why I was bothered by grouping together with the acrylates because the big question is -- and I'm not sure we know 100 percent because of the way the definitions are written -- have we captured all of the possible acrylate monomers, in other words, all the potential esters that are there, although it probably doesn't matter what ester -- have we captured them all in terms of sensitivity -- sensitization testing.

Probably we haven't, but again I'm not sure it matters what ester. But it might because usually the way this is going to go with an acrylate is you're going to get a Michael addition to the -- gamma position of the 1,4 unsaturated carbonyl compound and that's (inaudible) that will then be recognized by the immune system.

So, actually, it stays a sterified and generating (inaudible), then it actually could matter what the ester is on the other end. So, have we captured, in terms of sensitization data, the whole range of possible acrylate esters that could appear in these, and I don't think we actually have.

So, if we had data to say it's always below 5 ppm from every vender out there that we never have a cosmetic ingredient where, oops, somebody has 50 ppm of that particular acrylate monomer then that would be one thing. We're not given that data. We don't have that data. And as far as I'm concerned, that's data I'd need to conclude, yes, safe or no, we had a question mark and an issue here on sensitization. And for that matter, it's something that could go on in the mucus membranes where there could be exposure.

DR. MARKS: Well, we have irritation sensitization data on 100 percent of this syntrian as well as other polyacrylates and we have low residual monomer, less than 5 parts per million, so the data we have, I think we have enough to say -- and then we add in this report before us, the draft report, although we don't know the concentrations tested again with a styrene acrylate copolymer's irritation sensitization is okay with sun smears and opulents. So, I thought there was enough in that to say it was safe on the irritation sensitization point of view.

Any other comments? Since a large amount of the discussion talked about impurities and monomers, obviously, Wilbur, that's going to be an important part of the discussion with these since that's what we're really focused on in terms of these are all large molecules and we aren't worried about them, per se, it's residual monomer and any impurity. So, I think we need to capture that in the next -- and you will, obviously, the tentative report.

Is there any guidance, Tom or Rons, that you want to give Wilbur in doing that? Or do you think what we discussed is enough?

DR. SLAGA: I think --

DR. MARKS: Okay. So, tomorrow I'm going to move that a tentative report be issued with a safe conclusion on all 35 of these ingredients and, Ron Hill, feel free to comment in the discussion part of that when it comes up and we'll see where it goes.

Okay. Let's see here. That was -- Wilbur, are off the hot seat now?

MR. JOHNSON: Yeah. I'm cooling off.

DR. MARKS: Well, now you've had a preview. We'll see what the other team feels like.

Day 2 of the June 9-10, 2014 CIR Expert Panel Meeting – Full Panel

Styrene and Vinyl-type Styrene Copolymers

DR. MARKS: This is the first review of the Styrene and vital vinyl type Styrene ingredients. There were 35 of them, which our team felt were okay to be included in this report. After reviewing the data in this report along with the Wave 2 data, we felt we could issue a tentative report with a conclusion of safe.

DR. BELSITO: Second.

DR. BERGFIELD: Any other discussion?

DR. BELSITO: Yes, the discussion needs this to be very bold about the fact that the 1,3 Butadine and Styrene residuals are well below the level of toxicological concern. Otherwise, the discussion -- I mean that's really all we felt needed to be there.

DR. SLAGA: Well even Styrene.

DR. BELSITO: Right. I said 1,3 Butadine and Styrene.

DR. BERGFIELD: Okay, anything else? Seeing no other comment then we'll move this question, safe as stated. All those in favor, please indicate by raising your hands. Thank you, unanimous.

Styrene and Vinyl-type Styrene Copolymers Check List for September, 2014. Analyst – Wilbur Johnson

			Acute toxicity					Repeated dose toxicity				Irritation			Sensitization					
	Skin Penetration	Penetration Enhancement	ADME	Oral	Parenteral	Dermal	Inhale	Oral	Parenteral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Ethylene/Propylene/Styrene Copolymer																				
Butylene/Ethylene/Styrene Copolymer																				
Acrylates/Ethylhexyl Acrylate/Styrene Copolymer																				
Butyl Acrylate/Styrene Copolymer																				
C4-6 Olefin/Styrene Copolymer																				
C5-6 Olefin/Styrene Copolymer																				
Hydrogenated Butadiene/ Isoprene/Styrene Copolymer																				
Hydrogenated Butylene/ Ethylene/Styrene Copolymer																				
Hydrogenated Ethylene/ Propylene/Styrene Copolymer																				
Hydrogenated Styrene/Butadiene Copolymer																				
Hydrogenated Styrene/Isoprene Copolymer																				
Isobutylene/Styrene Copolymer																				
Methacrylic Acid/Styrene/VP Copolymer																				
Methylstyrene/Vinyltoluene Copolymer																				
Polystyrene																		X	X	
Polystyrene/Hydrogenated Polyisopentene Copolymer																				
Sodium Methacrylate/Styrene Copolymer																				
Sodium Styrene/Acrylates Copolymer																				
Sodium Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer																				
Styrene/Acrylates Copolymer				X		X	X				X	X	X	X		X		X		X
Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer																				
Styrene/Butadiene Copolymer																			X	
Styrene/Isoprene																				

Styrene and Vinyl-type Styrene Copolymers Check List for September, 2014. Analyst – Wilbur Johnson

			Acute toxicity					Repeated dose toxicity				Irritation			Sensitization					
	Skin Penetration	Penetration Enhancement	ADME	Oral	Parenteral	Dermal	Inhale	Oral	Parenteral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Copolymer																				
Styrene/Methylstyrene Copolymer																				
Styrene/Stearyl Methacrylate Crosspolymer																				
Styrene/VA Copolymer																				
Styrene/VP Copolymer																				
Polyacrylate											X							X	X	
Polyacrylate-2																				
Polyacrylate-5																				
Polyacrylate-12																				
Polyacrylate-15																				
Polyacrylate-16																				
Polyacrylate-18																				
Polyacrylate-21																				
Polyacrylate-30																				

Search Strategy – Styrene and Vinyl-type Styrene Copolymers

12/12-13/13 Search-Pubmed: name +CAS; Search-Scifinder: name
Searches updated (Scifinder) on: 7/28/2014

List of Ingredients:

1. Ethylene/Propylene/Styrene Copolymer
2. Butylene/Ethylene/Styrene Copolymer
3. Acrylates/Ethylhexyl Acrylate/Styrene Copolymer
4. Butyl Acrylate/Styrene Copolymer
5. C4-6 Olefin/Styrene Copolymer
6. C5-6 Olefin/Styrene Copolymer
7. Hydrogenated Butadiene/ Isoprene/Styrene Copolymer
8. Hydrogenated Butylene/ Ethylene/Styrene Copolymer
9. Hydrogenated Ethylene/ Propylene/Styrene Copolymer
10. Hydrogenated Styrene/Butadiene Copolymer
11. Hydrogenated Styrene/Isoprene Copolymer
12. Isobutylene/Styrene Copolymer
13. Methacrylic Acid/Styrene/VP Copolymer
14. Methylstyrene/Vinyltoluene Copolymer
15. Polystyrene
16. Polystyrene/Hydrogenated Polyisopentene Copolymer
17. Sodium Methacrylate/Styrene Copolymer
18. Sodium Styrene/Acrylates Copolymer
19. Sodium Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer
20. Styrene/Acrylates Copolymer
21. Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer
22. Styrene/Butadiene Copolymer
23. Styrene/Isoprene Copolymer
24. Styrene/Methylstyrene Copolymer
25. Styrene/Stearyl Methacrylate Crosspolymer
26. Styrene/VA Copolymer
27. Styrene/VP Copolymer
28. Polyacrylate-2
29. Polyacrylate-5
30. Polyacrylate-12
31. Polyacrylate-15
32. Polyacrylate-16
33. Polyacrylate-18
34. Polyacrylate-21
35. Polyacrylate-30

Safety Assessment of Styrene and Vinyl-type Styrene Copolymers as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	August 18, 2014
Panel Date:	September 8-9, 2014

The 2014 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst and Bart Heldreth, Ph.D., Chemist.

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ABSTRACT: These styrene and vinyl-type styrene copolymers function mostly as viscosity increasing agents, opacifying agents, and film formers in cosmetic products. After considering the large sizes of these molecules, the Panel agreed that percutaneous absorption is not expected. The absence of the potential for percutaneous absorption and the negative results of toxicity tests provided the Panel with a sufficient basis to assess the safety of these polymers as used in cosmetics. The Panel concluded that the 35 styrene and vinyl-type styrene copolymers are safe in the present practices of use and concentration in cosmetics, as described in this safety assessment.

INTRODUCTION

This report presents information relevant to evaluating the safety of styrene and vinyl-type styrene copolymers as used in cosmetics. Film-former is the most frequent function reported for these ingredients. Other common functions include opacifying agent and viscosity increasing agent. Given the toxicity of two of the component monomers present in styrene and vinyl-type styrene copolymers, styrene and 1,3-butadiene, carcinogenicity data on these monomers are included. Styrene is a component of all of the copolymers reviewed in this safety assessment; however, butadiene monomer is a component of only three copolymers included in this review.

CHEMISTRY

Definition and Structure

Polystyrene is the polymerization product of vinylbenzene (a.k.a. styrene). The other ingredients in this report are all vinyl-type copolymers with vinylbenzene. The term "vinyl-type copolymers" means that all of the monomers, utilized to make these polymer ingredients, have in common an ethylene unit whose pi electrons are directly involved in the polymerization process. Typically, a catalyst is utilized to initiate the polymerization.[1] There is a large multitude of relevant initiating catalysts, ranging from UV light to Ziegler-Natta-type catalysts, which can result in a variety of differences in the characteristics (e.g. crystallinity and resultant hardness) of the copolymer formed. The synthesis of these ingredients is typically carried out in one or more organic solvents, with one or more catalysts.

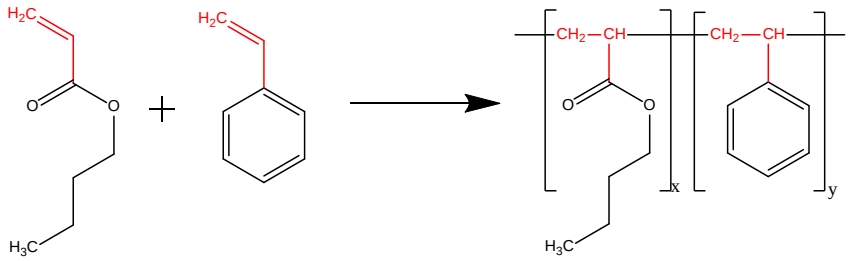


Figure 1. Butylacrylate/Styrene Copolymer

These ingredients are high molecular weight, large molecular volume, inert polymers. While not truly soluble, these ingredients may be swellable in certain organic solvents.

The molecular structures and definitions of styrene and vinyl-type styrene copolymers are presented in Table 1.[2]

Physical and Chemical Properties

Polystyrene

Properties of polystyrene are presented in Table 2.[3,4,5] Some of the properties include physical state (colorless solid in various forms), molecular mass (10,000 to 300,000), relative density (1.04 to 1.13), melting point (240°C), flash point (345 to 360°C), and auto-ignition temperature (427°C).

The thermal degradation of high impact polystyrene to styrene and other thermal degradation products occurred at a temperature of 250°C.[6] Reportedly, the principal limitations of polystyrene in industry are brittleness, inability to withstand the temperature of boiling water, and poor oil resistance.[7] Thus, polystyrene is often modified, e.g., by copolymerization with acrylonitrile and/or butadiene. Regarding this process, the most common styrene polymers are poly(acrylonitrile-butadiene-styrene) and styrene-butadiene copolymer.

Styrene

Styrene is a component of each styrene and vinyl-type styrene copolymer reviewed in this safety assessment. The vinyl group of styrene is reactive, and styrene polymerizes at a significant rate at room temperature.[8] Polymerization proceeds more rapidly at elevated temperatures or in the presence of many commonly available reagents. Commercially available grades of styrene contain an inhibitor of styrene polymerization (e.g., 4-*t*-butylcatechol). Additionally, upon exposure to light and air, styrene undergoes polymerization and oxidation, with the formation of peroxides.[4] Additional properties of styrene are presented in Table 3.[4]

Styrene-Butadiene Copolymer

Properties of styrene-butadiene copolymer are presented in Table 4.[5]

1,3-Butadiene

Properties of 1,3-butadiene are presented in Table 5.[9]

Composition/Impurities

Polystyrene

Polystyrene is available in the United States in a variety of grades, and the following are considered major grades:[5] crystalline or straight polystyrene, (2) impact-modified grades, which typically contain approximately 5% polybutadiene elastomer, and (3) expandable beads, which contain a small amount of *n*-pentane entrapped in each globule.

During the early years of polystyrene production, the residual monomer content was as high as 2%, and, at the beginning of the 1960's, it was approximately 1%.[10] Since that time, polystyrene grades with concentrations of ≤ 500 ppm residual styrene, have been developed. Additionally, compositon/impurities data from a 2013 safety dossier on a polystyrene trade name material summarized in Table 6 indicates that the residual monomer content of polystyrene is < 5 ppm.

Styrene-Butadiene Copolymer

The following styrene-butadiene copolymers are available in the United States:[5] (1) styrene-butadiene elastomers (commonly called SBR, or styrene-butadiene rubber), (2) styrene block polymers with butadiene, and (3) styrene-butadiene copolymer latexes. Dry SBR (produced by emulsion polymerization) contains styrene units (23% to 25%) and butadiene units (75% to 77%) on a polymer basis. When produced via solution polymerization, the composition of dry SBR varies; however, typical grades contain styrene units (~ 10% to 25%) and butadiene units (75% to 90%). Styrene block polymers with butadiene are available with a styrene content of 25% to 50%, and the most widely used grades contain 30% styrene units.

Trade Name Materials

Composition/impurities data on styrene and vinyl-type styrene copolymer trade name materials are presented in Table 6. Data on properties of these trade name materials are also included.

