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# Safety Assessment of Trimellitic Anhydride Copolymers as Used in Cosmetics

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Status: Draft Final Report for Panel Review  
Release Date: September 2, 2016  
Panel Meeting Date: September 26-27, 2016

The 2016 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel 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 safety assessment was prepared by Monice M. Fiume, Assistant Director/Senior Scientific Analyst/Writer and Bart Heldreth, Ph.D., Chemist.



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### Memorandum

To: CIR Expert Panel Members and Liaisons  
From: Monice M. Fiume *MMF*  
Assistant Director/Senior Scientific Analyst  
Date: September 2, 2016  
Subject: Safety Assessment of Trimellitic Anhydride Copolymers as Used in Cosmetics

Enclosed is the Draft Final Report on the Safety Assessment of Trimellitic Anhydride Copolymers as Used in Cosmetics. (It is identified as *melply092016rep* in the pdf document.) At the March 2016 meeting, the Panel issued a Tentative Amended Report with the conclusion that **the data are insufficient to support the safety of the 6 trimellitic anhydride copolymers named in this report under conditions of intended uses.**

The Panel amended its original tentative conclusion (issued at the December 2015 meeting) of safe in nail products and insufficient data for use in all other types of cosmetic formulations because upon further deliberation, the Panel expressed concern that these copolymers are essentially chemically undefined. In the absence of fundamental data about the chemistry of these ingredients, the Panel stated that safety cannot be evaluated for the use of these copolymers in any type of cosmetic formulation.

Based on data from the FDA VCRP and the Council concentration of use survey, two of the trimellitic anhydride copolymers are reported to be in use. Both sources report that these ingredients are used in nail formulations, but only the VCRP data indicate that one of these ingredients is used in formulations that result in dermal contact.

The Panel stated that the following are needed to evaluate the safety of these ingredients in nail products:

- Method of manufacture; and
- Composition data.

In addition, the following are needed to evaluate the safety of these ingredients in cosmetics other than nail products:

- Molecular weight;
- Impurities, specifically, the amount of residual monomer in each copolymer
- Metabolism, specifically, whether these ingredients are metabolized in the skin;
- Dermal absorption; if absorbed, then genotoxicity and reproductive toxicity data are needed; and
- Dermal irritation and sensitization at maximum leave-on concentration of use.

One data submission was received, and it provided information on the method of manufacture and composition of Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer (*melply092016data*); these data address some, but not all, of the data needs. A NICNAS assessment recently issued for Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer stated that the ingredient cannot be classified for sensitization, and the assessment provided some physical and chemical properties data.

The new information included in the report is indicated with green highlighting.

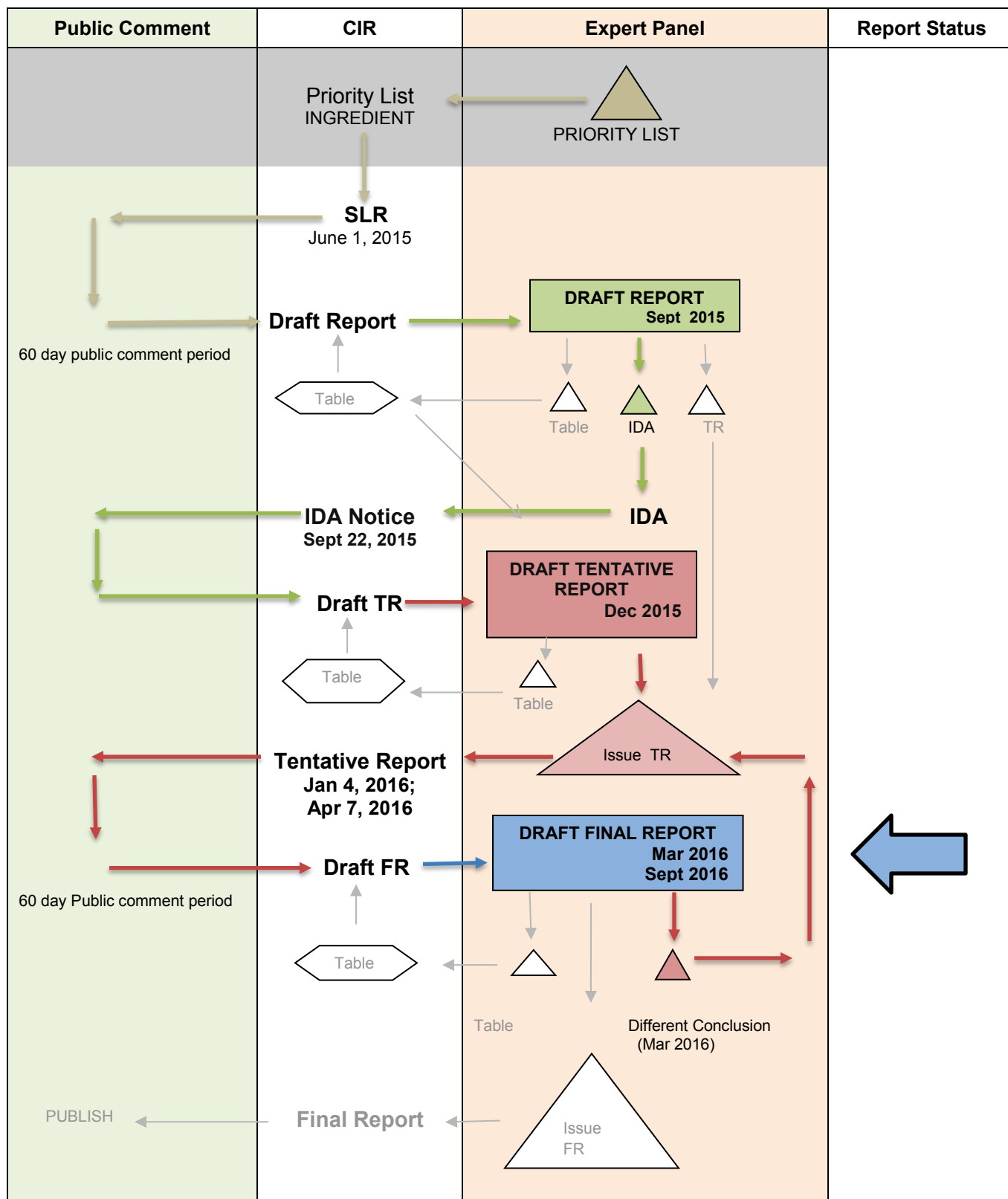
Comments received from the Council have been addressed (*melply092016pcpc\_1*; *melply092016pcpc\_2*).

Please review the Discussion to ensure that it captures the rationale for the report conclusion. The Panel should be prepared to issue a Final Report.

# SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Trimellitic Anhydride Copolymers

MEETING Sept 2016



## **TRIMELLITIC ANHYDRIDE COPOLYMER**

### **September 2015: Draft Report**

The Panel issued an insufficient data announcement, with the following data needed:

- Molecular weight;
- Method of manufacture and impurities data, specifically, the amount of residual monomer in each copolymer;
- Metabolism data, specifically, are these ingredients metabolized in the skin;
- Dermal absorption; if absorbed, then genotoxicity and reproductive toxicity data are needed;
- Irritation and sensitization data at the maximum leave-on concentration of 1% adipic acid/neopentyl glycol/trimellitic anhydride copolymer;
- however, if there are leave-on uses at higher concentrations, and/or with other ingredients, test data should be submitted at those concentrations and/or for those ingredients, as well; and
- Irritation and sensitization data relating to nail use.
- Additionally, some of the reported uses are in “other manicuring preparations”. The Panel would like clarification of the other uses.

### **December 2015: draft Tentative Report**

The Panel reviewed updated concentration of use data, as well as several unpublished dermal irritation and sensitization studies that were received in response to the IDA. A Tentative Report with a conclusion that the 6 trimellitic anhydride copolymers named in this report are safe in nail products in the present practices of use and concentration described in this safety assessment, but the data are insufficient to determine safety for use in all other types of cosmetic formulations, was issued.

### **March 31- April 1, 2016: draft Final Report**

VCRP data were updated.

The Panel noted the lack of data in this safety assessment and expressed concern that these copolymers are essentially chemically undefined. Because of an absence of fundamental data about the chemistry of these ingredients, the Panel amended its previous conclusion of safe in nail products and insufficient data for use in all other types of cosmetic formulations, and issued a tentative amended report with a conclusion that the data are insufficient to support safety.

The following are needed to evaluate the safety of these ingredients in nail products:

- Method of manufacture; and
- Composition data.

In addition, the following are needed to evaluate the safety of these ingredients in cosmetics other than nail products:

- Molecular weight;
- Impurities, specifically, the amount of residual monomer in each copolymer
- Metabolism, specifically, whether these ingredients are metabolized in the skin;
- Dermal absorption; if absorbed, then genotoxicity and reproductive toxicity data are needed; and
- Dermal irritation and sensitization at maximum leave-on concentration of use.

### **September 26-27, 2016: draft Final Report**

Data on the method of manufacture and composition of Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer were received.

## Trimellitic Anhydride Copolymers – Sept 2016 – Monice Fiume

[illegible]

| INFORMATION ON MONOMERS |                 |                |                   |                            |                          |                           |                              |                             |                               |                    |              |                 |                 |                   |                     |                             |                             |
|-------------------------|-----------------|----------------|-------------------|----------------------------|--------------------------|---------------------------|------------------------------|-----------------------------|-------------------------------|--------------------|--------------|-----------------|-----------------|-------------------|---------------------|-----------------------------|-----------------------------|
|                         | Reviewed by CIR | Toxicokinetics | Dermal Absorption | Animal Tox - Acute, Dermal | Animal Tox - Acute, Oral | Animal Tox, Acute, Inhal. | Animal Tox - Rptd Dose, Derm | Animal Tox, Rptd Dose, Oral | Animal Tox - Rptd Dose, Inhal | Repro/Dev Toxicity | Genotoxicity | Carcinogenicity | Dermal Irr/Sens | Ocular Irritation | Mucous Membrane Irr | Respiratory Effects - Human | Recommended Exposure Limits |
| trimellitic anhydride   |                 | X              |                   | X                          | X                        | X                         |                              | X                           | X                             | X                  | X            |                 | X               | X                 |                     | X                           | X                           |
| adipic acid             | X               | X              |                   |                            | X                        |                           |                              | X                           | X                             | X                  | X            | X               | X               | X                 |                     |                             |                             |
| cyclohexanedimethanol   |                 | X              |                   |                            | X                        |                           |                              | X                           |                               | X                  | X            |                 | X               | X                 |                     |                             |                             |
| ethylene glycol         | X               |                |                   |                            |                          |                           |                              |                             |                               | X                  |              |                 |                 |                   |                     |                             |                             |
| isophthalic acid        |                 | X              |                   | X                          | X                        | X                         |                              | X                           | X                             | X                  | X            |                 | X               | X                 |                     |                             |                             |
| maleic anhydride        | X               | X              |                   | X                          | X                        |                           |                              | X                           | X                             | X                  | X            | X               | X               | X                 |                     | X                           | X                           |
| neopentyl glycol        |                 | X              |                   | X                          | X                        |                           |                              | X                           | X                             | X                  | X            |                 | X               | X                 |                     |                             |                             |
| phthalic anhydride      |                 | X              |                   |                            | X                        |                           |                              | X                           |                               | X                  | X            | X               | X               | X                 | X                   | X                           | X                           |
| propylene glycol        | X               | X              | X                 |                            | X                        |                           |                              | X                           | X                             | X                  | X            | X               | X               |                   |                     |                             |                             |
| sebacic acid            | X               | X              |                   |                            |                          |                           |                              | X                           |                               | X                  |              |                 |                 |                   |                     |                             |                             |
| trimethylpentanediol    |                 |                |                   | X                          | X                        | X                         |                              | X                           |                               | X                  | X            |                 | X               | X                 |                     |                             |                             |
| trimethylolpropane      |                 |                |                   | X                          | X                        | X                         |                              | X                           |                               | X                  | X            |                 | X               | X                 |                     |                             |                             |