Methods of Production

Ethylene/Propylene/Styrene Copolymer and Butylene/Ethylene/Styrene Copolymer

The ethylene/propylene/styrene copolymer and butylene/ethylene/styrene copolymer used as thickeners are made by anionic polymerization, which results in little or no residual monomer in the polymer.[11]

Polystyrene

Polystyrene is produced from styrene by mass, solution, suspension, or emulsion polymerization processes.[7] Polystyrene resins are typically produced by a modified mass polymerization process in a continuous manner.[5] The liquid styrene monomer is diluted with a relatively small amount of a diluent, e.g., 5% to 15% of ethylbenzene. In some cases, more diluent is used, and the process may then be called a solution process. The heated mixture of styrene, solvent, and initiator is reacted at 120°C to 160°C. Unreacted monomer and solvent are removed after polymerization is complete.

Styrene/Butadiene Copolymer

Dry SBR is produced via an emulsion polymerization (cold or hot) or solution polymerization process.[5] Composition data on styrene/butadiene copolymer resulting from either process are presented in the Composition/Impurities section.

The following components (in parts per 100 monomer) comprise a typical recipe for SBR produced by cold emulsion polymerization:[5] butadiene (70), styrene (30), water (180), fatty acid soap (2.25), disproportioned rosin soap (2.25), potassium chloride (0.3), potassium hydroxide (0.3), *t*-dodecyl mercaptan (0.23), sodium formaldehyde β-naphthalene sulfonate (0.04), sodium formaldehyde sulphoxylate (0.04), *p*-methane hydroperoxide (0.04), tetrasodium ethylenediaminetetraacetate (0.025), and ferrous sulfate heptahydrate.

A typical recipe (component data in parts per 100 monomer) for SBR produced by hot emulsion polymerization is as follows:[5] butadiene (75), styrene (25), water (180), fatty acid or rosin soap (5), *n*-dodecyl mercaptan (0.5), and potassium persulfate (0.3).

Recipes for SBR produced by solution polymerization are said to vary greatly, and depend upon the properties desired.[5] SBR is vulcanized (typically 1.5 to 2.0 parts sulfur per 100 parts of polymer are used). Furthermore, accelerators, antioxidants, activators, fillers (e.g., carbon black), and softeners may be used, depending on the properties of the finished rubber that are desired. SBR is also extended with aromatic and naphthenic oils to improve handling and processing.

Styrene block copolymers with butadiene are typically produced by anionic solution polymerization with *sec*-butyllithium or *n*-butyllithium in a solvent such as cyclohexane, isopentane, *n*-hexane, or mixtures.[5] The styrene is homopolymerized, followed by the addition of butadiene; more styrene is then added. The polymer is coagulated from the solution with water. Styrene block polymers are usually compounded with fillers, extenders oils, and, sometimes, other polymers (e.g., polyindene or polystyrene).

USE

Cosmetic

Styrene and vinyl-type styrene copolymers function mostly as viscosity increasing agents, opacifying agents, and film formers in cosmetic products.[2]

Information on the use of these ingredients as a function of product type was supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP).[12] The highest use frequency was reported for ethylene/propylene/styrene copolymer, followed by butylene/ethylene/styrene copolymer. The Personal Care Products Council conducted a survey of ingredient use concentrations in 2013-2014, and maximum use concentrations ranging from 0.000038% (styrene/VP copolymer, in skin care preparations) to 36.5% (polystyrene, in skin cleansing products) were reported.[13] The highest maximum reported use concentrations for rinse-off and leave on products were 36.5% (polystyrene) and 35% (styrene/acrylates copolymer, in basecoats and undercoats), respectively. Ingredient frequency of use and concentration data are presented in Table 7.

Cosmetic products containing styrene and vinyl-type styrene copolymers may be applied to the skin and hair or, incidentally, these products may come in contact with the eyes. Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

The following ingredients are used in products that are sprayed (maximum concentrations reported): hair sprays (styrene/acrylates copolymer [0.35%,]; styrene/VP copolymer [0.12%, in pump spray]), suntan sprays (styrene/acrylates copolymer [3.5%]), and body and hand sprays (ethylene/propylene/styrene copolymer [0.5%]). Additionally, isobutylene/styrene copolymer is used in face powders at a maximum concentration of 1%. Because styrene/acrylates copolymer, styrene/VP copolymer, and ethylene/propylene/styrene copolymer are used in products that are sprayed and isobutylene/styrene copolymer is used in face powders they could possibly be inhaled. 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.[14,15,14,16] 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.[14,15]

Noncosmetic

Polystyrene

Polystyrene is used as a plasticizer in the bottled water industry**,** and studies have shown that styrene leaches continuously from polystyrene bottles.[17] The skin adhesive layer of a pressure ulcer preventive dressing may contain styrene block copolymer as an adhesive compound.[18] Polystyrene foam is widely used for thermal insulation.[7]

Additionally, polystyrene may be safely used as a component of articles intended for use in contact with food. For this purpose, polystyrene shall contain not more than 1 weight percent of total residual styrene monomer.[19] The exception to this limit relates to use in contact with fatty foods, whereas such polystyrene basic polymers shall contain not more than 0.5 weight percent of total residual styrene monomer.

Styrene

Styrene is listed among the synthetic flavoring substances and adjuvants that may be safely used in food.[20] It should be used in the minimum quantity required to produce the intended effect, and, otherwise, in accordance with all principles of good manufacturing practice.

Styrene/Butadiene Copolymer

Butadiene-styrene rubber (styrene/butadiene copolymer) is included on the list of FDA-approved direct food additives.[21]

TOXICOKINETICS

Polyacrylate-15, Polyacrylate-18,
Polyacrylate-19, Polyacrylate-21, and Polystyrene

Because of the large size of the following copolymers, bioavailability from inhalation, oral, or dermal exposure is not expected: polyacrylate-15 (Syntran® PC 5208),[22] polyacrylate-18 and polyacrylate-19 mixtures (Syntran® PC 5117 and Syntran® PC 5107),[23,24] polyacrylate-21(Syntran® PC 5100CG),[25] and polystyrene (Syntran® 5900).[26]

Styrene

Nine male volunteers were exposed for 10 to 30 minutes by dipping one hand in liquid styrene. Urine and breath were sampled periodically for metabolites (mandelic and phenylglyoxylic acids) and styrene analyses respectively. The results obtained show that the rate of absorption of styrene through the skin was very low, averaging 1 ± 0.5 µg/cm^2/minute.[27,29]

A field study comparing the urinary excretion of styrene metabolites in 4 groups of workers who performed the same task, but wore different protective equipment, was performed.[27] It was concluded that the percutaneous absorption of styrene was not an important contribution to the body burden.

Several studies have suggested that styrene accumulates in the subcutaneous fat.[27] However, based on the measurement of urinary metabolites, there was no styrene accumulation in workers exposed to 37 ppm (160 mg/m^3) styrene in air during the work week.

Styrene is primarily metabolized to styrene 7,8-oxide by cytochrome P450 (CYP) enzymes.[27] Epoxide hydrolase metabolizes the oxide to phenylethylene glycol, and then to mandelic, phenylglyoxylic, and benzoic acids. Additional routes of metabolism include ring hydroxylation, but this appears to be a minor pathway in humans. Another pathway is the conversion of styrene to 1- and 2-phenylethanol, which is further metabolized to phenylacetaldehyde, phenylacetic acid, phenylaceturic acid, and hippuric acid. Styrene 7,8-oxide may also be metabolized by conjugation with glutathione to form mercapturic acids. The conversion of styrene to mercapturic acids, considered a minor pathway in humans, is < 1% of the absorbed dose of styrene.[30]

Small amounts of styrene (0.7% to 4.4%) are exhaled unchanged.[27] This finding has been confirmed in additional studes in which 0.7% to 2.2% of the amount of inhaled styrene was found unchanged in the exhaled breath of 4 subjects exposed to 50 ppm [213 mg/m^3) styrene in air for 2 h. Small amounts of styrene are also excreted unmetabolized in the urine.

The pharmacokinetics of inhaled styrene (80 ppm [341 mg/m^3]) was studied using 4 volunteers.[27,31] Calculated half-life values of 0.6 h and 13.0 h for the 2 phases of elimination were reported. In a study of blood styrene concentrations in 76 exposed workers at the end of their work shift and in the morning thereafter, the half-life of blood styrene was 3.9 h at 16 h after the end of the workshift.

1,3-Butadiene and Styrene

Nine minutes after rabbits were exposed to 1,3-butadiene at concentrations of 250,000 ppm in air, the test chemical was found in the femoral artery at a concentration of 0.26 mg/ml and in the femoral vein at a concentration of 0.18 mg/ml.[28]

Mice and rats were exposed (dynamic flow exposure: 2 h [mice] and 4 h [rats]) to butadiene or styrene vapors.[28,32] The number, strain, and sex of the animals tested were not specified. LC_{50} values were: 270 mg/liter (butadiene [mice]), 285 mg/liter (butadiene [rats]), 21 mg/liter (styrene [mice]), and 11.8 mg/liter (styrene [rats]). The concentratons of butadiene and styrene in tissues at the LC_{50} exposure concentration were determined by gas liquid chromatography. Various tissues from rats were analyzed, but only brain tissue from mice was analyzed. Mean concentrations in tissues from rats are included below:

- 50.8 mg butadiene/100g brain (10 tests)
- 25 mg styrene/100g brain (7 tests)
- 51.4 mg butadiene/100g liver (10 tests)
- 20 mg styrene/100g liver (7 tests)
- 36.3 mg butadiene/100g kidney (7 tests)
- 14.7 mg styrene/100g kidney (7 tests)
- 45 mg butadiene/100g spleen (7 tests)
- 19.1 mg styrene/100 g spleen (7 tests)
- 152.1 mg butadiene/100g perinephric fat (7 tests)
- 132.8 mg styrene/100g perinephric fat (7 tests)

Mean concentrations in brain tissue from mice were 54.4 mg butadiene/100cc brain (10 tests) and 18.02 mg styrene/100cc brain (7 tests). In a subsequent experiment series (rats, same procedure), mean concentrations in the brain and liver were determined at various times for up to 90 minutes after removal from the chamber. By 90 minutes, mean tissue concentrations were:[28,32]

- 0 to traces of butadiene/100cc brain (4 tests)
- traces to 4.4 mg styrene/100 cc brain (4 tests)
- 0 to traces of butadiene/100cc liver (4 tests)
- 5.2 to 11 mg styrene/100cc liver (4 tests)

The first step in butadiene metabolism involves cytochrome P450 (CYP)-mediated oxidation to epoxybutene.[9] At low concentrations of butadiene, metabolism via CYP2E1 predominates. Epoxybutene may be metabolized by conjugation with glutathione (GSH), mediated by glutathione *S*-transferase (GST), or by hydrolysis, catalyzed by epoxide hydrolase (EH). Epoxybutene may also be oxidized to multiple diastereomers of diepoxybutane. Dihydroxybutene formed by hydrolysis of epoxybutene may be oxidized to epoxybutanediol. The latter epoxides are also detoxified by GST or EH. The partial hydrolysis of diepoxybutane also produces epoxybutanediol.

TOXICOLOGY

Composition data on copolymer trade name mixtures evaluated in toxicity tests are included in Table 6.

Acute Inhalation Toxicity

Styrene/Acrylates Copolymer

In an acute inhalation toxicity study on Sunspheres™ Powder, an LC_{50} of > 5.3 mg/L was reported. The test protocol was not provided.[33]

An acute inhalation LC_{50} (4 h) value of > 5.11 mg/L air was reported for ACUDYNE™ Shine Polymer and ACUDYNE™ Bold Polymer.[34,35] The test protocol was not described. The animal species was not stated, but it was noted that no clinical signs or mortalities were observed.

Acute Oral Toxicity

Ethylene/Propylene/Styrene Copolymer and Butylene/Ethylene/Styrene Copolymer (mixture)

A trade name mixture containing ethylene/propylene/styrene copolymer (4 to 15%) and butylene/ethylene/styrene copolymer (0.1 to 2%) was evaluated in an acute oral toxicity study.[36] The mixture was fed in large doses to male and female rats (number of animals not stated). Details relating to the test protocol were not included. The estimated acute oral LD_{50} was > 5,050 mg/kg (nontoxic). It was noted that this finding was expected because the primary ingredient of the trade name mixture is white mineral oil.

Styrene/Acrylates Copolymer

OPULYN™ 302B Opacifier was evaluated in an acute oral toxicity study involving rats, and an LD_{50} of > 5 ml/kg was reported. The test protocol was not stated.[37]

An oral LD_{50} of > 2,000 mg/kg body weight (rats) for Syntran® 5903 was reported in a study performed according to OECD guideline n˚423.[38] There were no effects on body weight change, and no clinical and behavioral signs or mortalities were observed after dosing. In a toxicological assessment certificate on Syntran® 5907 (another styrene acrylates copolymer trade name material), it was noted that the acute oral toxicity data on Syntran® 5903 can be extrapolated to Syntran® 5907.[39] Similarly, in toxicological assessment reports on Syntran® 5904 and Syntran® 5905 it was determined that the acute oral toxicity study results for Syntran® 5903 are applicable to Syntran® 5904 and Syntran® 5905.[40,41]

Acute Dermal Toxicity

Styrene/Acrylates Copolymer

OPULYN™ 302B Opacifier was evaluated in an acute dermal toxicity study involving rats, and an LD_{50} of > 5 g/kg was reported. The test protocol was not stated.[37]

Repeated Dose Toxicity

Inhalation

Polyacrylate

Polyacrylate, a polymer of acrylic acid and sodium acrylate, was tested in a repeated dose toxicity study involving groups of Fischer 344 rats (ages and number per group not specified).[42] It was noted that the large particle size of polyacrylate used in manufacturing makes this material non-respirable, i.e., less than 1% of received material is < 40 microns. The particle size used in this study was reduced (by milling) to make it highly respirable in test animals (mass mean aerodynamic diameter [MMAD] = 1.95 to 2.07 microns). Four groups of animals were exposed to concentrations of 0.05, 0.2, 1, and 10 mg/m^3, respectively, 5 days per week (6 h/day) for up to 26 consecutive weeks. The control group was exposed to filtered room air. No adverse effects were observed at concentrations of 0.05 and 0.2 mg/m^3. Mild to moderate pulmonary inflammation, which resolved during the recovery period, was observed in the 1.0 mg/m^3 exposure group. Exposure to 10 mg/m^3 (at this concentration, threshold for clearing inhaled test material from the lungs was exceeded) caused adverse pulmonary effects (marked inflammation and benign alveolar/bronchiolar adenoma) that are not relevant to subthreshold exposure concentrations. Inflammation decreased during the recovery period. The authors stated that these results support the inhalation safety of the polyacrylate material under both occupational and consumer exposure conditions. The 0.05 and 0.2 mg/m^3 concentrations were considered no-adverse-effect levels.

Three groups of 120 F344 rats (60 males, 60 females/group) were exposed for 24 months to respirable polyacrylate particles (MMAD ≈ 2 to 3 microns) at concentrations of 0.05, 0.2, and 0.8 mg/m^3, respectively.[43]

Gross necropsy was performed at 6, 12, and 24 months. Gross necropsy results at 24 months indicated no visible effects in males or females exposed to 0.05 mg/m^3. Lung nodules were observed in 1 male and 3 females exposed to 0.2 mg/m^3. The numbers of pulmonary nodules were even higher in the 0.8 mg/m^3 exposure group (7 males and 23 females with nodules). Only one animal (1 female) in the air-exposed control group had a pulmonary nodule. Interim necropsy results at 6 and 12 months indicated the absence of nodule formation in all exposure groups. The authors noted that characterization of the nodules was not possible, and it was determined that conclusions regarding the lung nodule incidence and its significance (if any) in this study could not be made.

Styrene/Acrylates Copolymer

ACUDYNE™ Shine Polymer and ACUDYNE™ Bold Polymer were evaluated in a 2-week aerosol (nose only) exposure study involving rats.[34,35] The test protocol was not stated. There were no signs of clinical toxicity at any administered dose. The no-observed-effect-concentration (NOEC) was 10.8 mg polymer solids/m^3, based on slight irritant effects in the lungs at a concentration of 100 mg/m^3.

In a 13-week aerosol (nose only) study on ACUDYNE™ Shine Polymer and ACUDYNE™ Bold Polymer involving rats, the no-observable adverse-effect level (NOAEL) for changes in the lung (and related lymph nodes) was 8.3 mg/m^3.[34,35]

Oral

Styrene

The Environmental Protection Agency (EPA) has established a reference dose for chronic oral exposure (RfD) to styrene of 1 mg/kg/day, based on effects on red blood cells and the liver of dogs.[44] The RfD is based on the assumption that thresholds exist for certain toxic effects, such as cellular necrosis. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

Ocular Irritation

Non-Human

Ethylene/Propylene/Styrene Copolymer and Butylene/Ethylene/Styrene Copolymer (mixture)

A mixture containing ethylene/propylene/styrene copolymer (4 to 15%) and butylene/ethylene/styrene copolymer (0.1 to 2%) was evaluated in an ocular irritation study involving albino rabbits (number of animals not stated).[45] Details relating to the test protocol were not included. The mixture was not a primary ocular irritant in this study. It was noted that, under EPA Guideline No. 81-4, this mixture was "minimally irritating" in rinsed and unrinsed eyes. Additionally, the minimal irritation observed was reversible and the material was assigned to Category IV, EPA's lowest toxicity category for ocular irritation.

Styrene/Acrylates Copolymer

In the embryonic hen's egg chorioallantoic membrane (HET-CAM) assay, a 5% dilution of Syntran® 5903 in distilled water was classified as a weak irritant.[26,38] In this test system, the hen's egg chorioallantoic membrane was treated with the test material for 20 seconds and the following endpoints were evaluated: hyperemia, hemorrhage, and coagulation (including opacity and thrombosis).

Sunspheres™ Powder was classified as minimally irritating to the eyes of rabbits.[33] The test protocol was not stated.

In an ocular irritation study involving rabbits, OPULYN™ 302B Opacifier was classified as a non-iritant. The test protocol was not stated.[37]

Human

1,3-Butadiene

Workers exposed to 1,3-butadiene at concentrations of 8,000 ppm for 8 hours complained of eye irritation and blurred vision.[46]

In Vitro

Polyacrylate-15, Polyacrylate-18, Polyacrylate-19, and Polyacrylate-21

In the *in vitro* EpiOcular™ ocular irritation screening assay, the following copolymers were classified as non-irritating to the eye: polyacrylate-15 (Syntran® PC 5208),[22] polyacrylate-18 and polyacrylate-19 mixtures (Syntran® PC 5117 and Syntran® PC 5107),[23,24] and a product (100.58BM) closely related to polyacrylate-21 (Syntran® PC 5100CG).[25]

Styrene/Acrylates Copolymer

The ocular irritation potential of ACUDYNE™ Shine Polymer was evaluated in the bovine corneal opacity and permeability test *in vitro*. The test protocol was not stated. Results were negative.[34]

ACUDYNE™ Bold Polymer was classified as a non-irritant in the bovine corneal opacity and permeability test *in vitro*.[35] The test protocol was not stated.

Skin Irritation and Sensitization

Non-Human

Ethylene/Propylene/Styrene Copolymer and Butylene/Ethylene/Styrene Copolymer (mixture)

A mixture containing ethylene/propylene/styrene copolymer (4 to 15%) and butylene/ethylene/styrene copolymer (0.1 to 2%) was evaluated in a skin irritation study involving albino rabbits (number of animals not stated).[47] Details relating to the test protocol were not included. The material was not a primary skin irritant in this study. It was noted that the descriptive rating (under EPA Guideline No. 81-5) for this mixture was "slightly irritating", the lowest descriptive rating possible. Additionally, because this slight irritation was reversible, the trade name material was assigned to the EPA's lowest toxicity category (Categorty IV) for dermal irritation.

Styrene/Acrylates Copolymer

In a skin irritation study involving rabbits, OPULYN™ 302B Opacifier was classified as a non-iritant. The test protocol was not stated.[37]

The skin irritation potential of ACUDYNE™ Shine Polymer and ACUDYNE™ Bold Polymer was evaluated in the EpiDermal *in vitro* assay.[34,35] The test protocol was not stated. Results were negative.

Styrene/Acrylates Copolymer and Polystyrene

Syntran® 5903 (undiluted) was classified as a non-sensitizer in a guinea pig sensitization test, performed according to OECD guideline n˚406.[26,38] Based on these results for Syntran® 5903, Syntran® 5904 (another styrene/acrylates copolymer trade name material), Syntran® 5907 (another styrene/acrylates copolymer trade name material), Syntran® 5905 (another styrene/acrylates copolymer trade name material), and Syntran® 5900 (polystyrene trade name material) were classified as non-sensitizers.[26,40,39,41]

ACUDYNE™ Shine Polymer and ACUDYNE™ Bold Polymer were classified as non-sensitizers in the mouse local lymph node assay.[34,35] The test protocol was not stated.

Styrene and Methylstyrene

The skin sensitization potential of styrene was evaluated in the guinea pig maximization test (15 guinea pigs).[48] Details relating to the test protocol were not included. The test procedure involved intradermal injections of 10% (w/v) styrene, topical application of 20% (w/v) styrene, and challenge with 2% (w/v) styrene in acetone. Skin sensitization was not observed in any of the animals tested. Methylstyrene was also evaluated in a maximization test involving 15 guinea pigs, and the procedure involved intradermal injections of 2.5% (w/v) methylstyrene, topical application of 5% (w/v) methylstyrene, and challenge with 0.5% (w/v) methylstyrene in acetone. The results were also negative.

Human

Styrene/Acrylates Copolymer and Polystyrene

Syntran® 5903 (5% in distilled water) was classified as having good skin compatibility in 10 volunteers patch tested (single application patch test). Study details were not provided.[26,38] No signs of irritation were recorded, and observations throughout the test interval were within normal limits. Based on these results for Syntran® 5903, Syntran® 5904 (another styrene acrylates copolymer trade name material), Syntran® 5907 (another styrene/acrylates copolymer trade name material), Syntran® 5905 (another styrene/acrylates copolymer trade name material), and Syntran® 5900 (polystyrene trade name material) were classified as non-irritants.[26,40,39,41]

Styrene/Acrylates Copolymer

In a 21-day cumulative skin irritation study, OPULYN™ 302B Opacifier was classified as non-irritating and non-sensitizing. The test protocol was not stated.[37]

OPULYN™ 301 Opacifier was also classified as non-irritating and non-sensitizing in a 21-day cumulative irritation study. The test protocol was not stated.[50]

Styrene and Methylstyrene

Styrene (5% w/v in petrolatum) was evaluated in a skin sensitization study involving 303 patients (diagnoses not stated).[48] Details relating to the test procedure were not provided. Negative results were reported for all patients. Negative results for methylstyrene (1% w/v in ethanol) in these patients were also reported.

Ethylene/Propylene/Styrene Copolymer and Butylene/Ethylene/Styrene Copolymer (mixture)

A mixture containing ethylene/propylene/styrene copolymer (4 to 15%) and butylene/ethylene/styrene copolymer (0.1 to 2%) was evaluated in a human repeated insult patch test involving 117 subjects.[49] Details relating to the test protocol were not included. The subjects were evaluated for redness, swelling, “flares” and itching. The mixture did not induce allergic contact dermatitis in any of the subjects. It was noted that this conclusion was confirmed by a board-certified dermatologist.

In Vitro

Styrene/Acrylates Copolymer and Polystyrene

In the embryonic hen’s egg chorioallantoic membrane (HET-CAM) assay, a 5% dilution of Syntran® 5903 in distilled water was classified as a weak irritant.[26,38] In this test system, the hen’s egg chorioallantoic membrane was treated with the test material for 20 seconds and the following endpoints were evaluated: hyperemia,

hemorrhage, and coagulation (including opacity and thrombosis). Based on these results for Syntran® 5903, Syntran® 5904 (another styrene/acrylates copolymer trade name material), Syntran® 5907 (another styrene/acrylates copolymer trade name material), Syntran® 5905 (another styrene/acrylates copolymer trade name material), and Syntran® 5900 (polystyrene trade name material) were also classified as weakly irritating to the chorioallantoic membrane.[26,40,39,41] Based on the minimal irritation potential of Syntran® 5903 in the HET-CAM assay (generally used to evaluate ocular irritation potential), it was concluded that it is not likely that this trade name material, or the other trade name materials, would produce dermal irritation.

Polyacrylate-15, Polyacrylate-18, Polyacrylate-19, and Polyacrylate-21

Based on negative results in the *in vitro* EpiOcular™ ocular irritation screening assay (see preceding section), it is expected that the following copolymers would not produce dermal irritation: polyacrylate-15 (Syntran® PC 5208),[22] polyacrylate-18 and polyacrylate-19 mixtures (Syntran® PC 5117 and Syntran® PC 5107),[23,24] and a product (100.58BM) closely related to polyacrylate-21 (Syntran® PC 5100CG).[25]

Polyacrylate-15

In a cosmetic ingredient safety dossier on Syntran® PC 5208, skin irritation data on this trade name material were not included.[22] However, it was noted that the absence of ocular irritation potential in the EpiOcular™ assay on Syntran® PC 5208 indicates that this trade name material is not likely to produce skin sensitization, since skin is less susceptible to irritation than eye tissue.

Polyacrylate-18 and Polyacrylate-19 (mixture)

Skin irritation data were not included in a cosmetic ingredient safety dossier on polyacrylate-18 and polyacrylate-19 (Syntran® PC 5117).[23] However, it was noted that the absence of ocular irritation potential in the EpiOcular™ assay on a closely related product (Syntran® 5100, composition not stated) indicates that Syntran® PC 5117 is not likely to produce dermal sensitization, since skin is less susceptible to irritation than eye tissue. These statements are also applicable to Syntran® PC 5107 (polyacrylate-18 and polyacrylate-19).[24]

Polyacrylate-21

In a cosmetic ingredient safety dossier on polyacrylate-21 (Syntran® PC 5100CG), skin irritation data on this trade name material were not included.[25] However, it was noted that the absence of ocular irritation potential in the EpiOcular™ assay on a closely related product (100.58BM, composition data not provided) indicates that Syntran® PC 5100CG is not likely to produce dermal sensitization, since skin is less susceptible to irritation than eye tissue.

Case Reports

Styrene and Methylstyrene

A 40-year-old man with a history of bronchitis and contact allergy to styrene cross-reacted when patch-tested with 3- and 4-vinytoluene (also known as 3- and 4-methylstyrene, respectively).[48] The vinyltoluene compounds were patch-tested at concentrations equimolar to 0.1% w/v styrene. The patient also had a positive reaction to styrene (0.1% and 5% v/v in methy ethyl ketone).

In a subsequent case report, the same patient cross-reacted when patch tested with 2-, 3-, and 4-vinyltoluene (2-, 3-, and 4-methylstyrene, respectively) and to the metabolites styrene epoxide and 4-vinylphenol (4-hydroxystyrene).[51] It is assumed that styrene is a prohapten metabolized in the skin by aryl hydrocarbon hydroxylase (AHH) to styrene epoxide, which acts as a true hapten.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Styrene

The National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) Expert Panel concluded that styrene does not cause developmental or reproductive toxicity in experimental animals.[52] In developmental toxicity studies in rats and rabbits, the highest exposure concentration/dose on gestation days 6-15 (600 ppm by inhalation or 300 mg/kg body weight/day by oral dosing) did not have any observable adverse effects on fetuses. Rats and rabbits were used in inhalation studies, and rats only were involved in the oral dosing study. The effects of styrene exposure on reproduction and post-natal development were assessed in 2 multigeneration studies involving rats. Neither study produced results indicating a styrene-induced reproductive effect, even at the highest concentrations administered. However, in one of the studies, there was decreased birth weight and delays in the postnatal development of pups from parents exposed (by inhalation) to 500 ppm styrene from 70 days prior to mating through gestation day 20. This concentration of styrene also caused a significantly reduced body weight gain in the dams. Thus, the NTP-CERHR Expert Panel concluded that it was not possible to separate the observed effects in the offspring from the effects on maternal weight. Inhalation exposure to 500 ppm styrene did not cause developmental neurotoxicity.