**Trimellitic Anhydride Copolymers**

| Ingredient                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | VCRP | InfoBase       | PubMed        | SciFinder                                                                                                                                                                                                                               | ChemPortal           | NTIS | FDA | ECHA | HPV | IUCLID/SIDS | EU             | NICNAS       | Web                                                                 |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|----------------|---------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|------|-----|------|-----|-------------|----------------|--------------|---------------------------------------------------------------------|
| <b>Adipic Acid/CHDM/MA/Neopentyl Glycol/Trimellitic Anhydride Copolymer</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 0    | ---            | 5 hits/5 used | <p>by CAS # - refined by document type – 6 hits/0 useful</p> <p>trimellitic anhydride copolymer – 286 hits/4 useful</p> <p>1,2,4-Benzenetricarboxylic anhydride – 68 hits/4 useful</p> <p>nothing new searching by individual names</p> | 0                    | 0    | 0   | 0    | 0   | 0           | no restriction | 0            | Google ChemID<br><br><u>No hits:</u><br>PubChem<br>HSDB<br>ChemSpdr |
| <b>Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer</b><br>(CAS # 28407-73-0)<br><u>Technical Names:</u> Adipic Acid, Polyester with 1,2,4-Benzenetricarboxylic Acid Cyclic 1,2-Anhydride and 2,2-Dimethyl-1,3-Propanediol; Hexanedioic Acid, Polymer with 1,3-Dihydro-1,3-Dioxo-5-Isobenzofurancarboxylic Acid and 2,2-Dimethyl-1,3-Propanediol; 1,2,4-Benzenetricarboxylic acid, cyclic 1,2-anhydride, polyester with adipic acid and 2,2-dimethyl-1,3-propanediol; 1,3-Propanediol, 2,2-dimethyl-, polyester with adipic acid and 1,2,4-benzenetricarboxylic acid cyclic 1,2-anhydride ; 1,3-Propanediol, 2,2-dimethyl-, polymer with 1,3-dihydro-1,3-dioxo-5-isobenzofurancarboxylic acid and hexanedioic acid; 5-Isobenzofurancarboxylic acid, 1,3-dihydro-1,3-dioxo-, polymer with 2,2-dimethyl-1,3-propanediol and hexanedioic acid; Adipic acid-1,2,4-benzenetricarboxylic anhydride-neopentyl glycol copolymer; Adipic acid-1,2,4-benzenetricarboxylic anhydride-neopentyl glycol polymer; Adipic acid-neopentyl glycol-trimellitic anhydride copolymer; Adipic acid-neopentyl glycol-trimellitic anhydride polymer<br><u>Supplier/Trade Names:</u> Uniplex 670-P (Unitex Chemical Corporation) | 411  | CAS#: supplier |               |                                                                                                                                                                                                                                         | there/nothing useful | 0    | 0   | 0    | 0   | 0           | no restriction | not assessed | Google; PubChem; ChemID<br><br><u>No hits</u><br>HSDB<br>ChemSpdr   |
| <b>Isostearoyl Trimellitic Anhydride/Trimethylolpropane Copolymer</b><br>(CAS # 1190965-82-2)<br><u>Supplier/Trade Names:</u> Schercemol ISTC Ester (Lubrizol Advanced Materials, Inc.)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 0    | CAS#: supplier |               |                                                                                                                                                                                                                                         | 0                    | 0    | 0   | 0    | 0   | 0           | no restriction | 0            | <u>No hits:</u><br>PubChem<br>ChemID<br>HSDB<br>ChemSpdr;<br>Google |

| Ingredient                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | VCRP | InfoBase                        | PubMed | SciFinder | ChemPortal | NTIS | FDA | ECHA | HPV | IUCLID/SIDS | EU             | NICNAS    | Web                                                          |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|---------------------------------|--------|-----------|------------|------|-----|------|-----|-------------|----------------|-----------|--------------------------------------------------------------|
| <b>Phthalic Anhydride/ Trimellitic Anhydride/ Glycols Copolymer</b><br>(CAS # 186688-25-5)<br>Technical Names: Phthalic Anhydride/Trimellitic Anhydride/Glycol/Neopentyl Glycol Copolymer;<br>Phthalic/Trimellitic/Glycols Copolymer;<br>5-Isobenzofurancarboxylic acid, 1,3-dihydro-1,3-dioxo-, polymer with 2,2-dimethyl-1,3-propanediol, 1,2-ethanediol and 1,3-isobenzofurandione;<br>1,2-Ethanediol, polymer with 1,3-dihydro-1,3-dioxo-5-isobenzofurancarboxylic acid, 2,2-dimethyl-1,3-propanediol and 1,3-isobenzofurandione;<br>1,3-Isobenzofurandione, polymer with 1,3-dihydro-1,3-dioxo-5-isobenzofurancarboxylic acid, 2,2-dimethyl-1,3-propanediol and 1,2-ethanediol;<br>1,3-Propanediol, 2,2-dimethyl-, polymer with 1,3-dihydro-1,3-dioxo-5-isobenzofurancarboxylic acid, 1,2-ethanediol and 1,3-isobenzofurandione;<br>Ethylene glycol-neopentyl glycol-phthalic anhydride-trimellitic anhydride copolymer<br>Supplier/Trade Names: Polynex Resin (Estron Chemical, Inc.) | 74   | CAS#: supplier; TRN 20 (7) 2006 |        |           | 0          | 0    | 0   | 0    | 0   | 0           | no restriction | June 2016 | No hits:<br>PubChem<br>ChemIDHS<br>DB<br>ChemSpdr;<br>Google |
| <b>Propylene Glycol/Sebacic Acid/Trimellitic Anhydride Copolymer</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 0    | ---                             |        |           | 0          | 0    | 0   | 0    | 0   | 0           | no restriction | 0         | No hits:<br>PubChem<br>ChemID<br>HSDB<br>ChemSpdr            |
| <b>Trimethylpentanediol/Isophthalic Acid/Trimellitic Anhydride Copolymer</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0    | ---                             |        |           | 0          | 0    | 0   | 0    | 0   | 0           | no restriction | 0         | No hits:<br>PubChem<br>ChemID<br>HSDB<br>ChemSpdr            |

**SciFinder – Feb 24 2015:** trimellitic anhydride copolymer (refined by document type) – 286 hits/4 useful

Search by CAS # (28407-73-0; 1190965-82-2; 186688-25-5) (refined by document type) – 6hits/0 useful

1,2,4-Benzenetricarboxylic anhydride – 68 hits/4 useful

Searched by individual names – nothing additional found

Set up Keep Me Posted alerts for all SciFinder search strategies

**PubMed – Feb 24 2015:** (((((((((Adipic Acid/CHDM/MA/Neopentyl Glycol/Trimellitic Anhydride Copolymer) OR Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer) OR 28407-73-0[EC/RN Number]) OR Isostearoyl Trimellitic Anhydride/Trimethylolpropane Copolymer) OR 1190965-82-2[EC/RN Number]) OR Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer) OR 186688-25-5[EC/RN Number]) OR Propylene Glycol/Sebacic Acid/Trimellitic Anhydride Copolymer) OR TDI/Trimellitic Anhydride Copolymer) OR Trimethylpentanediol/Isophthalic Acid/Trimellitic Anhydride Copolymer – 4 hits

((28407-73-0[EC/RN Number]) OR 1190965-82-2[EC/RN Number]) OR 186688-25-5[EC/RN Number] – 0 hits

Trimellitic AND Anhydride AND Copolymer – 5 hits/5 useful

1,2,4-Benzenetricarboxylic anhydride – 7 hits/0 useful

((trimellitic OR benzenetricarboxylic) AND anhydride) AND (irrita\* OR sensiti\*) – 202 hits/17 useful

**TRIMELLITIC ANHYDRIDE COPOLYMERS - transcripts**

**MARCH 2016 – FULL PANEL**

DR. BERGFELD: Moving on to the second ingredient under final reports, Dr. Marks and the trimellitic copolymers.

DR. KLASSEN: Which one was this?

DR. BELSITO: Trimellitic copolymers.

DR. KLASSEN: The last one?

DR. BELSITO: Yes.

DR. MARKS: So this is the draft final report of these ingredients. Our team moves that we add a final report with the conclusion that it's safe in nail products an insufficient for other uses.

DR. BERGFELD: There is a smile coming from Don. Don, you wish to comment, is that a motion, though?

DR. BELSITO: Yes, that's what I said.

DR. BERGFELD: Is there a second? Second from Paul?

DR. SNYDER: Okay.

DR. BERGFELD: Okay, Don, you want to comment?

DR. BELSTIO: Yeah, I mean that was our conclusion at the end of the last meeting and this team actually wanted molecular weight method manufacturing purity data on the residual monomer, even for nail products and at yesterday's meeting, Dan felt very strongly that these chemicals were totally undefined and was not comfortably moving forward on safety, even in nail products, for chemicals where we had no concept on molecular weight, on impurities, on manufacturing and he felt that we should go forward as an insufficient actually for all of them for molecular weight and method manufacturing impurities data.

I was sitting on the fence; I think Curt was. We moved over towards Dan's side. I know that Paul, I felt did not so Dan, perhaps you want to speak to this.

DR. LIEBLER: Sure, I made this point in our last meeting as well, as the transcript will show. I think the starting point for any safety evaluation is to define the chemical substance and any contaminants that may influence the safety evaluation.

We have gotten nothing. Nothing from industry to define this material, to define residual monomers and I think that is something, since I've been on the panel, we've never tolerated and I think that point has gotten lost in the idea that these are only applied to the nail and that with products applied to the nail, that tends to mitigate a lot of concerns about absorption and potential toxicities because they are only applied to the nail.

I think that it's quite likely that these ingredients will turn out to be just fine but we don't have the data that we almost always that we always insist on and I don't see any reason not to adhere to that policy this time so that's the reason I cannot support this. I still feel it's insufficient and if we let this go, I think it's a very bad precedent for the panel.

DR. BERGFELD: Ron Hill?

DR. HILL: I was just relying on the data that we did have for phthalates but I agree with Dan. We had data for the phthalates, we had a pretty good paper comparing these, the trimellitics with the phthalates in terms of their characteristics and the other part was that this was happening on the nail but I agree with everything you said.

DR. BERGFELD: Ron Shank? Tom, go ahead.

DR. SHANK: I was happy with if the application is only on the nail, molecularly, weight doesn't make any difference to me. The impurities I agree, we usually have that information but we also have exposures other than only to the nail.

DR. BERGFELD: Tom?

DR. SLAGA: I agree. I'll go with the (inaudible)

DR. BERGFELD: Okay, we have a motion that has been seconded. Is there a retraction of the motion or

DR. LIEBLER: I just want to say one thing. I do not disagree with the reasoning in terms of safety that my colleagues have expressed, but we can't let them do this to us.

DR. BERGFELD: Curt, do you want to make a statement since everyone else has?

DR. KLASSEN: Yes, I go along with Dan's comment and overall what he said both previously and at the end.

DR. MARKS: So I will retract my motion and Don, you can

DR. BERGFELD: Well we have to have a retraction of the second as well.

DR. MARKS: Oh.

DR. BELSITO: Agreed.

DR. BERGFELD: Okay, so the motion then is retracted. Is there another motion?

DR. MARKS: Yeah from what I gather in the discussion is we would move forward insufficient for method of manufacture and impurities in these ingredients and so it would be an insufficient. It would be an amended final report that is insufficient because of method of manufacturing in impurities, did I understand you correctly, Dan?

DR. BELSITO: Specifically the amount of residual monomer in each copolymer, for now. These were also reported to have non nail uses so for non-nail, there is an additional list of data needs that are the same as we had previously requested; those have not changed.

DR. BERGFELD: Understood. Is there a second, then?

DR. BELSITO: Second.

DR. LANGE: I just have a question process-wise, if they can go final since the conclusion is changing?

DR. BELSITO: No, it's not final, it's going back.

DR. LANGE: Okay, it's going back, okay.

DR. BELSITO: That's why I said amended.

DR. BERGFELD: Any other comments. We've had a motion yes, Don?

DR. BELSITO: Yeah, just in the discussion, I would agree with the introduction rather than I would agree with the Personal Care Products Council but the information there is an amount of information in the after you have a list of chemicals, the first full paragraph, the second paragraph, the whole second half of that paragraph, starting with "however, no information has been submitted regarding" all the way through the following paragraph was really data, it belongs in the document under data and then perhaps again under discussion but not in the introduction so I would move that.

DR. BERGFELD: Okay, so we will consider that editorial move. Any other discussion points? Ron Hill?

DR. HILL: It's probably again editorial cleanup but we had a discussion about the last paragraph of the discussion yesterday where it says sensory respiratory respiratory sensory irritant and we indicated that there was hypersensitivity type information available for these and that it wasn't just respiratory sensory irritant but also hyper sensitization is what I was fishing for. The last paragraph of the discussion, right before the conclusion.