In the second multigeneration study, a subset of animals (COBS (SD) BR rats) from a 2-year chronic toxicity study in which styrene was administered at concentrations up to 250 ppm in drinking water (estimated intake = 18 mg/kg body weight/day (for males) and 23 mg/kg body weight/day (for females) were used. The parental generations were cohabited after 90 days on study. Results indicated no treatment-related effects on maternal food consumption or weight gain, and no significant developmental effects on the pups. The NTP-CERHR Expert Panel considered these data to be relevant for the assessment of potential human hazard.

The NTP-CERHR Expert Panel determined that there was insufficient information available to arrive at conclusions about reproductive and developmental outcomes from studies of humans exposed to styrene. Studies performed in occupational settings suggest that the exposure of women to styrene is associated with slightly increased levels of prolactin in blood serum and possible depletion of peripheral blood dopamine metabolizing activities, when compared to levels in women not occupationally exposed to styrene. The Panel determined that the clinical relevance of these effects is uncertain for the following 2 reasons: (1) the average elevation in prolactin concentrations in blood serum was small and within the normal range of blood serum values and (2) menstrual function and other reproductive endpoints were not evaluated in these studies.[52]

1,3-Butadiene

According to the 1984 NTP report on the toxicology and carcinogenesis of 1,3-butadiene,[28] the fertility of rats was not severely impaired when they were exposed (via inhalation) to 1,3-butadiene at concentrations of 600-6,700 ppm for 7.5 hours per day, 6 days per week, for 8 months; however, the decreased fecundity observed may have been related to exposure. No evidence of degenerative testicular changes in males was seen, and all embryos appeared normal at necropsy.

When female rats were exposed (via inhalation) to 1,3-butadiene for 4 months at 45 ppm, increased embryonic mortality and teratogenesis were reported.

Pregnant female Sprague-Dawley rats exposed (via inhalation) to 1,3-butadiene at concentrations of 0, 200, 1,000, or 8,000 ppm for 6 hours per day during days 6-15 of gestation showed embryonic growth retardation and slight embryo-mortality at all concentrations. At the highest exposure concentration, evidence of teratogenicity (major fetal defects such as cardiovascular, sternebral, and thoracic abnormalities) was seen.[28]

GENOTOXICITY

In Vitro

Styrene/Acrylates Copolymer and Polystyrene

In the Ames test (OECD guideline n˚471), Syntran® 5903 (doses up to 5,000 µg/plate) was non-genotoxic with and without metabolic activation in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and in *Escherichia coli* strains WP2, pKM101, and uvr A^{-}.[26,38] Based on these results for Syntran® 5903, Syntran® 5904 (another styrene/acrylates copolymer trade name material), Syntran® 5907 (another styrene/acrylates copolymer trade name material), Syntran® 5905 (another styrene/acrylates copolymer trade name material), and Syntran® 5900 (polystyrene trade name material) were classified as non-genotoxic.[26,40,39,41]

The genotoxicity of polystyrene was evaluated in the Ames test using the following *Salmonella typhimurium* strains, with and without metabolic activation: TA97, TA98, TA100, and TA1535.[53] Concentrations of the test substance were not stated; however, at least 5 concentrations were tested. Methyl ethyl ketone served as the vehicle and the control. Polystyrene was not genotoxic with or without metabolic activation in any of the bacterial strains tested. The positive controls in experiments without metabolic activation were: 2-nitrofluorene, 4-nitro-o-phenylenediamine, sodium azide, 9-aminoacridine, mitomycin C, and methyl methanesulfonate. The positive control for the metabolic activation experiments was 2-aminoanthracene. Results for the vehicle control or positive controls were not stated.

Polyacrylate

The genotoxicity of polyacrylate (polymer of acrylic acid and sodium acrylate) was evaluated in the following Ames *Salmonella* assay, and results were negative.[42]

Polyacryate-18 and Polyacrylate-19 (mixture)

When Syntran® PC 5117 (polyacrylate-18 and polyacrylate-19) was evaluated for genotoxicity in the preceding Ames test (same strains, except strain WP2 *uvr*A was the only *E. coli* strain tested; doses up to 5,000 µg/plate), results were negative with and without metabolic activation.[23] These statements are also applicable to Syntran® PC 5107 (polyacrylate-18 and polyacrylate-19).[24]

Polyacrylate-21

When Syntran® PC 5100 (mixture of polyacrylate-21 and acrylates/dimethylaminoethyl methacrylate copolymer)[2] was evaluated for genotoxicity in the preceding Ames test (same strains, except strain WP2 *uvr*A was the only *E. coli* strain tested; doses up to 5,000 µg/plate), results were negative with and without metabolic activation.[25] Genotoxicity data on polyacrylate-21 (Syntran® 5100CG) were not provided, and data on a closely related product (Syntran® PC 5100) were used to evaluate the genotoxicity of Syntran® 5100CG. It was noted that negative results would be expected for Syntran® 5100CG.

Styrene/Acrylates Copolymer

OPULYN™ 302B Opacifier was not genotoxic in the Ames test, with or without metabolic activation. The test protocol was not stated.[37]

In the Ames test, ACUDYNE™ Shine Polymer and ACUDYNE™ Bold Polymer were not genotoxic.[34,35]

OPULYN™ 301 Opacifier was not genotoxic in the Ames test, with or without metabolic activation.[50]

Styrene/Acrylates Copolymer

OPULYN™ 302B Opacifier was not genotoxic in the *in vitro* cytogenetic assay, with or without metabolic activation. The test protocol was not stated.[37]

OPULYN™ 301 Opacifier also was not genotoxic in the *in vitro* cytogenetic assay, with or without metabolic activation. The test protocol was not stated.[50]

In the chromosomal aberrations test *in vitro* (test protocol not stated), ACUDYNE™ Shine Polymer and ACUDYNE™ Bold Polymer were not genotoxic.[34,35]

Polyacrylate

The genotoxicity of polyacrylate (polymer of acrylic acid and sodium acrylate) was evaluated in the following assays:[42] unscheduled DNA synthesis assay (rat hepatocytes), the mouse lymphoma mammalian cell assay, and the *in vivo* cytogenetics assay (rat bone marrow cells). Neither the test concentrations nor details relating to the test protocols were stated. However, it was stated that polyacrylate was not genotoxic in any of the assays.

CARCINOGENICITY

Information relating to the carcinogenicity of styrene and vinyl-type styrene copolymers and component monomers is presented in Table 8. Particularly, 1,3-butadiene and styrene monomer components have been classified as carcinogenic. In additon to the information presented in Table 8, a committee of the National Research Council (NRC) conducted a scientific peer review of the styrene assessment presented in the *12th Report on Carcinogens* (RoC). The committee found that the overall conclusion reached by the NTP in 2011, that styrene is "reasonably anticipated to be a human carcinogen", is appropriate.[54]

It should be noted that polyacrylates are included on the 2013 list of substances that have been nominated to the NTP's *Report on Carcinogens* (RoC), but have not yet been approved for formal review.[55]

OTHER EFFECTS

Hormonal Activity

Polystyrene

The estrogenic (uterotrophic) activity of low molecular weight polystyrene (identified as F2L5250) was studied in the Tiecco test using groups of 10 weanling female Wistar outbred rats (HsdCpb:WU strain).[56] The test substance was fed to 5 groups at the following dietary concentrations, respectively, during a 4-day period: 10 ppm, 20 ppm, 40 ppm, 80 ppm, and 160 ppm. The control group was fed standard diet only. Diethylstilbesterol (DES) served as the positive control. The mean absolute and relative uterine weights of the treatment groups were used for qualitative and quantitative assessment of possible uterotrophic activity. There were no significant differences in mean absolute and relative uterus weights between the control group and the 10 ppm, 20 ppm, 40 ppm, or 80 ppm group. However, significant and dose -related increases in mean absolute and relative uterus weights were observed in the 160 ppm group and in groups fed 5 ppb, 10 ppb, and 20 ppb DES, respectively. The results of this study indicated that the highest no-effect-level for estrogenic activity was 80 ppm polystyrene in the diet, which corresponded to a daily intake of 13.3 mg polyacrylate/kg body weight. It was noted that 100 ppm polyacrylate induced the same level of estrogenic activity as 5 ppb DES. It was concluded that the potentcy (estrogenic activity) of low molecular weight polyacrylate (F2L5250) was a factor of 20,000 less than that of DES.

SUMMARY

The safety of 35 styrene and vinyl-type styrene copolymers as used in cosmetics is evaluated in this safety assessment. These ingredients function mostly as viscosity increasing agents, opacifying agents, and film formers in cosmetic products. Very limited safety test data on the styrene and vinyl-type styrene copolymers reviewed in this safety assessment were found in the published literature. However, data on monomers, styrene and 1,3-butadiene, are included.

Information on the use of these ingredients as a function of product type was supplied to the FDA by industry as part of the VCRP in 2014. The highest use frequency was reported for ethylene/propylene/styrene copolymer, followed by butylene/ethylene/styrene copolymer. The Personal Care Products Council conducted a survey of ingredient use concentrations in 2013-2014, and maximum use concentrations ranging from 0.000038% (styrene/VP copolymer) to 36.5% (polystyrene) were reported. The highest maximum reported use concentrations for rinse-off and leave-on products were 36.5% (polystyrene) and 35% (styrene/acrylates copolymer), respectively.

Polystyrene grades with low concentrations of residual styrene (≤ 500 ppm) have been developed.

The absorption of styrene was low (averaging 1 μg/cm^2/minute) in human volunteers exposed by placing one hand in liquid styrene for 10 to 30 minutes. The percutaneous absorption of styrene was not an important contribution to the body burden in a field study comparing the urinary excretion of styrene metabolites in 4 groups of workers, all performing the same task, but wearing different protective equipment. It was concluded that the percutaneous absorption of styrene was not an important contribution to the body burden. Styrene is primarily metabolized to styrene 7,8-oxide by cytochrome P450 enzymes.

Nine minutes after rabbits were exposed to 1,3-butadiene at concentrations of 250,000 ppm, the test chemical was found in the femoral artery at a concentration of 0.26 mg/ml and in the femoral vein at a concentration of 0.18 mg/ml. Following 1 h of exposure to 130,000 ppm 1,3-butadiene in rats, the chemical was detected in the brain and liver. At 2 h post-exposure to the same concentration (rats), 1,3-butadiene was detected in the perirenal fat, liver, brain, spleen, and kidneys. The first step in butadiene metabolism involves cytochrome P450-mediated oxidation to epoxybutene.

Polyacrylate, a polymer of acrylic acid and sodium acrylate, was tested in a repeated dose inhalation toxicity study involving groups of Fischer 344 rats. The particle size (MMAD) used in this study was 1.95 to 2.07 microns. The animals were exposed to polyacrylate at concentrations of 0.05, 0.2, 1, and 10 mg/m^3. Mild to moderate pulmonary inflammation and benign alveolar/bronchiolar adenomas were reported, and the 0.05 and 0.2 mg/m^3 concentrations were considered no-adverse-effect levels.

The EPA has estimated the safe dose of styrene for human oral exposure during a lifetime to be 1 mg/kg-day.

Workers exposed to 1,3-butadiene at concentrations of 8,000 ppm for 8 hours complained of eye irritation and blurred vision.

In the maximization test, sensitization was not observed in 15 guinea pigs challenged with 2% (w/v) styrene in acetone. Results were also negative for sensitization in 303 patients tested with 5% (w/v) styrene in petrolatum.

The National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) Expert Panel concluded that styrene does not cause developmental or reproductive toxicity in experimental animals. The highest doses/exposure concentrations in developmental toxicity studies (rats and rabbits) evaluated were 600 ppm (inhalation) or 300 mg/kg body weight/day by oral dosing. The NTP-CERHR Expert Panel determined that there was insufficient information available to arrive at conclusions on reproductive and developmental outcomes from studies of humans exposed (occupational exposure) to styrene.

The fertility of rats was not severely impaired when they were exposed to 1,3-butadiene at concentrations of 600-6,700 ppm for 8 months (6 days/week). However, it was noted that the decreased fecundity observed may have been exposure-related. There was no evidence of degenerative testicular changes in males. The results of other studies indicated increased embryonic mortality and teratogenesis at exposure concentrations as low as 45 ppm (4-month exposure) and embryonic growth retardation and embryo mortality at exposure concentrations ranging from 200 ppm to 8,000 ppm. Teratogenicity was observed only at the highest concentration of 8,000 ppm.

Polystyrene was not genotoxic with or without metabolic activation in the Ames test. Polyacrylate was not genotoxic in the following tests: Ames test, unscheduled DNA synthesis assay (rat hepatocytes), mouse lymphoma mammalian cell assay, and the *in vivo* cytogenetics assay (rat bone marrow cells).

The subcutaneous implantation of various physical forms of polystyrene produced sarcomas in rats. In an NTP oral carcinogenicity bioassay on styrene, it was concluded that there was no convincing evidence of carcinogencity in rats or mice receiving doses up to 2,000 mg/kg for 78 or 103 weeks (rats) or 78 weeks (mice). However, the NTP has concluded that styrene is reasonably anticipated to be a human carcinogen based on the results of occupational cohort studies. The EPA and IARC have also classified styrene as possibly carcinogenic to humans. A committee of the NRC conducted a scientific peer review of the styrene assessment presented in the NTP 12th Report on Carcinogens, and concluded that the overall conclusion reached by the NTP is appropriate.

In NTP inhalation carcinogenicity studies, 1,3-butadiene was carcinogenic in B6C3F$_1$ mice at concentrations ≥ 20 ppm (male mice) and ≥ 6.25 ppm (female mice). Inhalation exposure was also associated with non-neoplastic lesions in the respiratory epithelium, liver necrosis, and testicular or ovarian atrophy. It should be noted that EPA and IARC have concluded that 1,3-butadiene is carcinogenic in humans by inhalation exposure.

The IARC has determined that epidemiological information on styrene-butadiene copolymer workers, which indicates lymphato-hematopoietic malignancies, clearly requires elucidation by further studies.

A cross-sectional respiratory survey of workers (164 workers: 153 men, 11 women; average age = 28.4 years) exposed to polyacrylate dust was performed to assess possible respiratory effects. There was no evidence of an excess risk of lung cancer or chest x-ray abnormalities in exposed workers. However, there were exposure-related decrements in lung function.

Polyacrylates are included on the 2013 list of substances that have been nominated to the NTP's *Report on Carcinogen*s, but have not yet been approved for formal review.

With certain exceptions, results were negative in the following toxicity tests: acute inhalation, acute oral, acute dermal, ocular irritation, skin irritation, skin sensitization, and genotoxicity. The exceptions include: In an *in vitro* skin irritation test, styrene/ acrylates copolymer (Syntran® PC5903) was classified as a weak irritant. Styrene/acrylates copolymer (Sunspheres™ powder) was minimally irritating to the eyes of rabbits. In a 2-week aerosol (nose-only) study on 2 styrene/acrylates copolymer trade name materials (Acudyne™ Bold Polymer and Acudyne™ Shine Polymer), a slight irritant effect on the lungs was noted at a concentration of 100 mg/m^3. In light of these findings, it should be noted that a 13-week aerosol (nose-only) study on these 2 trade name materials yielded an NOAEL of 8.3 mg/m^3.

Low molecular weight polystyrene was found to have estrogenic (uterotrophic) activity in rats fed a dietary concentration of 160 ppm during a 4-day period.

DISCUSSION

After considering the large sizes of these molecules, the Panel agreed that percutaneous absorption is not expected. The absence of the potential for percutaneous absorption and the negative results of toxicity tests provided the Panel with a sufficient basis to assess the safety of these polymers as used in cosmetics. Styrene monomer, a component of all of the copolymers reviewed in this safety assessment, and 1,3-butadiene monomer are classified as carcinogenic in animals and in humans. Data provided by industry suggest that the residual monomer content of styrene and vinyl-type styrene copolymer trade name materials is < 500 ppm. Taking into consideration ingredient use concentrations and the data on residual monomer content, the Panel agreed that any detectable levels of residual styrene or 1,3-butadiene in cosmetic products would be substantially below levels of concern.

The Panel also discussed the potential for incidental inhalation exposures to these ingredients in products that are sprayed or in powder form and agreed that, based on likely airborne particle size distributions and concentrations in the breathing zone, ingredient use concentrations, and negative results in toxicity tests, incidental inhalation would not lead to local respiratory effects or systemic effects.

CONCLUSION

The CIR Expert Panel concluded that the following 35 ingredients are safe in the present practices of use and concentration in cosmetics, as described in this safety assessment.

Ethylene/Propylene/Styrene Copolymer
Butylene/Ethylene/Styrene Copolymer
Acrylates/Ethylhexyl Acrylate/Styrene Copolymer*
Butyl Acrylate/Styrene Copolymer
C4-6 Olefin/Styrene Copolymer*
C5-6 Olefin/Styrene Copolymer*
Hydrogenated Butadiene/Isoprene/Styrene Copolymer*
Hydrogenated Butylene/Ethylene/Styrene Copolymer
Hydrogenated Ethylene/ Propylene/Styrene Copolymer
Hydrogenated Styrene/Butadiene Copolymer
Hydrogenated Styrene/Isoprene Copolymer
Isobutylene/Styrene Copolymer
Methacrylic Acid/Styrene/VP Copolymer*
Methylstyrene/Vinyltoluene Copolymer
Polystyrene
Polystyrene/Hydrogenated Polyisopentene Copolymer
Sodium Methacrylate/Styrene Copolymer*
Sodium Styrene/Acrylates Copolymer
Sodium Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer*
Styrene/Acrylates Copolymer
Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer*
Styrene/Butadiene Copolymer
Styrene/Isoprene Copolymer*
Styrene/Methylstyrene Copolymer*
Styrene/Stearyl Methacrylate Crosspolymer*
Styrene/VA Copolymer*
Styrene/VP Copolymer
Polyacrylate-2*
Polyacrylate-5
Polyacrylate-12*
Polyacrylate-15
Polyacrylate-16
Polyacrylate-18*
Polyacrylate-21
Polyacrylate-30*

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

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[2]

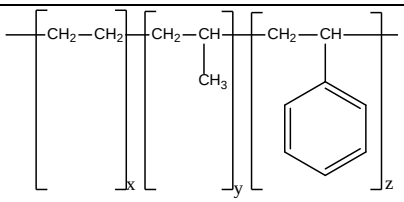
Ingredient CAS No.	Definition		Function(s)
Ethylene/Propylene/Styrene Copolymer 68648-89-5	Ethylene/Propylene/Styrene Copolymer is a polymer of ethylene, propylene and styrene monomers that has been terminated by hydrogenation.		Viscosity increasing agent-nonaqueous

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[2]

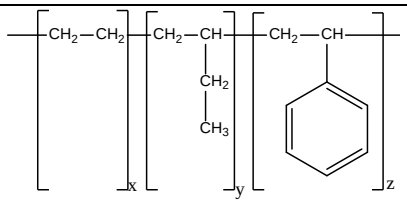
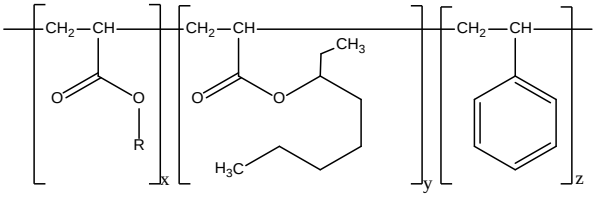
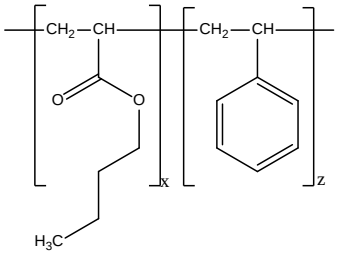
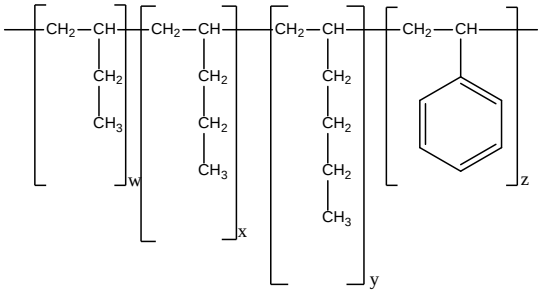
Ingredient CAS No.	Definition	Function(s)
Butylene/Ethylene/Styrene Copolymer 66070-58-4	Butylene/Ethylene/Styrene Copolymer is a polymer of butylene, ethylene and styrene monomers terminated by hydrogenation. 	Viscosity increasing agent-nonaqueous
Acrylates/Ethylhexyl Acrylate/Styrene Copolymer	Acrylates/Ethylhexyl Acrylate/Styrene Copolymer is a copolymer of ethylhexyl acrylate, styrene and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters. wherein R is hydrogen, methyl, ethyl, propyl, or butyl. 	Film formers
Butyl Acrylate/Styrene Copolymer	Butyl Acrylate/Styrene Copolymer is a copolymer of butyl acrylate and styrene monomers. 	Film formers
C4-6 Olefin/Styrene Copolymer	C4-6 Olefin/Styrene Copolymer is a copolymer of C4-6 olefins and styrene monomers. 	Epilating agents
C5-6 Olefin/Styrene Copolymer	C5-6 Olefin/Styrene Copolymer is the copolymer of C5-6 olefins and styrene monomers.	Epilating agents

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[2]

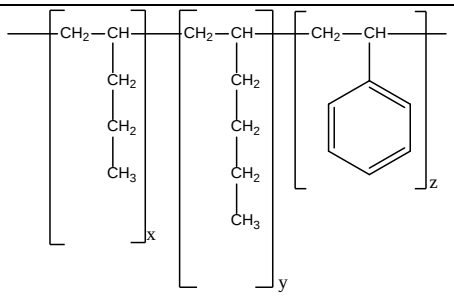
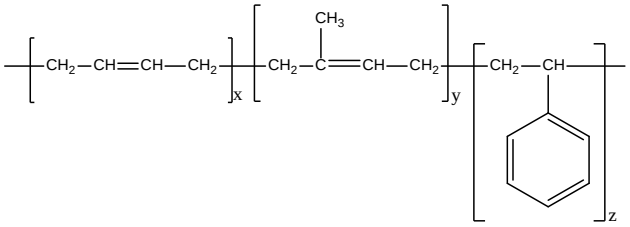
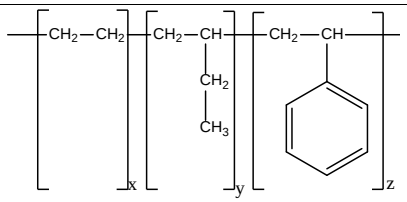
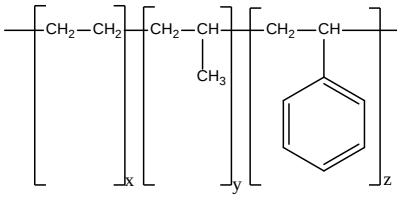
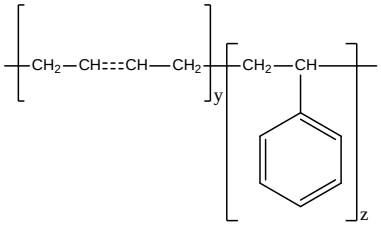
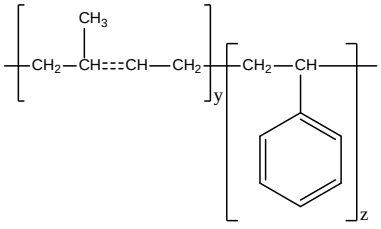
Ingredient CAS No.	Definition	Function(s)
		
Hydrogenated Butadiene/ Isoprene/Styrene Copolymer 132778-07-5	Hydrogenated Butadiene/Isoprene/Styrene Copolymer is the end-product of the controlled hydrogenation of a block copolymer composed of 1,3-butadiene, isoprene and styrene monomers. 	Film formers
Hydrogenated Butylene/ Ethylene/Styrene Copolymer	Hydrogenated Butylene/Ethylene/Styrene Copolymer is a polymer of butylene, ethylene and styrene that has been hydrogenated. 	Viscosity increasing agents-nonaqueous
Hydrogenated Ethylene/ Propylene/Styrene Copolymer	Hydrogenated Ethylene/Propylene/Styrene Copolymer is a polymer of ethylene, propylene and styrene that has been hydrogenated. 	Viscosity increasing agents-nonaqueous
Hydrogenated Styrene/Butadiene Copolymer 66070-58-4	Hydrogenated Styrene/Butadiene Copolymer is the hydrogenated polymer of styrene and 1,4-butadiene. 	Film formers; viscosity increasing agents-nonaqueous
Hydrogenated Styrene/Isoprene Copolymer 68648-89-5	Hydrogenated Styrene/Isoprene Copolymer is the end product of the controlled hydrogenation of Styrene/Isoprene Copolymer. 	Viscosity increasing agents-nonaqueous

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[2]

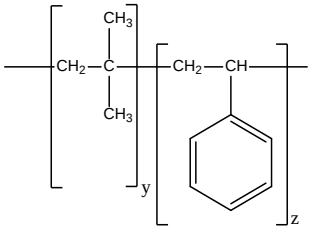
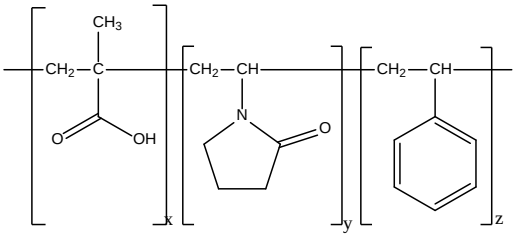
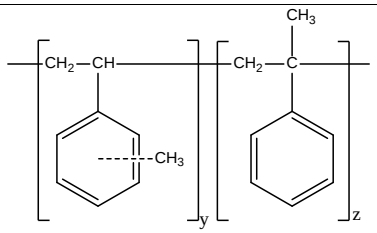
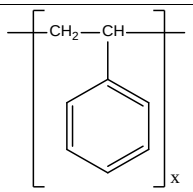
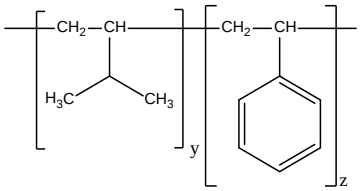
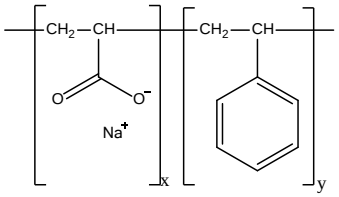
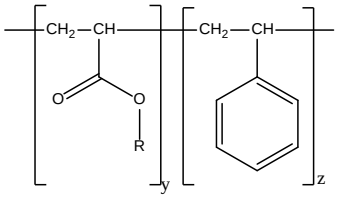
Ingredient CAS No.	Definition		Function(s)
Isobutylene/Styrene Copolymer 9011-12-5	Isobutylene/Styrene Copolymer is a copolymer of isobutylene and styrene monomers.		Film formers
Methacrylic Acid/Styrene/VP Copolymer 27554-92-3	Methacrylic Acid/Styrene/VP Copolymer is a copolymer of styrene, methacrylic acid and vinyl pyrrolidone.		Opacifying agents
Methylstyrene/Vinyltoluene Copolymer 9017-27-0	Methylstyrene/Vinyltoluene Copolymer is the polymer of methylstyrene and vinyltoluene monomers.		Viscosity increasing agents-nonaqueous
Polystyrene 9003-53-6	Polystyrene is the polymer that conforms to the formula. *Polystyrene is the homo-polymer formed from the polymerization of vinylbenzene.*		Film formers; viscosity increasing agents-nonaqueous
Polystyrene/Hydrogenated Polyisopentene Copolymer	Polystyrene/Hydrogenated Polyisopentene Copolymer is a copolymer of polystyrene and hydrogenated polyisopentene.		Not reported
Sodium Methacrylate/Styrene Copolymer 33970-45-5	Sodium Methacrylate/Styrene Copolymer is a copolymer of sodium methacrylate and styrene monomers.		Opacifying agents
Sodium Styrene/Acrylates Copolymer 9010-92-8	Sodium Styrene/Acrylates Copolymer is the sodium salt of a polymer of styrene and a monomer consisting of acrylic acid, methacrylic acid or one of their simple esters.	 wherein R is a lone pair of electrons with a sodium cation, methyl, ethyl, propyl, or butyl.	Film formers; viscosity increasing agents-aqueous