DR. BERGFELD: Paul?

DR. SNYDER: Yeah, I pinged that area, the respiratory sensory irritant and I wasn't certain what they were saying was sensitizer and an irritant or not, we need clarification of that; I indicated in my book.

DR. BERGFELD: Okay, any other questions or comments or discussion? Seeing none, I call for the vote to go insufficient. All those in favor, please indicate by raising your hands. Thank you, unanimous.

(Motion passed unanimously)

### **Belsito Team**

DR. BELSITO: We're going to trimellitic copolymers the first one. So at the last meeting we issued a tentative report that the six trimellitic were safe in nail products and the data were insufficient to determine safety for use in all other types of cosmetic formulations. We've received no new data to support their safety in use of other cosmetic formulations so I think it is safe as used in now products and insufficient for others. I'll open it up to the group.

DR. LIEBLER: I have the same objection to this one that I had before which is that chemically these are undefined and we don't have method of manufacture impurities and I realize they're just being used on the (inaudible). As I said last time I can't sign off on anything that is chemically undefined so that's where I still am.

DR. BELSITO: Even on nail?

DR. LIEBLER: Doesn't matter.

DR. BELSITO: So your concern is the amount of residual monomer?

DR. LIEBLER: No it is just that we don't know what this substance is. We have a very general description but we don't know what the substance is.

DR. SNYDER: The only comment I had was on the table two we don't have any residual monomer at all is that correct?

DR. BELSITO: Yes.

MS. FIUME: Well we did not receive it.

DR. KLAASEN: Well I think somewhat of a philosophical view is how low can the bar go on a compound that you put on the nails only and this is I mean I guess I feel a little damned I don't have an absolute decision in that regard but I think we should have more about the chemical and its impurities as a minimum.

DR. SNYDER: Well we're not going safe as use we're going safe only for nail application.

DR. BELSITO: Right what Dan is saying that he feels uncomfortable even with nail products because he doesn't know what these are or what the impurities are.

DR. LIEBLER: It's not really for me about the impurities it is about not defining what the ingredient actually is. All we have is a name and we have a list of the monomeric components that go into making the ingredient. We've had other polymers that we've considered where we haven't had a truly precise description of what is there and I understand that is polymer chemistry and perhaps the manufacturer will worry about protecting a trade secret but it is possible to provide an adequate enough description of what this is and there has been no effort on the part of the supplier to do that to meet the request that I know have come from staff. I should also point out on Table 3 the minimum molecular weight is listed as this 442 which is probably can't be true and the citation is for reference 34 which is a pub chem entry which if you look at the pub chem entry they just have three monomers sitting there unconnected in a little viewing and the molecular weight calculator calculated 442 by summing up one molecule each of the three monomers. So it's a nonsensical number. So it is a little thing but anyway.

DR. BELSITO: Okay so where do we go here? In December had sent this out as a tentative final safe and now products, insufficient in others and we had given our a list of insufficiencies that at least sound partly like what Dan would like for all of them molecular weight, method of manufactured impurities data is that what you're asking for?

DR. LIEBLER: Sure yeah.

DR. BELSITO: Then we had gone on to ask for metabolism specifically whether these ingredients metabolized in the skin we would not need that for now right?

DR. LIEBLER: Right and these things are going to be because of their uses they're not small molecules. We're talking about molecules that are likely to be pretty big. This is just a matter of principle. I understand we've talked about it before, I'm not expecting anyone else to accept my position but I have my position and we don't need to waste any time arguing about it.

DR. BELSITO: I don't remember you being this strong about it last time.

DR. LIEBLER: Well I was.

DR. SNYDER: on three to one but I'm trying to think of the other nail use only ones that we've done and we've done two others haven't we at least one if not two?

DR. BELSITO: We we've done hydroquinone from various mutations.

DR. LIEBLER: Since I've been on the panel we haven't had any ingredient that the vendor has simply refuse to define and that's what we have and when you do that in my opinion I refuse to consider it further despite whatever other merits and logic can be applied. The fact that they're applied to the nail doesn't change that. I understand the reasoning is it's applied to the nail and we don't have as many potential concerns about absorption and so on but I agree with all that. But if you don't define the ingredient for us then I don't think we should consider it. I've explained my position and I don't think I can put it any differently and I'll still like you all in the morning if you don't vote with me but I'm going to support this one.

DR. SNYDER: Doesn't the dictionary define it?

DR. LIEBLER: No.

MS. FIUME: Only as a table one.

DR. LIEBLER: I'm not going to filibuster.

DR. BELSITO: I don't want a filibuster I mean I guess I just don't recall your objection being that strong and not being a chemist as far as I'm concerned we had some HRIPT here on a now product and it looked to so that's in essence really my due diligence is the skin part and maybe I was just distracted and I just didn't recall and I respect you and I didn't recall your objection being that strong so I'm sort of sitting on the fence now and looking at my other colleagues.

DR. SNYDER: I was in your camp I didn't have any issues and it seemed like what we were going with was insufficient for anything other than nail use but I am also sympathetic to Dan's concern about it not being chemically defined so we're really kind of proving something that we really don't know what it is.

DR. BELSITO: Which is some ways is going down a slippery slope.

DR. SNYDER: But reversing at this stage of the game

DR. BELSITO: You can reverse at any stage of the game. You can reopen and make it unsafe something you made safe before.

DR. DEWA: So we would go back out as insufficient?

DR. BELSITO: But it went insufficient for everything but nail. Now we're talking about going insufficient for everything now.

DR. BELSITO: So I think this was one of those mixed conclusions where you have a safe and insufficient. So it would have to go back out there would be my assumption.

DR. ANSELL: Yes it would be just how far back would it have to go?

DR. BELSITO: Yes and I would probably going out at such a short report because like Dan said there is no information there.

MS. FIUME: It would have to go out as a tentative report again.

DR. BELSITO: Right.

MS. FIUME: It wouldn't need to go IDA because IDA has already been done. We've asked for the data after the

DR. SNYDER: Yeah but you asked for the data in September, it was resolved in December.

MS. FIUME: Yeah but we never received the data so it could go out as a draft tentative with an insufficient conclusion. The name would be tentative amended report because we're changing the conclusion but they've already requested the data so it wouldn't be insufficient data because it would be the same data that wasn't received before.

DR. DEWA: Well no it would have to be insufficient again because the panel announced in December that they were resolved.

MS. FIUME: But it was the same data. So a tentative amended report with an insufficient conclusion would go out. So that's the stage it would have to go back to.

DR. BELSITO: Right. I'm comfortable putting it back there. Again I apologize I didn't realize how strongly you felt about that.

DR. KLAASEN: Yes well number one I do remember that Dan felt quite strongly about this before because we didn't know what it was and I guess my feeling is that while I don't think it is probably a problem because of this on the fingernail I think we need more information. If you go back and think about what we asked for on the methacrylates at one time for fingernails it was a lot more than this as I recall. So I would go along with Dan and say that it is insufficient.

DR. ANSELL: For molecular weight.

DR. LIEBLER: Method of manufacture, composition and impurities.

DR. ANSELL: And that information if it comes back would be substantive in terms of the assessment of the safety of the materials? If it's just the single chain it's going to be already at 500 and what monomer level would be too high for this.

DR. LIEBLER: This is literally just a matter of principle. They didn't check the box. To me the assessment of any of the safety ingredient begins with the description of the ingredient and the precision of that description of the ingredient is going to depend on the nature of the molecule and we all know polymers are a mix of things but all we have is the statement that this is a polymer made of a, b, c, and d period that's it and that is not enough. It is possible to satisfy my objection without ruining any trade secrets but this is just like contempt for the panel.

DR. BELSITO: So Paul are you okay with this?

DR. SNYDER: I'm a little conflicted because I think we're doing some disservice here with the last time just reading the minutes.

DR. BELSITO: I understand that but we've done disservice before so you wouldn't be comfortable with a safe and now so we're at a three and one and I'll present that tomorrow. I don't think we have to belabor it. Let's see what the Marks team says. I'm more inclined to agree with Dan and Curt seems to be sitting on the fence.

DR. LIEBLER: It is manufactured as a polymer. It is stated to be manufactured as a polymer. It isn't want of those things that polymerizes on the nail.

DR. SNYDER: So Ron Hill said that these are actually pre polymerized. These are polymers that are added to the nail product unlike the other acrylic which was polymerization in situ.

DR. LIEBLER: So last time on the panel we had Curt and I voted no and Ron abstained, Ron Hill abstained.

DR. BELSITO: Well we'll open it up for discussion tomorrow and see where Mark's team is. Now there were also comments from Personal Care Products Council that the second in the introduction once you get past the list of chemicals in the second paragraph the last two thirds of it and the next to third paragraph. So in the second paragraph it says however no information had been submitted regarding residual a monomer blah blah blah going all the way down to table two. Personal Care Products Council felt that these really didn't belong in the introduction they were more should be put into where the relevant data groups are and I would agree with that. That's not to me an introduction.

DR. LIEBLER: I agree.

DR. BELSITO: So I would make the requested changes that PCPC did and the way that that was ordered so I mean basically with the second paragraph according to the international dictionary this is how it is defined and then the next paragraph and after (inaudible) terminated by isostearic acid and then start up with the last paragraph of the introduction the safety of several of the non anhydromonomers and all the other information can be put into the relevant sections. Are you following me?

MS. FIUME: I'm not I'm sorry.

DR. BELSITO: Okay so in the introduction according to the International Cosmetic and then the next paragraph starts with the ingredients in this report are related as copolymers. Then follow it down four lines down to isostearic acid reference one. Starting with however, the rest of that paragraph and the next paragraph really I don't think belong in the introduction; they are statements of data on these materials that should be removed from the introduction and put into the relevant sections. So when we say impurities no data regarding the residual monomer. So take those bits of information and put them in the report where they belong and then they can always come back in the discussion. I think many of these are also discussion points but they need to be put into the data first and not into the introduction.

DR. LIEBLER: So basically in that second paragraph beginning with accordingly down to the end of the paragraph that follows which ends with Table 2.

DR. BELSITO: That was my only comment on this. So let me recap what I have here. So we're going insufficient for now what we want as molecular weight, method of manufacturing impurities, specifically residual monomer and for other non-nail uses we need that plus the additional data we had previously requested.

DR. LIEBLER: Correct.

DR. SNYDER: We have that and we also have metabolites right?

DR. BELSITO: No not for nail. Do you want metabolites for nail?

DR. LIEBLER: No.

DR. BELSITO: For now we want molecular weight, manufacture impurities, residual monomer. For non nail uses we want those plus everything else we had previously asked for.

### **Marks Team**

DR. MARKS: Okay, let's move on to the trimellitic copolymers, unless we have any more comments on the priorities. So at the December meeting the panel issued a tentative report with a conclusion that these six copolymers are safe in nail products in the present practice of use and concentration. But the data was insufficient to discern, determine safety for use in all other types of cosmetic formulation. So I tomorrow for our team would move to issue a final report with that conclusion, safe in nails and insufficient for other uses. And does that sound good? And then there's some concern again about the whether we should remove respiratory irritation from the introduction discussion, but I'll move on to that in a minute. A safe, does that sound good?

DR. SHANK: Yes.

DR. MARKS: As a final report? Okay, and then the comment about respiratory irritation.

DR. HILL: Page 31, right before the conclusion, is the paragraph in question.

DR. EISENMANN: I don't know if it's about removing it, other than making it a little different emphasis, I think. I always thought that sensitization was the bigger issue. But I could be wrong. So maybe irritation and sensitization in there or something like that. I just thought maybe you would want to look at what the emphasis was.

DR. HILL: What do they mean by respiratory sensory irritant? Something that makes you cough when you snort it? Who wrote this?

DR. MARKS: Monice, did you get a sense of what that was referring to? Christina?

MS. FIUME: For?

DR. MARKS: It's in the introduction, it says, "It can be a respiratory sensory irritant." The symptoms listed such as asthma and allergic rhinitis.

MS. FIUME: Without having the paper in front of me, my guess is that's how it was described in the text of the report. Especially in an occupational setting, that they have seen all of these effects. And I think the so that would have been the terms they would have used in the paper.

DR. HILL: Well I thought sensitization was the issue too. So that's why I also reiterated to look at this, even though the Council had also flagged it.

DR. MARKS: What is it, Carol, that you didn't like about that?

DR. EISENMANN: Maybe it's just the emphasis that maybe it should say can be (inaudible) sensitizers and the emphasis should be sensitization not irritation.

DR. HILL: I've read I didn't go back and look at the paper, if we had papers on that, but I thought that was the deal too. I can go back and look.

DR. EISENMANN: Especially since, I mean those symptoms, asthma, allergic rhinitis, at least those two elevated antibody levels suggest an immunologic reaction rather than just irritation. So I just thought without that first sentence, without saying sensitization, that the emphasis might not be quite right. I'm not questioning that it's not an irritant, but I just thought maybe, it might also want to put sensitization in that first sentence.

DR. HILL: Yeah, I thought the major concern I know I have the paper on here; I'm just not taking time to go back. And I apologize I didn't, since I had the issue noted down, but I thought the issue was sensitization in the workplace. Because of these anhydrides which react generate heptanes and over time people tend to get sensitized. That's what I thought the issue was. Because a lot of the data that was out there was for the phthalates instead of the trimellitates but then we had a couple of papers that compared them and we had a decent SAR and I thought it was sensitization that was the issue.

And I'm not sure the meaning of respiratory sensory irritants, if that's a thing, I guess I'd like to be sure we are saying what we mean. Is it something like formaldehyde, where you, you know, when you breathe enough of it you cough. That's what I thought we meant by that, but that's not what I thought we meant we were talking about here. I could be wrong too. I need to go back and look. I could do that this evening or early tomorrow morning.

MS. FIUME: Yeah, I'm trying to bring up the documents; it's just very slow coming up.

DR. MARKS: Yeah, where on page 27 in the introduction does it

DR. HILL: Oh, I'm on 31 in the conclusion, sorry. Or right before the conclusion.

DR. MARKS: 31, yes, so where in the introduction, going back to see the context, because the memo in the front, there in highlights, it's

DR. EISENMANN: It's in the second paragraph on the bottom of the introduction.

DR. MARKS: Oh, can be respiratory and exposure in the workplace. Or use and production so numerous adverse symptoms, such as

DR. HILL: Asthma, allergic rhinitis.

DR. MARKS: So this talks about just irritants. It doesn't talk about allergy in that paragraph.

DR. EISENMANN: I mean, asthma, allergic rhinitis and then elevated antibody levels. But yeah, the first sentence doesn't mention sensitization. That's why I wondered if that's really the emphasis if that's the correct emphasis for that paragraph.

DR. MARKS: Yeah, elevated antibody levels that's got to mean allergic.

DR. EISENMANN: Usually, yes.

DR. MARKS: Well I don't know any other way it can be interpreted, so you're right, in terms of, do you just add sensory irritants and allergens in that first sentence? The symptoms could be all from the irritants, but if you put elevated antibody levels then it's got to be

MS. FIUME: And we can very easily change it to respiratory sensitizers.

DR. EISENMANN: I think you could put both, irritant and sensitization and then that would be

DR. HILL: Here's what it says in table two. It has immunologic response TMA induced syndromes are related to high chemical reactivity which couples to humans seroalbumina and other proteins to form trimellitate protein conjugates and some of the TMA symptoms have been correlated to immunologic response to trimellitate haptenic in TNF plus, plus mice,

in late phase of TMA induced contact hypersensitivity, the peak of ear swelling responses occurred at 24 hours, with single challenge 8 hours after repeated challenge. So, I think it's both.

DR. MARKS: So on page 27, we can just add in that first sentence of that paragraph, can be respiratory sensory irritants and allergens. Is that what you said, Monice, to me includes the idea that there are both allergic and irritant reactions. Does that sound good, uh, Ron Hill?

DR. HILL: Mm hmm.

DR. MARKS: It's page 27, where in the discussion was the second (inaudible) Tom and Ron, does that this is editorial. I don't think this changes, obviously a conclusion, but

MS. FIUME: It's the last paragraph in the discussion.

DR. MARKS: And what page is that? 30

DR. SHANK: 31.

DR. MARKS: Yeah, so just respiratory irritants and allergens. Again, just repeat that. Carol, does that address your concern?

DR. EISENMANN: Yes, that's fine.

DR. HILL: Mine as well.

DR. MARKS: Okay. That's 31. Let me go back here to enter, add allergens in intro and discussion, page 27 and 31. Okay. So tomorrow I'm going to move that we issue a final report with the conclusion safe in its use in nails and nail products and insufficient for other uses. And then we'll just make the discussion points that add allergen as an adverse respiratory effect, in the introduction and in the discussion. Sound good team?

DR. SHANK: Yes.

DR. MARKS: Okay. Let me go ahead and close that.

#### **DEC 2015 – FULL PANEL**

DR. BERGFELD: So we're moving on to the reports advancing. And the next one is Dr. Belsito, one of the copolymers, trimellitic.

DR. BELSITO: Trimellitic anhydride copolymers. So at the September meeting we issued an insufficient data announcement requesting additional data on manufacturing impurities; molecular weight; metabolism; dermal absorption and, if absorbed, geno and repro toxicity; skin irritation and sensitization; and in terms of use, particularly in nail products. At that time we were told that there were three products that were non nail leave ons. We've not been told that there are no leave ons that are not used on the nail, that all the leave ons are all the uses are on nail products. So we thought we could go safe as used in nail products.

However, since we're also told that the other uses aren't going to be removed from the dictionary and will remain there, we thought that we could continue to say that for other uses it was insufficient for all the data needs we had originally requested.

DR. BERGFELD: And that's a motion?

DR. BELSITO: And that's a motion.

DR. BERGFELD: Any comment?

DR. MARKS: Yeah, our team concurred with that, I guess. You put in the tentative report, in the conclusion, safe for nail use only and then in the discussion mentioned insufficient for other uses, so I just it's a wording and it is a conclusion to say only include nail and not mention insufficient for others and put that in discussion. I don't think that's a big point, but we should settle it now so that when it's sent out which way do you prefer, Don or Dan?

DR. BERGFELD: Well, let's talk about what we've done in the past, though. Insufficient has always appeared in the conclusion. To bury it in the discussion is another new activity. What do you think?

DR. BELSITO: I think we should follow whatever mechanism we've used in the past and I believe that is always saying that the other uses would be insufficient and then putting in the discussion why.

DR. BERGFELD: Okay. Dan?

DR. LIEBLER: Wilma, I had a concern about these because we really don't have information about molecular weight, chemical composition, and impurities, method of manufacture for these compounds. Just because they're being used in nail products doesn't make that concern go away, that need go away in my mind. I personally don't feel comfortable evaluating

the safety of something that is chemically undefined. I mean, it's defined only in the sense that we're told that they're polymers of this, that, and the other. And there's a nice drawing of potential structures or units of these polymeric products, but we really should, I think, ask for the information that describes these well enough at least to evaluate their safety in terms of molecular weight, residual residues. These are things we commonly ask for.

I understand that there could be a concern about trade secrets as it came up in the discussion yesterday, but I think it's possible to thread that needle in a way that satisfies our needs and what I feel is our responsibilities to have that information as part of our evaluation. So that's why I can't support these as safe as used even in the nail products.

DR. BERGFELD: Other comments? Ron Hill? Ron Shank? No?

DR. SHANK: I don't have a problem with safe as used for nail products. If you had small molecular weight, small molecules in this mix, would that change your opinion for a nail product?

DR. LIEBLER: I acknowledge that putting these things on nails means there's probably going to be no absorption, but I object to reviewing anything for which we don't have a description of what the hell it is, period.

DR. BERGFELD: Ron Hill?

DR. HILL: The concern I had was actually more related to anything small and potentially volatilized when it was used in the nail area, so even that didn't fully resolve some of the concerns that I had that may be more related to phthalic anhydride than trimellitic anhydride if that's residual and we didn't get clear information on that in some cases. So I don't know, but I certainly shared his concerns.

And we talked in the context of high molecular weight, the high molecular weight ones used on the nail yesterday, knowing that absorption from the nail, per se, as long as it's only on the nail would definitely minimize the issues. But I totally agree with you about not being sure of what we're reviewing is a problem in my mind always.

DR. BERGFELD: Tom, do you have a comment?

DR. SLAGA: Well, I agree with Ron. I didn't have any problem with the nails and the safe as used, but I do understand Dan's concern. Sometimes we don't deal with that and we just let it slide by, but in this case, this would be a fixed you know, there wouldn't be any movement of these molecules even if there was some simple molecules.

DR. BERGFELD: Paul, any comment?

DR. SNYDER: No.

DR. BERGFELD: Curt?

DR. KLAASSEN: I can see both sides of the coin here. And if we go back and look at what we kind of asked for with the methacrylates and some of those compounds when they were putting on the nails, we sure requested, if I remember correctly, you know, how fast the reaction really proceeds. Is there any monomers left at the end? And things like that.

I mean, it almost gets to the point can you put anything on your fingernails? How low is the bar for fingernails? I mean, we're pretty low.

And I agree, it doesn't need to be as high as if you're putting it on mucus membranes, but it's kind of a philosophical question of how much I guess I would like to have some idea of how much monomer is left or how fast it polymerizes, which I'm sure is relatively fast. But how much monomer is left would be nice to know.

DR. HILL: Yeah. So these are actually pre polymerized. These are polymers that are added to the nail product unlike that other, the acrylate, where it was polymerization in situ, at least if I'm understanding correctly.

DR. KLAASSEN: Oh, I didn't check that.

DR. HILL: So these would just be residual in the polymers or anything that's small enough molecular weight that we might still have a problem.

DR. LIEBLER: So one of the physical chemical properties items in Table 3 on PDF 31 lists the molecular weight as 442. And Ron pointed this out in the last meeting that this is not a large molecule. And it turns out that this is probably not the actual molecular weight of one of these molecules or even within a range. And so I think this, at the very least, is perhaps incorrect in the report, but it's going to be incorrect until we have information about what these actually are.

DR. HILL: And 400 on the nail may still be within the realm of safety because as long as it's actually on the nail I don't have any sense of the epidemiology of, for example, cancers developing around the nail, but I've never heard that this is a big problem in the world, in the cuticle area and so forth.

DR. BERGFELD: They generally have some kind of cover that covers the cuticle when they apply these products. Don, you want to make a comment about your respective conclusion?

DR. BELSITO: No.

DR. BERGFELD: No. And it's been seconded. Everyone has commented, everyone's been heard and recorded, so we'll call the question. All those in favor of safe for nail use? Okay, so six. And Dan opposed? Opposed?

DR. LIEBLER: Opposed.

DR. BERGFELD: Opposed?

DR. HILL: I'm abstaining.

DR. BERGFELD: Abstaining. Opposed, Curt?

DR. KLAASSEN: I'll oppose.

DR. BERGFELD: Two opposed, abstaining. I think that the yeses carry, so safe for nails.

I think, however, we need to make a statement here that we need to have the composition of these ingredients.

DR. LIEBLER: Starting tomorrow, right.

DR. BERGFELD: Starting tomorrow, yes. Monice?

MS. FIUME: Can I ask for some clarifications for the discussion? First, I have it stated that these monomer units industrially they're very irritating, sensory and respiratory irritants. Any language guidance for the discussion that you can give as to why that's not relevant? Is it because residual monomers are not expected and, therefore, it's not a concern? Just so that I have the language correct for the discussion.

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

DR. HILL: We have information that there can be residual monomer present in these polymers. And I think the idea is that because we've restricted to the nail, the absorption would be expected to be very low and toxicologically inconsequential. But, again, I just abstained from the conclusion because I feel like after our discussion I was not

MS. FIUME: Actually we have no residual monomer information. We have no

DR. HILL: I thought we had. I was pretty sure we had for at least one of the ingredients something about residual monomer levels. I will retrace my steps here, but I was pretty sure. That's not the same as having it for every single ingredient, which would be my preference certainly. And, again, I didn't vote in favor of the conclusion, only abstained, which is a weaselly position.

MS. FIUME: I was going to say we don't have residual monomer information. We have a statement saying that it can be designed to be manufactured with little to no residual monomer, but we have no information on the exact manufacturing process or the amount of residual monomer present.

DR. BELSITO: If there was significant residual monomer it wouldn't be a very good nail enamel, so one would have to presume that the levels were very low and that it occurs within a fairly rapid period of time because I don't think most women want to paint their nails and have to wait an hour to do something else.