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[2]

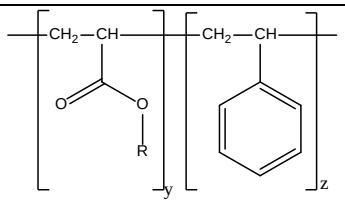
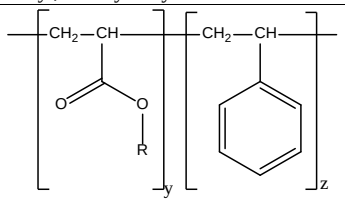
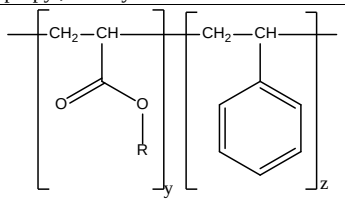
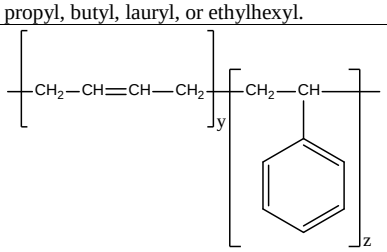
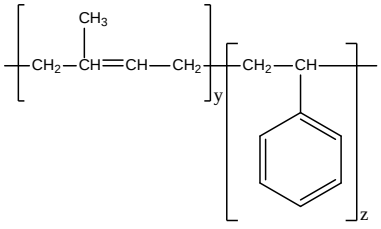
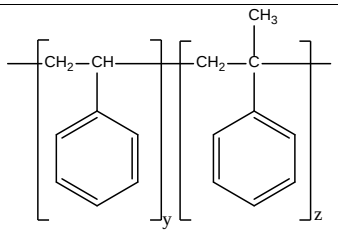
Ingredient CAS No.	Definition		Function(s)
Sodium Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer	Sodium Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer is the sodium salt of Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer	 wherein R is a lone pair of electrons with a sodium cation, methyl, ethyl, propyl, butyl, lauryl, or ethylhexyl.	Film formers
Styrene/Acrylates Copolymer 25034-86-0 25085-34-1 9010-92-8	Styrene/Acrylates Copolymer is a polymer of styrene and a monomer consisting of acrylic acid, methacrylic acid or one of their simple esters.	 wherein R is hydrogen, methyl, ethyl, propyl, or butyl.	Film formers; opacifying agents
Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer	Styrene/Acrylates/Ethylhexyl Acrylate/Lauryl Acrylate Copolymer is a coplymer of styrene, acrylates, ethylhexyl acrylate and lauryl acrylate.	 wherein R is a hydrogen, methyl, ethyl, propyl, butyl, lauryl, or ethylhexyl.	Film formers
Styrene/Butadiene Copolymer 9003-55-8	Styrene/Butadiene Copolymer is a copolymer of styrene and butadiene monomers.		Opacifying agents
Styrene/Isoprene Copolymer 25038-32-8	Styrene/Isoprene Copolymer is a copolymer of styrene and isoprene monomers.		Film formers; opacifying agents
Styrene/Methylstyrene Copolymer 37218-15-8 9011-11-4	Styrene/Methylstyrene Copolymer is a copolymer of styrene and methyl styrene monomers.		Binders; epilating agents

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[2]

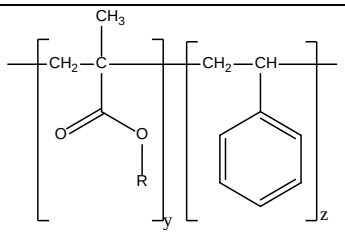
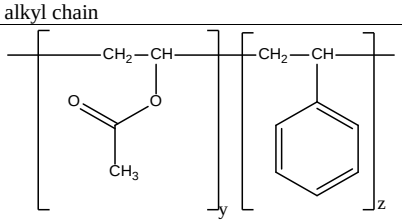
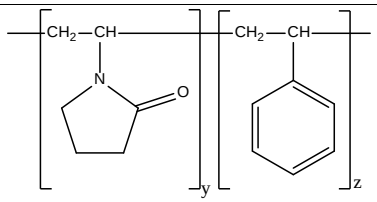
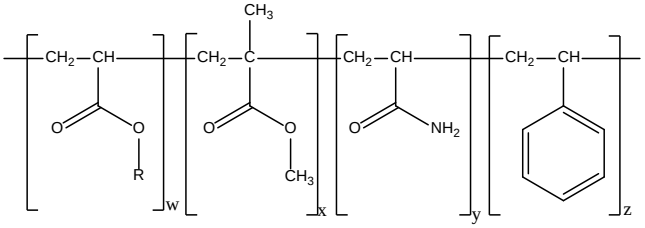
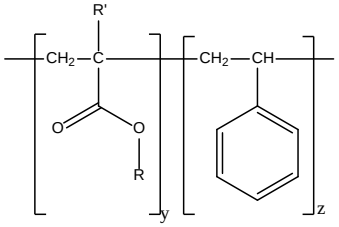
Ingredient CAS No.	Definition		Function(s)
Styrene/Stearyl Methacrylate Crosspolymer 91838-84-5	Styrene/Stearyl Methacrylate Crosspolymer is a copolymer of styrene and stearyl methacrylate monomers crosslinked with divinylbenzene.	 wherein R is an eighteen carbon, saturated alkyl chain	Absorbents; skin-conditioning agents-miscellaneous
Styrene/VA Copolymer	Styrene/VA Copolymer is a copolymer of styrene and vinyl acetate monomers.		Film formers;opacifying agents
Styrene/VP Copolymer 25086-29-7	Styrene/VP Copolymer is a copolymer prepared from vinylpyrrolidone and styrene monomers.		Film formers
Polyacrylate-2 31759-42-9	Polyacrylate-2 is a copolymer of styrene, acrylamide, octyl acrylate and methyl methacrylate monomers.		Film formers
Polyacrylate-5	Polyacrylate-5 is a copolymer of styrene, ethylhexyl acrylate, hydroxyethyl acrylate, and one or more monomers of acrylic acid, methacrylic acid, or one of their simple esters.	 wherein R is a hydrogen, methyl, ethyl, propyl, butyl, hydroxyethyl, or ethylhexyl. wherein R' is hydrogen, or in the cases where R is hydrogen, methyl, ethyl, propyl, or butyl, R' may also me methyl.	Film formers

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[2]

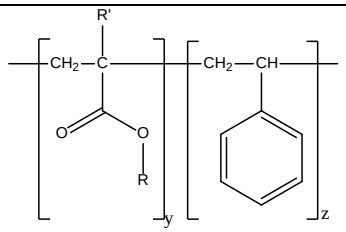
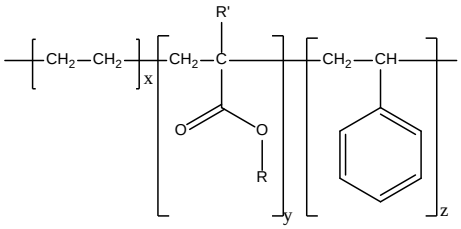
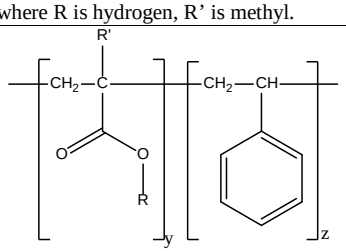
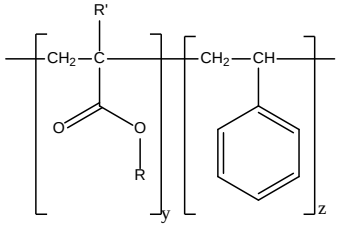
Ingredient CAS No.	Definition		Function(s)
Polyacrylate-12	Polyacrylate-12 is a copolymer of C3-11 acrylate, styrene, methacrylic Acid and acetoacetoxyethyl methacrylate monomers.	 wherein R is a hydrogen, methyl, an alkyl chain from 3 to 11 carbons in length methyl, or acetoacetoxyethyl wherein R' is hydrogen, or in the cases where R is methyl, or acetoacetoxyethyl, R' is methyl.	Film formers; nail conditioning agents
Polyacrylate-15 67892-91-5	Polyacrylate-15 is a copolymer of n-butyl acrylate, ethyl acrylate, methyl methacrylate, ethylene, methacrylic acid and styrene monomers	 wherein R is a hydrogen, methyl, ethyl , or butyl wherein R' is hydrogen, or in the case where R is hydrogen, R' is methyl.	Film formers; hair fixatives
Polyacrylate-16 67952-78-7	Polyacrylate-16 is a copolymer of n-butyl acrylate, diethylaminoethyl methacrylate, ethyl acrylate, methacrylic acid, hydroxypropyl methacrylate, methyl methacrylate and styrene monomers.	 wherein R is a hydrogen, methyl, diethylaminoethyl, or hydroxypropyl wherein R' is hydrogen, or in the cases where R is hydrogen, methyl, diethylaminoethyl, or hydroxypropyl, R' is methyl.	Film formers; hair fixatives
Polyacrylate-18	Polyacrylate-18 is a copolymer of n-butyl acrylate, ethyl acrylate, methacrylic acid, hydroxypropyl methacrylate and styrene monomers,	 wherein R is a hydrogen, ethyl, butyl, or hydroxypropyl wherein R' is hydrogen, or in the cases where R is hydrogen, butyl, or hydroxypropyl, R' is methyl.	Film formers; hair fixatives

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[2]

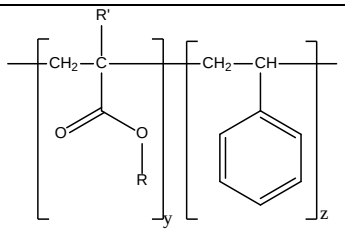
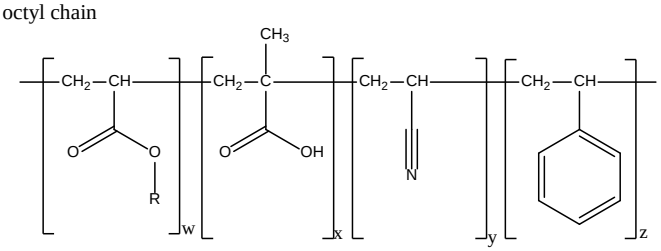
Ingredient CAS No.	Definition		Function(s)
Polyacrylate-21	Polyacrylate-21 is a copolymer of 2-ethylhexyl acrylate, butyl methacrylate, methacrylic acid, methyl methacrylate, hydroxypropyl methacrylate and styrene.		Binders; film formers; hair fixatives
Polyacrylate-30	Polyacrylate-30 is a copolymer of acrylonitrile, methacrylic acid, octyl acrylate, and styrene. wherein R is a hydrogen, methyl, butyl, ethylhexyl, or hydroxypropyl wherein R' is hydrogen, or in the cases where R is hydrogen, methyl, butyl, or hydroxypropyl, R' is methyl. wherein R is an octyl chain		Nail conditioning agents

Table 2. Properties of Polystyrene.[57,4,5]

Form	Transparent, hard solid; water-clear solid plastic
Molecular Mass	10,000 to 300,000
Density	1.04-1.065 (amorphous); 1.111 (crystalline)
Stability	Yellows on exposure to light
Solubility	Soluble in ethylbenzene, methyl isobutyl ketone, tetrahydrofuran, benzene, toluene, methylene chloride, and pyridine
Melting Point	240°C
Softening Temperature	Begins to soften at ≈ 85°C
Flash Point	345°C to 360°C
Auto-ignition Temperature	427°C
Refractive Index	1.591
Spectroscopy Data	λ_{max} at 260 nm, 215 nm, 194 nm abd 80 nm

Table 3. Properties of Styrene.[4]

Form	Colorless to yellowish, very refractive oily liquid
Density	0.9059
Solubility	Soluble in alcohol, ether, methanol, acetone, and carbon disulfide; sparingly soluble in water
Melting Point	30.6°
Boiling Point	145° to 146°
Flash point (closed cup)	31°C
Refractive Index	1.5463

Table 4. Properties of Styrene/Butadiene Copolymer.[5]

Form	Amorphous solid
Density	0.933
Refractive Index	1.5345
Melting Point	-59 to -64°C

Table 5. Properties of 1,3-Butadiene.[9]

Form	Colorless gas
Relative Molecular Mass	54.09
Solubility	Sparingly soluble in water (1 g/L at 20°C); slightly soluble in ethanol and methanol; soluble in benzene, carbon tetrachloride, and diethyl ether