MS. FIUME: Then I did have one other question. As far as one of the requests was the HRIPT and also irritation and sensitization for nails products. The data that were received were not at concentration of use, so if I could have some help with some language as to why the lower concentration is applicable to the higher concentrations, just so I can address it in the discussion.

And then I also didn't know for my own purposes in developing that, when they did the HRIPT the product was applied to the patch, allowed to volatilize or dry before being patch tested, and if that has any role in the results that needs to be addressed in the discussion.

DR. BELSITO: So in terms of allowing the monomer to dry, typically what I did before we had ethyl cyanoacrylate in petrolatum to test for, it's also what I do when I'm testing nail polishes as is. If you don't allow the monomer to dry it's very difficult to remove the patch test from the patient without ripping their skin off, so that is a typical manner for testing a glue or a nail polish.

I think in terms of the fact that our HRIPT on a nail product is lower than maximum concentration, again, one would assume that these are being applied to the nail and that there's little contact with skin itself. At most, perhaps, some contact with cuticular skin, which is largely dead corneocytes, so I didn't have any issue with that.

And also, in terms of reports of sensitization to these plasticizers there aren't any that I'm aware of in the literature.

DR. BERGFELD: Jim, you want to add to that?

DR. MARKS: No, I concur with everything Don said. The only other thing I would add is that we don't test it until it's dry, patch test until it's dry is because it can be quite irritating, also, so you let it dry besides pulling the skin off. So now I concur with everything Dr. Belsito said.

DR. BERGFELD: You okay then?

MS. FIUME: Yes, thank you.

DR. BERGFELD: Okay. Well, thank you very much. And if there are other questions that you need, you can contact either Dr. Belsito or Dr. Marks regarding that.

#### **Belsito Team**

DR. BELSITO: Okay, so we did silk, we did monoglyceryl monoesters. So this gets us to trimellitic anhydrides. At the September meeting we were insufficient, and we wanted manufacturing and impurities, molecular weight, metabolism, durable absorption, and if absorbed, genotox and reproductive tox, skin irritation and sensitization data relating to particularly the use in nail products, and we got irritation sensitization data nail product formulations, updated concentration of use, and there were no other data, but we're now told that it's only used in nail products. However, table 4 still indicates three products in the VCRP as none now. So the question again becomes, how do we address that? Because if we say safe as used, our table has three products where it's not a nail.

DR. EISENMANN: Well, you can say safe for use of nail products only.

DR. BELSITO: I was comfortable with that. Safe as used, and I said should we specify nail only, and we can do that. So safe as used in nail product, insufficient for other uses.

DR. EISENMANN: Now, are you going to include all the ingredients or just the two ingredients for which you have data?

DR. BELSITO: Now, I was fine with all the ingredients as safe as used in nail products, and then insufficient for other uses, as outlined in the previous thing.

DR. LIEBLER: I just can't quite swallow signing off on

DR. BELSITO: We don't want you to swallow it then.

DR. LIEBLER: I can't swallow signing off on anything for which we really don't have the basic description of the material. We have the idea of how it's synthesized in a reasonable speculation done in ChemDraw of what a structure might look like, but we got nothing when it comes to molecular weight, impurities, composition. And somebody knows this. This has to be known and we don't have it, and I think that that ought to be a bedrock principle for us, even if you're going to put it on a nail or put it on a doorknob.

DR. BELSITO: But it's adipic acid/neopentyl glycol/trimellitic anhydride copolymer, you can't figure that out?

DR. LIEBLER: I like Bart's nice drawing, but it really doesn't tell. The thing is that it looks like polymer, and then if you look at pdf 31 this is what Ron Hill pointed out in our last meeting on table 3, this adipic acid/CHDM/MA/neopentyl glycol/trimellitic anhydride copolymer has a molecular weight listed at 442 grams.

DR. EISENMANN: That source tends to provide, I'd say, a minimum molecular weight, except you add each of those components, the molecular weight of each component, that's what that molecular weight is.

DR. LIEBLER: Yes, okay, but that's like a wink and a nod, and we're supposed to know the secret code to interpreting that. We ought to be provided with the actual information or at least a range. If we know, for example, most polymers that we've ever looked at have at least a range of molecular weight. If the 442 is meant to be the unit that Bart drew in a structure, essentially, or the equivalent of that, that doesn't really tell us what the polymers looked like. The information will only make this look better, but I just have a problem with signing off on anything where we don't have that basic information.

DR. EISENMANN: The clients are not coming forth with it

DR. LIEBLER: Then they're not

DR. EISENMANN: and there's nothing I can do about it.

DR. LIEBLER: They're not coming forth with it. I'm not coming forth with my assent.

DR. EISENMANN: Well, that's why I suggest that maybe the two for which you have sensitization data are safe, and let the other ones go, because you don't even have sensitization. So you have some idea that there's no residual monomer that's causing

DR. LIEBLER: Right.

DR. EISENMANN: sensitization, and that would be the main issue, and it's a nail product use.

DR. LIEBLER: As you guys know, from listening to me on this panel for how many years I've been on it, I'm a pretty reasonable guy, and when it comes to reasonable inferences about chemical safety

DR. KLAASSEN: Oh, yeah?

DR. LIEBLER: but there's nothing here, and when you give me nothing, I can't go half the distance to the goal on nothing. So I'm not comfortable with it, and as far as I'm concerned, it's insufficient.

DR. BELSITO: For?

DR. LIEBLER: For molecular weight, chemical composition, and impurities, and method of manufacture while they're at it. These are the same things that we listed as insufficient before that were that we didn't get. So I'm still there.

DR. BELSITO: Even though they're used on nail.

DR. LIEBLER: I don't think we should concede not having that basic information in our reports no matter what they're used on, even if they're used on nail.

DR. BELSITO: Paul? Curt?

DR. KLAASSEN: Well, I'll admit that's not asking for very much. These chemical parameters are not that difficult to obtain. Some biological information is extremely costly to obtain, but I think things like molecular weight I mean, this is a polymer there should be at least a range of what percent is monomer, that's a

DR. BELSITO: But see, what I'm thinking is is that these are applied as monomers and polymerized on the nail, no?

DR. SNYDER: We do have three non nail uses?

DR. BELSITO: No, those have been withdrawn. That's what I said.

DR. SNYDER: Well, that's no problem with me.

MS. FIUME: They've been withdrawn according to the council survey this morning. According to VCRP those data, FDA confirmed this morning, those data are within the last 10 years, and those are where the non nail uses were found was in the VCRP.

DR. SNYDER: That's more of a problem for Curt than it is for me.

DR. BELSITO: Dan, these are all film formers, so it's like dealing with methacrylates and ethylmethacrylate in the nail. You put them on and you have a molecular weight of the monomer, and then within minutes, you've got residual monomer and molecular weight is the polymer, and so that's probably why you're not They can give you the molecular weight of the monomer, but these are plasticizers, they're polymerized.

DR. LIEBLER: Sure. No, I get that.

DR. BELSITO: Yes.

DR. LIEBLER: I understand that completely.

DR. BELSITO: So even if you have a molecular weight for a monomer, how does that help you?

DR. LIEBLER: Because I have it.

DR. EISENMANN: Well, don't you have the molecular weights of the monomers

DR. LIEBLER: Oh, the monomers, sure.

DR. EISENMANN: Right.

DR. LIEBLER: Actually, I'm sure that they have residual monomer less than a few ppm.

DR. EISENMANN: I'm sure they have it too, and I'm aware that companies that are buying this ingredients are getting the information from the supplier, but the supplier does not want their information on CIR's website, and it's been an issue. The report said, and Bart must have found information, that there are ways to manufacture these polymers without I can't remember the exact language. I just thought maybe you could repeat that language and put the onus on the finished product manufacturer that the products need to not because there's a sensitizer in this the product should not contain that sensitizer, and that they need to prepare these ingredients using methods that limit the monomer. The companies are getting this information, because they tried to send it to me, but I can't give it to you because the supplier says, no, we don't want it on CIR's website.

DR. LIEBLER: So they don't have to put all of their information on CIR's website to satisfy my concern. What they're putting up is no information, and that's where I have a problem. And you can tell that I'm not getting more compliant as the discussion is going on.

DR. EISENMANN: But I'm frustrated with the suppliers. I'm not jumping here either.

DR. LIEBLER: I made my point. I might do a Ron Hill and be a conscientious objector on chemistry.

DR. EISENMANN: I was hoping you might just do the two ingredients, because you have sensitization data, and for the other ingredients, say, well, you either need sensitization data or you need to know levels of monomer. You need one or the other.

DR. LIEBLER: So we do botanicals where we don't have the botanical ingredient fully described in detail.

DR. EISENMANN: Correct.

DR. LIEBLER: And so we already have a process where we often get information about constituents of concern in these, so we have a general description of what they are, and the limiting information about constituents of concern, i.e., monomers less than X% per X ppm residual monomer. If we had something like that, my objection would go away. What we have is nothing.

DR. EISENMANN: You have sensitization data provided (inaudible).

DR. LIEBLER: No, no, that's on the nature of the substance, okay.

DR. KLAASSEN: That might be, I think, what Carol's saying is that is another excuse for getting the information, is that

DR. LIEBLER: That we have sensitization data?

DR. KLAASSEN: Yes. So therefore we need to know how much monomer is in here.

DR. LIEBLER: Yes, these are clean on sensitization, right?

DR. KLAASSEN: Oh, I thought I can't remember.

DR. EISENMANN: There are case reports that some people said developed sensitization.

DR. KLAASSEN: Right.

DR. EISENMANN: But the studies that were provided were clean.

DR. LIEBLER: Yes, sensitization data, I understand how it's relevant as a part of our decision process overall, but it doesn't substitute for the impurities and some description of the chemical composition other than a list of the monomers, which is basically what we have right now.

DR. BELSITO: So if we go insufficient for them all, then in two years, unless the company coughs up the data we're asking for, it will be unsupported. So let's go insufficient for them all. Ask for the data if you feel that way, Dan. I guess it ticks me off at the idea of a company turning around and saying they're not going to give you such basic data. It's not like a perfumer who's giving you the exact amount of the 40 different fragrances they put in Chanel No. 5. We're just asking for residual monomer when it polymerizes, or a molecular weight.

DR. SNYDER: So we already have a draft discussion that lists insufficiencies, right?

DR. BELSITO: Yes, so we'll go insufficient, and tell your little company that in two years, it

DR. EISENMANN: Well, that's to say, I don't even know what company it is.

DR. BELSITO: Well, I guess we'll find out.

DR. EISENMANN: If they're still in business in two years.

DR. BELSITO: If they're still in business.

DR. KLAASSEN: So we should let the methacrylate people jump through hoops to get their products approved as I recall a few years ago on a similar situation.

DR. BELSITO: So insufficient for all the prior data needs except sensitization and irritation for the two we have.

DR. EISENMANN: And that other one goes away because of that company not making that product, this dermal skin. I don't have anybody that's making a skin product anymore.

DR. BELSITO: Well.

DR. KLAASSEN: That's as far as the report goes, we still got (inaudible).

DR. LIEBLER: If I take the metabolism data, insufficiency will go away.

DR. BELSITO: Yes, it would be nice if we got that out of the table listing, but if and when we ever get the data we asked for, it'll be safe as used in nail products, and if those three products are still listed in the table, then an insufficient for other uses. Okay, so insufficient for all our prior data needs except sensitization and irritation for Which two did we get? We got

DR. LIEBLER: Two with uses, right, for the two with sensitization.

DR. SNYDER: Pentyl glycol trimellitic and accurate up to 7.5%.

MS. FIUME: So Dr. Belsito, even though it wasn't received at the max concentration of use, we can get rid of that last request, because the data were received at up to 15% of the adipic acid neopentyl glycol trimellitic anhydride copolymer, and it's used at up to 32.8%.

DR. LIEBLER: You're the person that will understand.

MS. FIUME: I do, I just need to know for clarification for the discussion.

DR. BELSITO: So the sensitization, irritation was half the concentration of what is actually in use.

MS. FIUME: And when the tests were done, it was allowed to volatilize before it was applied. Does that matter for the testing?

DR. BELSITO: Okay, fine, so we'll just at this point, since we're going insufficient for all our prior data including sensitization and irritation, that concentration of use. Okay, okey doke. You think things are going to be a slam dunk and, mmm, you get dunked. Okay.