Table 6. Composition and Properties of Trade Name Materials

Ingredient Name and Trade Name	Composition/Impurities	Properties
Styrene/Acrylates Copolymer (Sunspheres™ LCG Polymer)	styrene/acrylates copolymer (up to 28%), individual residual monomers (< 100 ppm maximum; for styrene, butyl methacrylate, and methyl methacrylate), aqua ammonia (up to 0.1%), water (up to 74%), and mixture of 5-chloro-2-methyl-2H-isothiazol-3-one and 2-methyl-2H-isothiazol-3-one (3:1) (up to 23 ppm). Impurity: copper (0.7 ppm).[58]	pH: 6.50-7.5.[58]
Styrene/Acrylates Copolymer (Sunspheres™ Powder)	styrene/acrylates copolymer (up to 90%), individual residual monomers (≤ 100 ppm maximum; for styrene, butyl methacrylate, and methyl methacrylate), fatty acid ethoxylate (up to 11%), related reaction products (up to 2%), and water (up to 3%). Byproducts and impurities: 1,4-dioxane (1.23 ppm), toluene (< 0.05 ppm), 2-methyl-4-isothiazolin-3-one (5 ppm), and diethylene glycol (64 ppm), and iron (2 ppm).[33]	
Styrene/Acrylates Copolymer (OPULYN™ 302B Opacifier)	styrene/acrylic copolymers (up to 41%), individual residual monomers (< 500 ppm maximum), styrene (≤ 50 ppm), water (up to 61%), and benzoic acid (up to 0.5%). Impurities: iron (2,153 ppb) and magnesium (1,735 ppb).[37]	molecular weight: > 1,000,000.[37]
Styrene/Acrylates Copolymer (ACUDYNE™ Shine Polymer)	styrene/acrylates copolymer (up to 41%), individual residual monomers (< 100 ppm; for styrene, butyl acrylate, and 2-ethyl hexyl acrylate), water (up to 61%), and benzoic acid (up to 0.75%). Impurities: chromium (70 ppb), iron (333-1996 ppb), and nickel (92 ppb).[34]	pH: 3-5.[34]
Styrene/Acrylates Copolymer (SunSpheres™ PGL Polymer)	styrene/acrylates copolymer (up to 26%), residual monomers (< 100 ppm; for styrene, butyl methacrylate, and methyl methacrylate), aqua ammonia (up to 0.1%), pentylene glycol (up to 6%), and water (up to 69%). Impurity: iron (1 ppm).[59]	pH: 6.5-7.5.[59]
Styrene/Acrylates Copolymer (OPULYN™ 301 Opacifier)	styrene/acrylic copolymer (up to 41%), water (up to 61%), residual monomers (< 500 ppm), and styrene (≤ 20 ppm). Impurities: heavy metals not detected.[50]	molecular weight: > 1,000,000; pH: 2.05-2.50.[50]
Styrene/Acrylates Copolymer (ACUDYNE™ Bold Polymer)	styrene/acrylates copolymer (up to 41%), individual residual monomers (< 100 ppm; for styrene, butyl acrylate, 2-ethyl hexyl acrylate), water (up to 61%), and benzoic acid (up to 0.75%). Impurities: chromium (82 ppb), iron (2,270 ppb), and nickel (173 ppb).[35]	pH: 3-5.[35]
Styrene/Acrylates Copolymer (Syntran® 5903; corresponds to CAS Nos. 9011-14-7 and 9010-92-8)	dry extract of 35% styrene/acrylates copolymer + 65% water.[38]	white, milky dispersion (pH 7).[38]
Styrene/Acrylates Copolymer (Syntran® 5904; (corresponds to CAS Nos. 9011-14-7 and 9010-92-8)	dry extract of 40% styrene/acrylates copolymer + 60% water.[40]	white, milky dispersion (pH 2.5).[40]
Styrene/Acrylates Copolymer (Syntran® 5905; (corresponds to CAS Nos. 9011-14-7 and 9010-92-8)	dry extract of 40% styrene/acrylates copolymer + 60% water.[41]	white, milky dispersion (pH 2.5).[41]
Styrene/Acrylates Copolymer (Syntran® 5907; (corresponds to CAS Nos. 9003-63-8 and 9010-92-8)	dry extract of 40% styrene/acrylates copolymer + 60% water.[39]	white, milky dispersion (pH 2.5).[39]

Table 6. Composition and Properties of Trade Name Materials

Ingredient Name and Trade Name	Composition/Impurities	Properties
Ethylene/Propylene/Styrene Copolymer and Butylene/Ethylene/Styrene Copolymer	Both are used in ingredient mixtures in which the total polymer content is usually in the range of 5 to 20 weight % and the main component may be either of the following: mineral oil, isohexadecane, isododecane, hydrogenated polyisobutene, isopropyl palmitate, isononyl isononanoate, and residual monomer (below limit of detection [100 ppb])[11]	
Polyacrylate-15 (Syntran® PC 5208; corresponds to CAS No. 67892-91-5)	contains the following: olefin-acrylic graft polymer (37%), ethoxylated secondary alcohol (3%), 1,3-butanediol (2%), 0.20% methylparaben, 0.15% propylparaben, residual monomer (< 5 ppm), and water (58%).[22]	molecular weight reported as m + n > 100.[22]
Polyacrylate-18 and Polyacrylate-19 (Syntran® PC 5117; corresponds to CAS No. 848236-12-4)	contains the following: acrylate copolymer (35%), 1,3-butanediol (4%), methylparaben (0.20%), propylparaben (0.15%), residual monomer (< 5 ppm), and water (60%).[23]	molecular weight reported as n > 50.[23]
Polyacrylate-18 and Polyacrylate-19 (Syntran® PC 5107; corresponds to CAS No. 848236-12-4)	contains the following: acrylate copolymer (30%), 1,3-butanediol (4%), methylparaben (0.20%), propylparaben (0.15%), residual monomer (< 5 ppm), and water (65%).[24]	molecular weight reported as n > 50.[24]
Polyacrylate-21 (Syntran® PC 5100 CG (corresponds to CAS Nos. 68541-61-7 and 26316-50-7)	acrylate copolymers in an aqueous phase. dry extract of 25% non-volatiles.[25]	typical pH: 8.0.[25]
Polystyrene (Syntran® 5900)	contains the following: polystyrene (31% to 33%), surfactants (2% to 3%), residual monomer (< 5 ppm), and balance is water.[26]	molecular weight of ~ 50,000 daltons.[26]

Table 7. Frequency and Concentration of Use According to Duration and Type of Exposure.[12,13]

	Ethylene/Propylene/Styrene Copolymer		**Butylene/Ethylene/Styrene Copolymer**		**Butyl Acrylate/Styrene Copolymer**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	413	0.075-8.2	400	0.008-8.2	NR	0.25
Duration of Use						
Leave-On	408	0.075-8.2	395	0.008-8.2	NR	NR
Rinse off	5	0.18	5	0.11-0.95	NR	0.25
Diluted for (bath) Use	NR	NR	NR	0.95	NR	NR
Exposure Type						
Eye Area	16	0.075-2.3	19	0.01-0.25	NR	NR
Incidental Ingestion	324	6-8.2	314	1-8.2	NR	NR
Incidental Inhalation- Sprays	32	0.5	29	1.9**	NR	NR
Incidental Inhalation- Powders	27	0.17-3.9*	25	0.008-0.84*	NR	NR
Dermal Contact	72	0.075-3.9	70	0.008-1.9	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	3	1-2	2	NR	NR	0.25
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	2	3-5.7	2	0.18-1.9	NR	NR
Mucous Membrane	328	6-8.2	318	0.11-8.2	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Hydrogenated Butylene/Ethylene/Styrene Copolymer		**Hydrogenated Ethylene/Propylene/Styrene Copolymer**		**Hydrogenated Styrene/Butadiene Copolymer**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	22	10	23	1.5-4.4	13	0.33-18.7
Duration of Use						
Leave-On	19	NR	20	1.5-4.4	13	0.33-18.7
Rinse off	3	10	3	NR	NR	2
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	1	2	NR	2.3
Incidental Ingestion	7	NR	7	NR	8	0.33-18.7
Incidental Inhalation- Sprays	4**	NR	4**	NR	2**	NR
Incidental Inhalation- Powders	4*	NR	4*	NR	1	4*
Dermal Contact	7	10	8	1.5-4.4	2	2.3-4
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	8	NR	8	NR	3	2
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	7	NR	7	NR	8	0.33-18.7
Baby Products	NR	NR	NR	NR	NR	NR
	Hydrogenated Styrene/Isoprene Copolymer		**Isobutylene/Styrene Copolymer**		**Methylstyrene/Vinyltoluene Copolymer**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	78	0.89-4.2	1	1	2	0.58
Duration of Use						
Leave-On	78	0.89-4	1	1	2	0.58
Rinse off	NR	4.2	NR	NR	NR	NR
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	25	NR	NR	NR	NR	NR
Incidental Ingestion	30	2.5-3	NR	NR	2	NR
Incidental Inhalation- Sprays	2	4**	NR	NR	NR	NR
Incidental Inhalation- Powders	5	3*	1	1	NR	NR
Dermal Contact	45	0.89-4	1	1	NR	0.58
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	2	4.2	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	1	NR	NR	NR	NR	NR
Mucous Membrane	30	2.5-3	NR	NR	2	NR
Baby Products	3	NR	NR	NR	NR	NR

Table 7. Frequency and Concentration of Use According to Duration and Type of Exposure.[12,13]

	Polystyrene		**Polystyrene/Hydrogenated Polyisopentene Copolymer**		**Sodium Styrene/Acrylates Copolymer**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	19	0.08-36.5	16	0.0002-1.2	25	0.49
Duration of Use						
Leave-On	16	0.08-0.4	13	0.015-1.2	19	0.49
Rinse off	3	36.5	3	0.0002	4	NR
Diluted for (bath) Use	NR	NR	NR	NR	2	NR
Exposure Type						
Eye Area	2	NR	7	0.15-1.2	NR	NR
Incidental Ingestion	NR	NR	NR	0.05	NR	NR
Incidental Inhalation- Sprays	5	0.4**	2**	NR	4**	NR
Incidental Inhalation- Powders	4	0.08-0.4*	2**	NR	4*	NR
Dermal Contact	10	0.08-36.5	16	0.0002-1.2	22	NR
Deodorant (underarm)	NR	NR	NR	NR	13	NR
Hair - Non-Coloring	9	0.4	NR	NR	3	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	0.49
Mucous Membrane	2	NR	NR	0.05	2	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Styrene/Acrylates Copolymer		**Styrene/Butadiene Copolymer**		**Styrene/VP Copolymer**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	272	0.028-35	9	NR	82	0.000038-1
Duration of Use						
Leave-On	121	0.028-35	NR	NR	30	0.000038-0.4
Rinse off	135	0.04-12	9	NR	52	0.021-1
Diluted for (bath) Use	16	0.2-0.4	NR	NR	NR	NR
Exposure Type						
Eye Area	11	0.36-15	NR	NR	NR	0.2-0.4
Incidental Ingestion	3	0.13	NR	NR	1	NR
Incidental Inhalation- Sprays	34	0.35-3.5	NR	NR	22	0.12
Incidental Inhalation- Powders	21	0.028-14.8*	NR	NR	6	0.12-0.2*
Dermal Contact	201	0.028-17.7	8	NR	18	0.000038-0.4
Deodorant (underarm)	2	0.4	NR	NR	NR	NR
Hair - Non-Coloring	8	0.2-1	1	NR	36	0.032-1
Hair-Coloring	NR	0.04-12	NR	NR	25	0.04-0.7
Nail	57	0.52-35	NR	NR	2	NR
Mucous Membrane	133	0.04-7.7	8	NR	6	0.057
Baby Products	2	0.2	NR	NR	NR	NR
	Polyacrylate-5		**Polyacrylate-15**		**Polyacrylate-16**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	3	NR	22	0.38	4	1-11.3
Duration of Use						
Leave-On	3	NR	NR	0.38	4	1-11.3
Rinse off	NR	NR	22	NR	NR	NR
Diluted for (bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	4	1-4.5
Incidental Ingestion	2	NR	NR	NR	NR	11.3
Incidental Inhalation- Sprays	NR	NR	NR	NR	NR	NR
Incidental Inhalation- Powders	NR	NR	NR	0.38*	NR	NR
Dermal Contact	NR	NR	NR	0.38	4	1-4.5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	22	NR	NR	NR
Nail	1	NR	NR	NR	NR	NR
Mucous Membrane	2	NR	NR	NR	NR	11.3
Baby Products	NR	NR	NR	NR	NR	NR

Table 7. Frequency and Concentration of Use According to Duration and Type of Exposure.[12,13]

	Polyacrylate-21	
	# of Uses	Conc. (%)
Totals*/Conc. Range	NR	0.7-0.9
Duration of Use		
Leave-On	NR	0.7-0.9
Rinse off	NR	NR
Diluted for (bath) Use	NR	NR
Exposure Type		
Eye Area	NR	0.9
Incidental Ingestion	NR	NR
Incidental Inhalation-Sprays	NR	NR
Incidental Inhalation -Powders	NR	0.7
Dermal Contact	NR	0.7-0.9
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	NR	NR
Hair-Coloring	NR	NR
Nail	NR	NR
Mucous Membrane	NR	NR
Baby Products	NR	NR

NR = Not Reported; Totals = Rinse-off + Leave-on Product Uses.
*It is possible that these products may be powders, but it is not specified whether the reported uses are powders.
**It is possible that this product may be a spray, but it is not specified whether the reported use is a spray.
Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

Table 8. Carcinogenicity Studies/Reviews of Carcinogenic Potential on Copolymers/Monomers

Copolymer/Monomer	Test Protocol/Basis for Conclusion	Results/Conclusion
Polystyrene	Groups of Wistar rats. Subcutaneous implantation of various forms of polystyrene: smooth discs (47 rats); perforated discs (51 rats); rods, sphweres, and fibers (40 rats); and powder (number of rats not stated).	Sarcoma incidences: 37 of 47 rats (78.7%), 25 of 51 rats (49%), and 15 of 40 rats (37.5%). Powder did not induce sarcomas.[5,60]
Polystyrene	Wistar rats (from 3 different laboratory sources; number not stated).	Differences in incidence of local sarcomas (8% to 40%) found, depending on the animal strain.[5,61]
Styrene	Groups of Fischer 344 rats and B6C3F$_1$ mice (50 males, 50 females/species) in NTP oral carcinogenicity bioassay. Styrene (in corn oil, by gavage) 5 days per week at doses up to 2,000 mg/kg/day (rats) and 300 mg/kg/day (mice). Dosing for 78 weeks (rats: 1,000 and 2,000 mg/kg/day dose groups; mice: 150 and 300 mg/kg/day dose groups) and 103 weeks (rats: 500 mg/kg/day dose group)	No convincing evidence for carcinogenicity of styrene found in rats or mice of either sex.[62]
1,3-Butadiene	Groups of 50 male and 50 female B6C3F$_1$ mice in NTP inhalation carcinogenicity study. Exposure to air containing 625 ppm or 1,250 ppm 1,3-butadiene 5 days per week (6 h/day) for 60 or 61 weeks.	Clear evidence of carcinogenicity in male and female mice.[28]
1,3-Butadiene	Groups of 70 male and 70 female B6C3F$_1$ mice in NTP inhalation carcinogenicity study. Exposure to air containing 6.25, 20, 62.5, or 200 ppm 1,3-butadiene 5 days/week (6 h/day) for up to 2 years	Clear evidence of carcinogenicity in male and female mice.[63]
1,3-Butadiene	Groups of 90 male and 90 female B6C3F$_1$ mice in NTP inhalation carcinogenicity study. Exposure to 625 ppm 1,3-butadiene 5 days/week (6 h/day) for up to 2 years	Clear evidence of carcinogenicity in male and female mice.[63]
Styrene	Sufficient evidence of carcinogenicity from studies involving experimental animals. Limited evidence of carcinogenicity of styrene in humans based on studies of workers exposed to styrene that showed: (1) increased mortality from or incidence of cancer of the lymphohematopoietic system and (2) increased levels of DNA adducts and genetic damage in lymphocytes from exposed workers	According to the NTP, styrene reasonably anticipated to be a human carcinogen.[64]
Styrene	Limited evidence of carcinogenicity of styrene in humans and in experimental animals	According to IARC, styrene possibly carcinogenic to humans.[27]
Styrene		According to the the United States EPA, styrene possibly carcinogenic to humans.[65]
1,3-Butadiene	Unit cancer risk estimate of 0.08/ppm, based on linear modeling and extrapolation of human data	According to the United States EPA, 1,3-butadiene carcinogenic to humans by inhalation exposure.[66]
1,3-Butadiene	1,3-Butadiene causes cancer of the hematolymphatic organs. There is strong evidence that carciniogenicity of 1,3-butadiene in humans operates by a genotoxic mechanism that involves formation of reactive epoxides, the interaction of these direct-acting mutagenic epoxides with DNA, and resultant mutagenicity. There is strong evidence	According to IARC, sufficient evidence for carcinogenicity of 1,3-butadiene in humans and in experimental animals.[67]

Table 8. Carcinogenicity Studies/Reviews of Carcinogenic Potential on Copolymers/Monomers

Copolymer/Monomer	Test Protocol/Basis for Conclusion	Results/Conclusion
Styrene/Butadiene Copolymer	Multi-plant cohort studies of male styrene/butadiene rubber workers	Significantly increased cancer risks, including risks of non-Hodgkin's lymphoma (NHL), NHL-chronic lymphocytic leukemia, and leukemia.[68,69]
Styrene/Butadiene Copolymer	Epidemiological information on styrene/butadiene copolymer workers	According to IARC, this epidemiological information suggests elevated risk for lymphato-hematopoietic malignancies.[5]
Polyacrylate	Cross-sectional respiratory survey of 164 workers exposed to polyacrylate dust for average of 20.7 years	No evidence of excess risk of lung cancer.[70]

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2014 FDA VCRP Data

Polystyrene

03C - Eye Shadow	2
05C - Hair Straighteners	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	3
05I - Other Hair Preparations	8
07A - Blushers (all types)	1
07E - Lipstick	2
07I - Other Makeup Preparations	1
10E - Other Personal Cleanliness Products	2
12D - Body and Hand (exc shave)	2
12F - Moisturizing	2
Total	**24**

Butylene/Ethylene/Styrene Copolymer

03B - Eyeliner	1
03C - Eye Shadow	2
03D - Eye Lotion	1
03F - Mascara	12
03G - Other Eye Makeup Preparations	2
04B - Perfumes	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	2
07A - Blushers (all types)	1
07C - Foundations	3
07E - Lipstick	362
07I - Other Makeup Preparations	27
08B - Cuticle Softeners	1
10A - Bath Soaps and Detergents	2
10E - Other Personal Cleanliness Products	1
11E - Shaving Cream	1
12C - Face and Neck (exc shave)	3
12D - Body and Hand (exc shave)	3
12F - Moisturizing	7
12J - Other Skin Care Preps	2
13B - Indoor Tanning Preparations	1
Total	**435**

Ethylene/Propylene/Styrene Copolymer

03B - Eyeliner	1
03C - Eye Shadow	1
03D - Eye Lotion	1
03F - Mascara	11
03G - Other Eye Makeup Preparations	2
04B - Perfumes	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	2
07A - Blushers (all types)	1
07C - Foundations	3

07E - Lipstick	371
07I - Other Makeup Preparations	26
08B - Cuticle Softeners	1
10A - Bath Soaps and Detergents	2
10E - Other Personal Cleanliness Products	1
11E - Shaving Cream	1
12C - Face and Neck (exc shave)	3
12D - Body and Hand (exc shave)	3
12F - Moisturizing	8
12J - Other Skin Care Preps	2
13B - Indoor Tanning Preparations	1
Total	**442**

Hydrogenated Butylene/ Ethylene/Styrene Copolymer

05C - Hair Straighteners	2
05I - Other Hair Preparations	6
07E - Lipstick	7
07I - Other Makeup Preparations	1
12D - Body and Hand (exc shave)	2
12F - Moisturizing	2
12J - Other Skin Care Preps	1
Total	**21**

Hydrogenated Ethylene/ Propylene/Styrene Copolymer

03C - Eye Shadow	1
05C - Hair Straighteners	2
05I - Other Hair Preparations	6
07A - Blushers (all types)	1
07E - Lipstick	7
12D - Body and Hand (exc shave)	2
12F - Moisturizing	2
12J - Other Skin Care Preps	1
Total	**22**

Hydrogenated Styrene/Butadiene Copolymer

03C - Eye Shadow	2
05C - Hair Straighteners	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	1
05I - Other Hair Preparations	2
07E - Lipstick	16
07I - Other Makeup Preparations	2
12F - Moisturizing	1
Total	**25**

Hydrogenated Styrene/Isoprene Copolymer

01B - Baby Lotions, Oils, Powders, and Creams	3

03C - Eye Shadow	49
03G - Other Eye Makeup Preparations	1
05C - Hair Straighteners	1
05I - Other Hair Preparations	2
07C - Foundations	1
07E - Lipstick	46
07I - Other Makeup Preparations	13
12C - Face and Neck (exc shave)	2
12F - Moisturizing	2
12J - Other Skin Care Preps	1
Total	**121**

Isobutylene/Styrene Copolymer

07B - Face Powders	1
Total	**1**

Methylstyrene/Vinyltoluene Copolymer

07E - Lipstick	2
Total	**2**

Polystyrene/Hydrogenated Polyisopentene Copolymer

12A - Cleansing	2
12C - Face and Neck (exc shave)	1
12F - Moisturizing	1
12J - Other Skin Care Preps	2
Total	**6**

Sodium Styrene/Acrylates Copolymer

02B - Bubble Baths	1
02D - Other Bath Preparations	1
05F - Shampoos (non-coloring)	2
05I - Other Hair Preparations	1
10B - Deodorants (underarm)	14
12A - Cleansing	2
Total	**21**

Styrene/Acrylates Copolymer

01A - Baby Shampoos	1
01C - Other Baby Products	1
02B - Bubble Baths	6
02D - Other Bath Preparations	10
03B - Eyeliner	5
03G - Other Eye Makeup Preparations	3
04A - Cologne and Toilet waters	1
04E - Other Fragrance Preparation	7
05B - Hair Spray (aerosol fixatives)	1

05F - Shampoos (non-coloring)	10
05G - Tonics, Dressings, and Other Hair Grooming Aids	1
07C - Foundations	5
07E - Lipstick	3
07I - Other Makeup Preparations	1
08A - Basecoats and Undercoats	4
08C - Nail Creams and Lotions	4
08E - Nail Polish and Enamel	125
08F - Nail Polish and Enamel Removers	1
08G - Other Manicuring Preparations	4
10A - Bath Soaps and Detergents	87
10B - Deodorants (underarm)	2
10E - Other Personal Cleanliness Products	38
12A - Cleansing	13
12C - Face and Neck (exc shave)	12
12D - Body and Hand (exc shave)	3
12F - Moisturizing	7
12H - Paste Masks (mud packs)	1
12I - Skin Fresheners	1
12J - Other Skin Care Preps	7
13A - Suntan Gels, Creams, and Liquids	3
13B - Indoor Tanning Preparations	1
Total	**368**

Styrene/Butadiene Copolymer

05A - Hair Conditioner	1
05F - Shampoos (non-coloring)	1
10A - Bath Soaps and Detergents	1
10E - Other Personal Cleanliness Products	15
Total	**18**

Styrene/VP Copolymer

04A - Cologne and Toilet waters	1
04E - Other Fragrance Preparation	2
05A - Hair Conditioner	2
05C - Hair Straighteners	1
05D - Permanent Waves	10
05F - Shampoos (non-coloring)	6
05G - Tonics, Dressings, and Other Hair Grooming Aids	10
05H - Wave Sets	2
05I - Other Hair Preparations	2
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	6
06H - Other Hair Coloring Preparation	19
07E - Lipstick	1
08B - Cuticle Softeners	2
10A - Bath Soaps and Detergents	3

10E - Other Personal Cleanliness Products	2
12A - Cleansing	1
12C - Face and Neck (exc shave)	3
12D - Body and Hand (exc shave)	1
12F - Moisturizing	2
12I - Skin Fresheners	1
12J - Other Skin Care Preps	2
Total	**79**

Polyacrylate-15

06B - Hair Tints	22
Total	**22**

Polyacrylate-16

03B - Eyeliner	3
Total	**3**

Polyacrylate-5

07E - Lipstick	2
08E - Nail Polish and Enamel	1
Total	**3**

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Jay Ansell, Ph.D., D.A.B.T.
Industry Liaison to the CIR Expert Panel

DATE: July 10, 2014

SUBJECT: Comments on the Tentative Report: Safety Assessment of Styrene and Vinyl-Type Styrene Copolymers as Used in Cosmetics

Key Issues

Monomer levels - As these compounds are very large and will not penetrate the skin, the key to their safety is the information about monomer levels. Monomer levels reported by industry (see table 6) were all <100 ppm (styrene listed as <5 ppm to <100 ppm depending on the trade name mixture), with the exception of Styrene/Acrylates Copolymer sold under the trade name OPULYN 302B Opacifier that had monomer levels <500 ppm with a styrene level of ≤50 ppm. Therefore, it is misleading to cite a 1981 reference and state "Since that time [1960's], polystyrene concentrations of ≤500 ppm residual styrene have been developed."

The low monomer levels, especially the styrene and 1,3-butadiene levels should be noted in the Abstract and stated in the Summary and Discussion sections.

The Introduction and/or Chemistry section and Summary should state that these ingredients are sold to the industry as mixtures as described in Table 6.

Table 6 - It is misleading to just state the maximum concentration of Styrene/Acrylates Copolymer in each trade name material. The supplier provided specifications which included the minimum and maximum levels of the Copolymer in each trade name material. Without the minimum level, a reader may imply that levels could also be much lower than the "up to" value provided.

The INCI name and the concentration range of the copolymer in each trade name material needs to be stated in the description of each study in which it was tested, e.g., "OPULYN™ 302B (39-41% Styrene/Acrylates Copolymer) was evaluated in an acute oral toxicity study in rats, and an oral LD50 of >5 ml/kg was reported."

Additional Comments

p.2, Introduction - Rather than saying that 1,3-butadiene "is a component of a limited number of copolymers included in this review", please state that it "is a component of three copolymers included in this review".

p.5, Cosmetic Use, p.18, Summary - In the Cosmetic Use section and the Summary, please indicate the number of uses reported to the VCRP for the ingredients with the most uses, and state the FDA product categories in which the highest use concentrations are reported.

p.6, Toxicokinetics, p.7-9, Acute Exposure - In the first paragraph, please indicate that because of the large size of these compounds they are not expected to be bioavailable following inhalation, oral or dermal exposure. This statement can be referenced to information sheets provided by industry. In the acute exposure sections the following statements (occurs 13 times) should be deleted:, "According to an acute toxicity profile on Syntran® PC 5208, the large molecular size of this polymer limits its bioavailability and none of the components is considered to be acutely hazardous. Thus, little or no systemic toxicity would be expected via the inhalation [oral or dermal] route of exposure."

p.12-13, 14 - The six paragraphs describing the use of EpiOcular assay to predict potential skin irritation (3 paragraphs under *in vitro* skin irritation and 3 paragraphs under *in vitro* skin irritation and sensitization) should be deleted from the report. The Discussion should note that based on the EpiOcular assay, Polyacrylate 15, Polyacrylate 18 and Polyacrylate-21 (at the concentrations tested) are not predicted to be irritants.

p.14 - The mouse local lymph node assay is an animal study and should not be presented in the *in vitro* subsection.

p.15 - On which gestation days were the rats and rabbits treated in the developmental toxicity studies? What were the routes of exposure in the multigeneration studies in rats?

p.16 - As no genotoxicity studies on Polyacrylate-15 were completed, please delete the information on Syntran EX-105.

p.16, Polyacrylate 21 - Please state that according to the Dictionary, Syntran PC 5100 is a mixture of Polyacrylate-21 and Acrylates/Dimethylaminoethyl Methacrylate Copolymer.

p.18 - Please correct: "P450-mediated oxygen to epoxybutane"

p.18 - In the Summary, it is not necessary to give the particle size of Polyacrylate that was received. The particle size of the material that was tested is sufficient for the Summary.

p.19 - Please state the INCI names represented by the information on trade name materials that were provided by industry.

Table 1, p.5 - The function for Styrene/Methylstyrene Copolymer has been changed from depilating agents to epilating agents.

Table 6, p.10-11 - As noted above, it is not sufficient to just state the maximum level of the polymer contained in each trade name material. Please provide the range of concentration as provided by the supplier.

Please correct the spelling of "Styran" (misspelling occurs three times at the bottom of p. 10).

Table 7 - The draft use protocol in the administration book for the June meeting does not included moisturizer products in the Incidental Inhalation - Powders row. Therefore, the 0.17% concentration for Ethylene/Propylene/Styrene Copolymer, the 0.08% concentration for Polystyrene, and the 14.8% concentration for Styrene/Acrylates Copolymer (all concentrations in moisturizer products) should not be in the Incidental Inhalation-Powders row.

Table 8, p.15-16 - The reviews (NTP, IARC, EPA) of the carcinogenic potential of styrene and 1,3-butadiene should not be included in this table as they are not carcinogenicity "studies". The reviews should be presented in the text of the report.

Reference 35, p. 18 - Please correct the spelling of "Suntran"