DR. LIEBLER: I just don't want to be taken for granted.

DR. BELSITO: No, I understand that. Hey, I'm on your side now.

### **Marks Team**

DR. MARKS: Thank you, Ron. Next ingredient, trimellitic copolymers.

We have a draft tentative report on the trimellitic anhydride copolymers. We reviewed these ingredients in September and issued an Insufficient Data Announcement. In Monice's memo, they are listed, six data that we need.

One of the issues was this only was used for nail cosmetics, and would appear to be the case in what I read. Ron? Tom? Do we still need data? Is it only used for nails?

DR. SLAGA: I had we didn't need it for nails (inaudible).

DR. MARKS: Right, I agree with you, Tom. The use concentration of the adipic acid/neopentyl glycol/trimellitic anhydride copolymer, its use is 39 percent. We have an HRIPT of 15 percent. Even if it were used only on nails, I'd be concerned about paraneural skin, and sensitization has been reported with sculptured nails, multiple reports. You can get sensitization with just the application of nail cosmetics on the skin around the nails.

I thought we needed an HRIPT of 39 percent. Tom?

DR. SLAGA: Yes. I thought this was used only on nails.

DR. ANSELL: Yes, all the non nail uses it has been corrected to show only nail products.

DR. MARKS: Okay. I agree with Tom, I still like an HRIPT, at least now it will go out as a tentative report, insufficient data, and see if we get anything. I guess we could use the same sort of wording as with sculptured nails, but we know sculptured nails causes sensitivity. What is your sense, Ron?

DR. HILL: I didn't see the need for it.

DR. ANSELL: These concentrations were for a nail product?

MS. FIUME: Nail polish and enamel, 32.8.

DR. MARKS: We could cover it in the discussion that it would be applied only in nails and not get on the paraneural skin.

MS. FIUME: It's used in nail extenders at 22 percent, and I don't know if that would be similar to the sculptured nail issues.

DR. MARKS: Probably at 22 percent, I would say the HRIPT of 15 percent gives me reasonable confidence that it could be used safely.

DR. ANSELL: We thought to address the concern that adding safer use in nail products would be appropriate.

DR. MARKS: Okay. Other data needs, we will come back to that. We could say we don't need any more data as far as sensitization, but it's being used strictly on nails. Okay. Tentative report, safe for nail use.

The anhydride monomer respiratory sensory irritants, is that of any concern?

DR. HILL: I was just looking at that while you were discussing these others to try to find out I meant to look it up and forgot to do that.

DR. MARKS: Ron Shank?

DR. SHANK: I do have a concern.

DR. MARKS: Page 22.

DR. HILL: Because when people leave this on their nails, they certainly breathe whatever vapors are there.

DR. MARKS: Here it says "Paragraph to be completed pending Panel deliberations." "The Panel also discussed that anhydride monomers (e.g., trimellitic anhydride) can be respiratory sensory irritants and exposure in the work place to the anhydrides that are used in the production of these copolymers have resulted in numerous adverse effects."

I guess the question is this is in the work place where this is manufactured, not in the nail salon. It's of relevance.

DR. ANSELL: We would typically address that (inaudible). It's the monomer in the work place. That would be an appropriate discussion point.

DR. HILL: Yes, because in the impurity section, it's acknowledged that is a potential impurity.

DR. MARKS: How do you want to handle that? Ron Shank? Jay, how do you say it's the monomer, and you wouldn't expect enough monomer in the nail salon to be present to be an irritant?

DR. ANSELL: The cosmetic product is a polymer, it's the monomer in the work place where there is a potential for high exposure, where sensitization is an issue. One might want to address that within the discussion, particularly to the extent of recognizing that the polymer should be well reacted to.

MR. FIUME: I know one of our data requests was we don't know how much residual monomer is there, and that was actually one of the data requests. I would need help as to why that was no longer a concern.

DR. HILL: It is a concern for me.

DR. ANSELL: It's not that it is not a concern, it's that it is a warning to manufacturers to be aware of that.

DR. MARKS: You could put in something to the effect that the cosmetic product is a polymer, and therefore residual monomer in the nail salon should be at a level which is non irritating or something to that effect, I guess.

DR. HILL: This isn't only used in nail salons.

DR. MARKS: How about "use on the nail?"

DR. ANSELL: It's not the use that is the issue, it's the manufacture of the polymer. Whatever it may be used for, those manufacturers assure that there is minimum residual monitoring for sensitization potential.

DR. HILL: That is clear, but we don't have any sense of what levels show up and reducing to zero is probably impossible based on the nature of the product, so the question is how low is low, or how low does it have to be before somebody either vapors I don't guess it's hypersensitivity from vapors spilling over on the nails, hitting the skin and the fingers would be a big issue with dermatologists. Yet, I've never been around anybody, even my daughters painting their nails, without breathing fumes. Presumably what's that?

DR. ANSELL: Solvent, not polymer.

DR. HILL: I know I'm smelling the solvent but if it's volatilizable, we don't know. The sensitization in the manufacturing environment from exposure to powder, how are the industrial workers being sensitized and exposed if we know that's occurring. I think the volatility of this should be very low, because there is carboxylic acid there as well as the anhydride. I don't have a firm handle on this.

DR. ANSELL: We are unable to quantify, to have quantification on residual monomer. We do know anhydrides are highly reactive. It is not expected to be high, but we would support the inclusion of this in the discussion, to make people aware of the potential for sensitization.

DR. MARKS: Yes, sensitization versus irritation.

DR. HILL: I'm thinking sensitization because you have something that can react with proteins, if you have that possibility, then sensitization is a possibility. Is it just simply hypothetical here? That's probably the mechanism for it in the industrial work place. Is there any reason to think that carries over to something that people are painting on their nails. I don't know that there is. I'd be more comfortable if I saw an analysis showing there isn't any in there or we're not volatilizing we are not likely to have that. So, what do we do?

DR. MARKS: Ron Shank, how would you like to handle that part? The paragraph says respiratory irritant.

DR. SHANK: The monomer.

DR. MARKS: Yes, exactly.

DR. SHANK: In the work place environment, that exposure has to be several orders of magnitude greater than any person would be subject to in using this copolymer on the nail, so I don't think it's an issue.

DR. HILL: I can't disagree, at least I don't think I disagree.

DR. SHANK: I wouldn't hold up the report for that information. I'd handle it in the discussion and just say the exposure to monomer in nail product causes no concern to the Panel for respiratory responses. Something like that.

DR. MARKS: I have -- see if you like this as kind of coddling what Jay has said to Ron's. "The cosmetic product is a polymer, not a monomer, and therefore, not an irritant because there should be minimum monomer exposure in the nail product." Something to that effect.

Everything else, all that, metabolism data, we are all okay with that. If that's the case, presumably I'll second a motion that a tentative report issue it is safe for nail use, the conclusion. Ron? Tom?

DR. SHANK: I agree, limited to nail use.

DR. MARKS: Yes.

MS. FIUME: In the discussion, is there a need to say anything about non nail use or just leave it as safe for nail use?

DR. SHANK: Leave it just safe for nail use.

DR. HILL: I'm guessing if this is all that was found, it's not common, at least.

DR. MARKS: Exactly.

MS. FIUME: According to the VCRP data, there are two uses for the phthalic anhydride/trimellitic anhydride/glycols copolymer, and one for the adipic acid component that list dermal contact. We are going to just say safe for nail use?

DR. SHANK: The actual use is limited just to nail application.

MS. FIUME: The VCRP data are indicating there are dermal data.

DR. ANSELL: There was historical use. Currently, there are no uses.

MS. FIUME: The VCRP data indicate there are two other make up preparations and one make up face use. I feel I should be able to put some language in the discussion, if someone were to look at the use table, there are dermal uses. We just have no idea what concentration or

DR. SHANK: Then we will have to split the conclusion, safe for nail application, insufficient for dermal application. Then you need sensitization data.

DR. MARKS: Yes, just as I mentioned. I would want to see an HRIPT use concentration.

MS. FIUME: We don't have use concentrations because it wasn't reported

DR. MARKS: Can we not handle it in the discussion, just say even though the one database says it's being used -- Jay?

DR. ANSELL: Current reports.

DR. MARKS: Current reports that it's not being used.

DR. ANSELL: Carry that through to your conclusions, specifically stating

DR. MARKS: Yes. It's pretty clear in the conclusion, I think, if we say safe for nail use. If somebody wants to use it in another personal care product, we haven't determined it to be safe.

DR. GILL: It's a little disturbing that we're not paying attention to the VCRP data because we make a note in our reports that we assume it's being used because the VCRP has reports that it is being used. We are going to have to address the fact that the VCRP reporting says yes, and the most recent survey data says no. You're saying -- in our previous reports, we are saying we are going with VCRP as it is saying it is being used in one product or some products.

We really are going to have to deal with how we say that the current information suggests that it isn't being used, although the VCRP data indicates differently. Jay, you said historically, it may have been used that way. We don't look at the VCRP data necessarily as historical data. We look at it as current reporting.

DR. ANSELL: I think that type of thing in the discussion is fine. The conclusion would be modified consistent with that conflict between current uses -- we have gone back to manufacturers before and asked whether it's still there or not.

DR. GILL: I think we can do that this time.

DR. ANSELL: They said no.

DR. GILL: That's right.

MS. FIUME: When we have done that, we have had FDA representatives to double check that information. I don't know if they still can or not.

DR. GILL: We can ask.

DR. ANSELL: That would be our suggestion, carry this through to the discussion, discuss the conflict. We are comfortable with nails, and the industry is happy with that because that is really the only use for it. If someone wants to use it in another way, then they would have to

DR. MARKS: Safety data.

DR. GILL: In nail products, using it in nail products.

DR. MARKS: Ron, Ron, and Tom, does that sound reasonable, that in the discussion, the VCRP indicates dermal use, however, current data suggests only in nail use, and that would be the discussion.

DR. SHANK: That's fine. The conclusion is safe for nail use.

DR. MARKS: Yes, exactly. The conclusion would be safe for nail use. Okay. We will see what happens tomorrow.

Any further discussion? Let's see how we handle it tomorrow. It's still the tentative report. We will have time to adjust it if necessary.

DR. HILL: insufficiency for any uses for other than nail in the discussion or? We are not making a split conclusion now; right?

DR. MARKS: Correct. Actually, Ron, that's a good idea, insufficiency as irritation sensitization if in non nail use.

DR. HILL: Also, lacking concentrations of use. We had a molecular weight of 442 for one of them, a liquid, which suggests dermal penetrability, so then we're missing at least I had noted last time we were missing some systemic toxicology, if in fact there was penetrability, I mean nails would not be an issue, but for example, if we were to discover it was being used at five percent in something that would raise concerns that we are not needing to deal with here.

DR. MARKS: You would want number four, dermal absorption, insufficient as listed, if indeed it is a non nail use?

DR. HILL: Yes.

DR. MARKS: Tom? Ron?

DR. ANSELL: I wouldn't suggest that we go too far down that road, consistent with the discussion about skin application, but if we were to list all the data which isn't available for all the uses that it isn't used for, it would be a very extensive report. It's not used for inhalation, but were it to be, there would be a lot of different data.

I think here because we do have the reported use discussion and mention the data was insufficient, that might be appropriate.

DR. HILL: I agree.

DR. MARKS: Something, insufficient data, if other than nail use.

DR. HILL: We wouldn't have to go there if we didn't have this VCRP data, we wouldn't even need that one sentence.

DR. MARKS: Okay. Good. Thanks. I think there will be two things concerning that in the discussion, one, that the VCRP suggests dermal use, it indicates dermal use, however, our current data suggests only nail use. If there were other than nail, there would be insufficient data. I think just leave it at that. We don't have to go down, as you suggest, Jay, listing potential things.

Okay. Any other comments? (No response)

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DR. BELSITO: Trimellitic copolymers. Okay. For some reason I'm not finding it (inaudible). So, we thought this is if I'm correct, because I'm not finding my notes here that this is the first time we're looking at this group of ingredients. Is that correct? Okay, so thank you.

So, we looked at them. We thought these were insufficient for impurities, absorption, and if absorbed genotoxicity and reproductive toxicity. Sensitization and irritation at 1 percent they're primarily used in nail products. We weren't that much concerned about sensitization and irritation in nail products, but at 1 percent it was reported to be used in a facial foundation. That might go away if in fact we're subsequently told it's not used in other than nail products. And since we're going

insufficient and these could be applied to the nail and get on the cuticle, if there's any safety information as to sensitization or, in particular, irritation in nail products, we'd like to see that as well.

DR. MARKS: Second the motion. We had a couple more data needs. We were concerned are these metabolized, and is there any residual anhydride? Presumably it's low, but we weren't sure of that, so a method of manufacture we'd like to know that. But we agree with all the needs you expressed, Don. So, this would be just adding two more for this initial IDA.

DR. BELSITO: That's fine.

DR. BERGFELD: Ron Hill.

DR. HILL: You know, one of them we have actually, a molecular weight was given of 442, and so it's a polymer and so the question is, is that actually an average molecular weight for this polymer? If it is an average molecular weight, then that and it says it's a liquid, that puts it in the dermal absorption regime. So, that's one of the reasons we were interested in the possibility of getting that other information. It's sort of do we need to know this or not?

DR. BERGFELD: Any other discussion? Anyone else? All right, call the question then. This is going out as insufficient. I think the data needs have been expressed easily this time. All those in favor, yes?

ALL: Yes.

DR. BERGFELD: Okay, unanimous.

### **Belsito Team**

DR. BELSITO: Trimellitic anhydride copolymers, it's still Monice. I wasn't that far off. So, this is the first time that we are looking at these ingredients, there are six of them, and their function is film formers. So, the question this is one I did on paper Is it sufficient? Do we need more data? Where are we with these? Meanwhile I'm searching for my paper document, I'll turn it over to my teammates.

DR. LIEBLER: These have virtually no data at all, and but we know high molecular weight includes systemic exposure from dermal absorption, and I think that's very reasonable to conclude. I'm assuming that we would need irritation and sensitization data, at concentration of use, and I'll point out that the alkyl trimellitates were irritating.

DR. BELSITO: Yes. They were respiratory, and the irritants

DR. LIEBLER: So, we've got no irritation, sensitization dermal?

DR. BELSITO: Right, Dan, and

DR. LIEBLER: We have a few case reports.

DR. BELSITO: And impurities we don't really have a lot of impurity data, and we don't know the levels of the unreacted monomers that are left in the copolymers.

DR. LIEBLER: Correct.

DR. BELSITO: They are clearly respiratory irritants, you know, so I thought that these were insufficient for impurities, absorption, and if absorbed, we need repro toxicity, we had we don't have genotox for carcinogenicity, so we need repro and genotox

DR. LIEBLER: If absorbed.

DR. BELSITO: if absorbed. We need sensitization and irritation, at least at 1 percent, which was the highest level that I saw used in a leave on. Anything else?

DR. LIEBLER: Yes. I don't think we need absorption on these.

DR. BELSITO: No?

DR. LIEBLER: These are really big.

DR. BELSITO: So the discussion would be big, not absorbed, so we are not worried about the lack of repro or genotox?

DR. LIEBLER: Correct.

DR. SNYDER: Even monomer.

DR. BELSITO: We don't know the we don't know the impurities.

DR. LIEBLER: The impurities. If we have significant impurities and we worry about the absorption in the impurities, but I'm assuming that we'll we do need the impurity data, and I assume that when we have that, then we'll find out that we don't

have any residual monomer, so the anhydride is gone. That's going to be consumed, and then residual monomers are probably going to be washed away, and there's going to be very little. Actually I thought that there was a little bit of maybe it's not on this. Well, I thought we had a little data on the composition of these things.

DR. BELSITO: No. It says that, basically, on the impurities constituents, it says very little impurities data, and then without having a precise manufacturing method the amount of monomer present and we call polymers, and no

DR. LIEBLER: Yes. I'm thinking of the HM HT model, yes.

DR. BELSITO: Yes.

DR. ANSELL: And we do point out there is significant data on the monomers, so when we get to that

DR. LIEBLER: Most of them.

DR. ANSELL: Yes. When we get to that question, we have to start there.

DR. LIEBLER: Right. So, I mean, I think we are going to come out okay with these, I just think that we just don't have any of the data right now. It's just one of the thinnest data packages we've ever seen. I mean, it was hardly worth having the table with the X's there, it was all empty.

MS. FIUME: I told them it was not I just wondered. Dr. Belsito, can I actually ask a question for the irritation and sensitization?

DR. BELSITO: Yes.

MS. FIUME: On page 195 of the PDF, most of these are used in nail products.

DR. BELSITO: Right.

MS. FIUME: The 1 percent is a face and neck product, but the nail

DR. BELSITO: Right. That's why I said 1 percent; with nail it was much higher.

MS. FIUME: But what about the nail creams and lotions, would we expect skin effects there? Should that concentration be

DR. BELSITO: I suppose there could be an effect on the cuticle if

MS. FIUME: It's 6.2, and then other manicuring preparations, but I don't know if that's I don't know what that's defined as, if it's something that you put your fingers in during the manicure, and not exactly at 18.2.

DR. BELSITO: Yes. So I actually put a note here, you know, is it okay for nail products, and are we just going insufficient for the leave on, because there's really only then the question is, is that, report correct, right, because it was only one the only sorry, I actually did this on paper, which now I'm finding this to be much easier, other than I can't search it.

MS. FIUME: There was one reported use, according to VCRP with the dermal contact, and then that was it, and the concentration of use is 1 percent.

DR. BELSITO: Right. And every other use, 1 or in uses in nail, and one dermal contact toward the adipic acid, and 2 dermal contacts were the phthalic anhydride, with an NE (sic)

MS. FIUME: I'm sorry, that's a typo I believe.

DR. BELSITO: What?

MS. FIUME: I believe that's a typo.

DR. BELSITO: So, it's an NR?

MS. FIUME: Yes.

DR. BELSITO: So that all of the non nail uses, we have no reported concentrations which makes me wonder whether these are actually even used in products other than nail.

MS. FIUME: Except for, there is reported use at 1 percent in a face and neck product, for the trimellitic anhydride copolymer, and according to FDA it's used in one makeup phase. So, between the two they are both saying there's at least one use, that the Product was in.

DR. BELSITO: Yes. That's right. Dermal contact, so that's where I got the 1 percent. So then I mean So, what you are saying, Monice, is do we need sensitization and irritation at 1 percent, or do we need it up to the 32.8 percent that be used in a nail product?

MS. FIUME: Well, even the 18.2, not knowing what those other manicuring preparations are, if they are a soap or if it's a you know, something that would actually hit the skin.

DR. BELSITO: I mean, I guess I would be I'm not as concerned about the I mean, first of all, I don't see these as sensitizers, I see them as irritants. And I'm not as concerned about the irritating effect with a nail product as I would be with another dermal application. I mean, if the data is there, since we are going out insufficient, I mean, I suppose we could go, you know, sensitization and irritation at concentration of use, stressing that we particular want the leave on at 1 percent, but would appreciate any information they have on the nail products use.

DR. LIEBLER: So, Monice, when we have something that says, "Other manicuring preparations," that sounds like sort of rollup term, but is there actually information beneath all that, that allows to interpret dermal contact or not?

MS. FIUME: It depends. Sometimes when we receive something from industry, and it's one or the other, we will get it it will be defined for us, and other times it's not.

DR. BELSITO: I see.

MS. FIUME: But as far as the VCRP data, we don't know what it is.

DR. BELSITO: Okay.

DR. LIEBLER: Because I'm trying to determine what would be the concentration that we would want tested, and I don't think it needs to be 32.8 percent, it sounds like Don, doesn't think so either.

DR. SNYDER: I think that will help avert, if we can handle that in the discussion to say that we are not considering it inadvertently, dermal content, because otherwise it can

DR. LIEBLER: So the question is, because otherwise percent or 18 percent?

DR. SNYDER: Yes.

MS. FIUME: And I will say that for purposes of how we recategorize things in our concentration of use tables now, for the nail products, do we consider them we consider them leave ons, that information would be kept under a leave on use, the way we've categorized it.

DR. SNYDER: So we could have recombinant inadvertent dermal exposure from a non leave on nail product.

SPEAKER: Or you might want to say, on nail product?

DR. SNYDER: Yes.

DR. BELSITO: I'm sorry. I'm missing where this 18 percent is coming from, because it's not in the table.

DR. LIEBLER: PDF 195, it's the FDA concentration of use by concentration of use by FDA product category.

DR. BELSITO: So that did not appear in our Table 4?

DR. LIEBLER: No. It's not in the report, nor in the draft report. It's at the end near the

DR. BELSITO: So then that does the concentration of use in our draft report need to be updated, or is that data on

DR. LIEBLER: What PDF page is on your

DR. BELSITO: I printed it out.

MS. FIUME: The table is on 22, and I'm looking now at what I've done in the table versus what I just said, and I need to recheck how we do categories like FDA. And you won't see the 18.2 because nails is a composite category for our table, so we have range, but you have to look at the actual Council information to see what all those subcategories are within that range. So that's why that 18.2 does not show up.

DR. LIEBLER: Okay. So, that 18.2 is somewhere in the 5.4 to 42.8? Okay. Yes.

DR. BELSITO: But the 18.2 would potentially be, what you are seeing as the dermal contact product?

MS. FIUME: I have no idea. I'm just saying it's other manicuring preparations, so I mean, just going to a nail salon, I know sometimes you go and you sit, and you soak your nails for a little bit before they do anything to them. So, I just have no idea what it would be. So since we were going out as an insufficient data announcement rather than saying a 1 percent I didn't know, it should just say, high concentration of use, and then as you said, worry about that later on

DR. BELSITO: But then concentration of use would include up to 32.8 percent, and I don't You know, again, I think the issue is going to be sensitization, so maybe we should simply say, when formulated to be non sensitizing. We know that's a respiratory sensitizer I mean irritant not sensitizer.

DR. SNYDER: For this one, we could explain it, we could say, we don't need the non sensitizing caveat if we have negative 1 percent, and then we could say, based on the nail product, that it should be formulated to be non irritating. Because we'll have if we get negative sensitization and irritation at 1 percent for leave ons

DR. BELSITO: Right, that's what I'm saying.

DR. SNYDER: But we could, still, in the discussion, say that they would be found to be non irritating rather than because I don't think we are going to get data at the 32 point.

DR. BELSITO: Well, I mean, we are going insufficient, so we are going for impurities, if there is significant monomer, then we may need absorption, and if absorbed genotox with reductive toxicity. Otherwise, in the discussion these are large molecules, they won't be absorbed, so we are okay with the lack of that information, and then we are going to ask for sensitization and irritation and concentration of use, differentiate the 1 percent in the leave on facial versus the 33.8 percent, or whatever, in the nail. We would like to see as much information as industry can provide us and then we'll figure out what to do with a conclusion. At this point it's insufficient.

DR. SNYDER: But we are not going to ask for it, since it's (crosstalk)?

DR. BELSITO: We are not going to. We are going to specifically ask for 1 percent in the leave on, and any additional information the companies can provide us on the nail uses, with sensitization, irritation, concentration, product type, whatever, they can provide us in terms of what are these other nail uses. The only other question on these, Dan, were you okay with the chemical groupings here; because there were a lot of other things that were added to the trimellitic anhydride in the polymers. So does this make sense as a grouping for what else is going to be in there and could be monomers?

DR. SNYDER: Yes. Now they have a common nucleus that unifies the group, and then they have diverse substituent. But I thought that the grouping of the ingredients was reasonable. So, I don't have any problem with that.

DR. BELSITO: Okay.

DR. KLAASEN: And would there be any appreciable difference between the acidic monomers, versus the alcohol monomers? Dan, that was a question for you?

DR. LIEBLER: I'm not sure how you mean, your question; any potential difference between the acidic versus the alcohol models?

DR. SNYDER: Because she talked about the difference, that the monomers are either acidic or alcohol monomers. And so, if we receive in (inaudible) data, I guess we'll be able to clarify by then, if there are any particular issues related to the particular (inaudible) type

SPEAKER: Sebacic acid versus (crosstalk).

DR. ANSELL: I mean, the adipic acid, is the main acidic component, hence isostearic, ulcer basic, yes. That way, I don't see any reason to make a distinction between those and evaluating the safety. And is neopentyl alcohol in the dictionary? I'm just wondering if there would have ever been any safety assessment of neopentyl alcohol?

DR. BELSITO: I don't know. Anything else? Monice, do you have everything you need at this point?

MS. FIUME: I do, but I just wanted to double check because the next time it comes back it's, first of all it's not neopentyl glycol is.

DR. LIEBLER: It's not? Okay.

MS. FIUME: Not neopentyl alcohol.

DR. LIEBLER: Okay. Oh, neopentyl glycol is?

MS. FIUME: Yes, neopentyl glycol

DR. LIEBLER: Okay, and that's the that's what I meant, neopentyl glycol. Yes, so that's one of the monomeric ingredients in this.

MS. FIUME: And it has not been reviewed yet.

DR. LIEBLER: It has not been reviewed, but it is in the dictionary?

MS. FIUME: Yes. For the purposes of the discussion, that the next time it comes back, I could have at least the backbone of a draft discussion. Do you know is there anything specific talking about, I guess without knowing the residual monomer levels, we can't really say much about those, but as far as the respiratory irritation, is there specific language you'd like to see regarding that? Or does it all depend on the individual monomer levels?

DR. BELSITO: Well, the respiratory were all based on monomers, right. So, if it's a polymer, it's really not going to be inhaled, so I don't even know that you can do it, until we have some idea of the residual monomer.

MS. FIUME: Exactly.

DR. BELSITO: If they are high, then I think you know, then we are going to need absorption, and we are going to need a discussion about the respiratory irritation, and if they are not high, then I don't think that's a concern. It should go in the discussion, but the Panel is aware that the monomers can be respiratory irritants, however, you know, given the low concentration of residual monomer we don't think this is an issue.

MS. FIUME: Okay. So this is all going to depend on the overall

MS. FIUME: Everything here is driven by the residual monomers.

DR. BELSITO: Anything else? Okay.

### Marks Team

DR. MARKS: Next is trimellitic copolymers. This is the first time reviewing the six ingredients, and so we have a lot of data on the monomers. Does that support the safety of the copolymers, which we have little data? Tom, Ron, and Ron, are the first of all, are the six ingredients okay?

Okay, I see nonverbal yes. Ron Shank, Tom

DR. SLAGA: It'd be nice to have a little data.

DR. MARKS: So, do you want to turn the mic Dr. Slaga said it'd be nice to have a little data.

DR. HILL: I do have a question, but it's probably (inaudible) question is whether we this was the only phthalic and hydride polymer in the CIR database? Because while the structure of that and hydride is very closely related to the trimellitic and hydride, it's not the same. So, I just wondered if our searching's picked that up and I guess he'd have to answer that question or somebody who can quickly search the dictionary, because I didn't do that.

DR. MARKS: So, I will so as far as the six ingredients, Ron Shank and Tom Slaga, are you okay with the six that were chosen?

DR. SHANK: I am.

DR. MARKS: Yeah, okay. I can tell you what I wanted, from a skin point of view (inaudible). And Ron, and Tom, And Tom in the irritation/sensitization, the trimellitic and hydride so that's the monomer and all the copolymers sensitized at 10 percent. The thallic and hydride sensitizes at 10 percent. And then there are case reports of allergic contact dermatitis to the (inaudible) thallic and hydride trimellitic and hydride glycols copolymer.

Those were all from page 16, 20, and 23. So, my bent, from sensitization/irritation was, I wanted an insufficient data notice announcement that we need the HRIPT adipic acid. Neopentyl, glycol, trimellitic and hydride copolymer and the thallic and hydride the trimellitic and hydride glycols sebacic acid mouthfuls. And I chose those two because of their uses. The adipic acid one is 411. The thallic and hydride is 71, and they use it either 8 percent or 12 percent in leave ons. So, I'd like to see the HRIPT of those two, as an insufficient data announcement, since it's the first time.

DR. SHANK: I agree. Are these used only on the nail? I wasn't sure. If it's only applied only to the nail, then sensitization data is the only need. If there's reasonable skin contact, then we need more data.

DR. MARKS: Do we know that, Monice or Carol?

MS. FIUME: We do. Adipic acid neopentyl, glycol, trimellitic and hydride copolymer has at least one use in something that is applied to skin. It's at one percent on a face and neck product, according to the industry data. According to VCRP, it's used in a makeup base. And according to VCRP, the thallic and hydride, trimellitic and hydride glycols copolymer has two other makeup preparations.

DR. SHANK: Okay.

MS. FIUME: So, they do have some skin uses.

DR. SHANK: Okay. So, thank you for clarifying that for me. And I think we need molecular weights. And if there is skin penetration (inaudible) skin penetration.

DR. HILL: Yeah, my question directly related to that, while you're there is on page 22, in table three. There's a molecular weight of 442 given. So, I was surprised to see that with the polymer, and wondered, really, what that indicates because that would be a very powerful molecular weight, and it's saying that it's a liquid, a clear liquid so good question. It's too large for any of these individual components, so maybe it's I don't know what it is. I mean, molecular weight or the smallest molecular weight in there I'm not sure.

DR. MARKS: So, Ron Shank molecular weights and skin penetration. And obviously, if skin penetration, then you need

DR. SHANK: Genotox, reproductive, developmental

DR. MARKS: (inaudible).

DR. SHANK: Are these (inaudible) right? So, we may need metabolism data.

DR. MARKS: So, 28 day dermal, if it penetrates. Dermal, repro, genotox, and then what else do we need? What's the usual? I mean, it's all the things we normally ask if it penetrates the skin. We don't have the data which we don't have the data here, other than for monomers. Are we at you would think

DR. SHANK: And then for toxicokinetics are these metabolized?

DR. MARKS: And then you would want to know what the metabolic products are, huh?

DR. SHANK: Yes, please.

DR. MARKS: Is there one particular? Because the monomers are you concerned about the monomers in these, or

DR. HILL: I was not.

DR. SHANK: Okay, well

DR. HILL: But that doesn't mean you couldn't be.

DR. MARKS: Since it's insufficient data announcement, we can obviously modify that, but it's okay. Anything else? So, need HRIPT of two of the copolymers. We need molecular weights and skin penetration of as much as we have or those two, do you think, would be representative of the rest the ones that have the highest use (inaudible) how do you say that?

DR. HILL: Adipic.

DR. MARKS: Adipic acid (inaudible) and then the thallic and hydride (inaudible). Would that be enough for weight and skin penetration, Ron, if we got those?

DR. HILL: I was looking for enough about the method of manufacture to know whether residual and hydrides would be a significant concern at all. Wouldn't need to be specific so much as what steps are taken to ensure that residual and hydride is low, because, for me, the toxicology would be driven by any such residual and otherwise what Dr. Shank was asking for.

DR. MARKS: Okay. We (inaudible) put that in there. So, that'll make four data needs we're looking for, and we can always change that. So, molecular weight, skin penetration are they metabolized residual and hydride low method of manufacturing. Other than the HRIPT, none of the others require any study. So, we either get it or not. The information already exists. Anything else?

DR. HILL: I had just been prepared to pretty much ignore all of that if it was only used on the nail, but

DR. MARKS: Yeah. So, used I should put that up top there on nail and on skin, because you had a makeup, and you had another one you mentioned there as leave ons. Okay. Any other comments?

So, again, I think tomorrow, I'll be seconding a motion we'll see if it's an insufficient data announcement. Okay.

## **Safety Assessment of Trimellitic Anhydride Copolymers as Used in Cosmetics**

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The 2016 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel 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 safety assessment was prepared by Monice M. Fiume, Assistant Director/Senior Scientific Analyst/Writer and Bart Heldreth, Ph.D., Chemist.

## **ABSTRACT**

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of 6 trimellitic anhydride copolymers as used in cosmetics. These ingredients are related as copolymers in that they all share trimellitic anhydride (aka 1,2,4-benzenetricarboxylic acid anhydride) as a monomer, are reported to function as film formers in cosmetics, and are primarily reported to be used in nail products. Very limited data were available, and these copolymers are essentially chemically undefined in this assessment. The Panel concluded that the available data are insufficient to make a determination that the trimellitic anhydride copolymers are safe under the intended conditions of use in cosmetic formulations.

## **INTRODUCTION**

This assessment reviews the safety of the following 6 trimellitic anhydride copolymers as used in cosmetic formulations:

- Adipic Acid/CHDM/MA/Neopentyl Glycol/Trimellitic Anhydride Copolymer
- Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer
- Isostearoyl Trimellitic Anhydride/Trimethylolpropane Copolymer
- Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer
- Propylene Glycol/Sebacic Acid/Trimellitic Anhydride Copolymer
- Trimethylpentanediol/Isophthalic Acid/Trimellitic Anhydride Copolymer

According to the *International Cosmetic Ingredient Dictionary and Handbook*, most of the trimellitic anhydride copolymers are reported to function as film formers in cosmetic formulations<sup>1</sup> (Table 1).

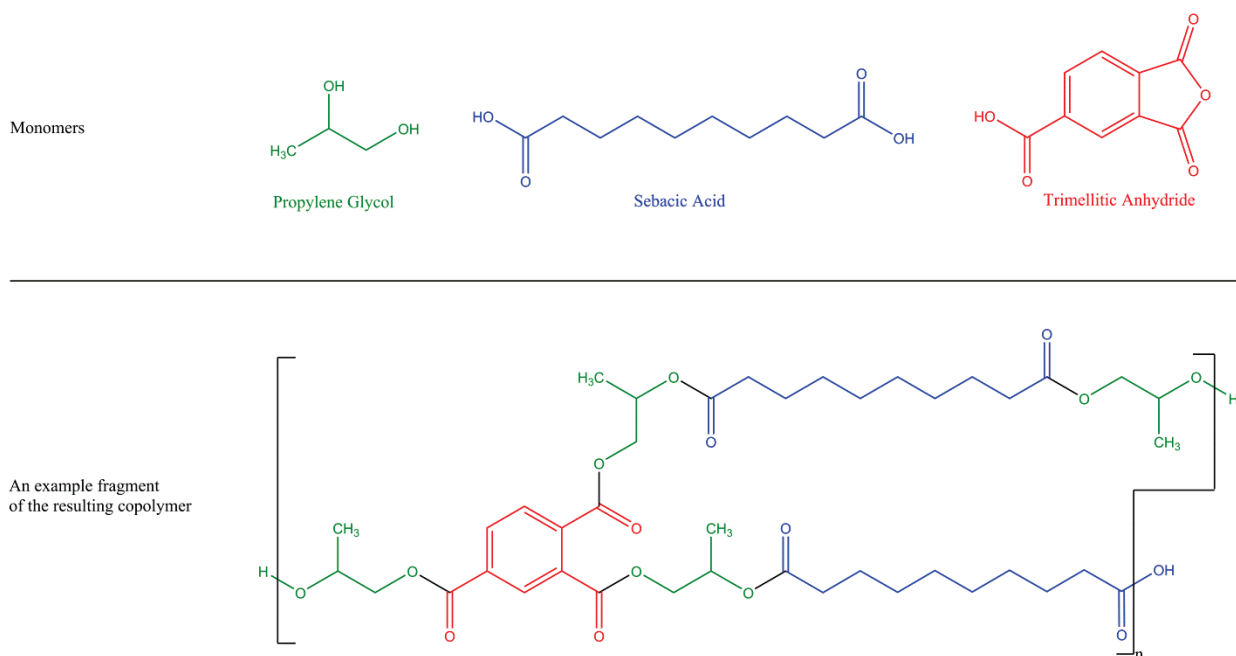
The ingredients in this report are related as copolymers in that they all share trimellitic anhydride (aka 1,2,4-benzenetricarboxylic acid anhydride) as a monomer. Each copolymer is also composed of 1 to 4 of the following additional monomers: adipic acid, cyclohexanedimethanol (CHDM), ethylene glycol, isophthalic acid, maleic anhydride, neopentyl glycol, phthalic anhydride, propylene glycol, sebacic acid, trimethylpentanediol, or trimethylolpropane (chain-terminated by isostearic acid).<sup>1</sup> Relevant information on the toxicity of these monomers is presented in Table 2.<sup>2-31</sup> This information is not intended to be exhaustive or complete, but purely summary information intended to provide insight as to any possible toxicity concerns for these monomers.

The safety of several of the non-anhydride monomers has previously been reviewed by the Panel. In 2012, the Panel concluded that adipic acid and sebacic acid are safe in the present practices of use and concentration,<sup>8</sup> and that propylene glycol is safe as used in cosmetic formulations at the present practices of use and concentration when formulated to be non-irritating.<sup>26</sup> In 1999, the Panel published a special report on the reproductive and developmental toxicity of ethylene glycol and its ethers, concluding that the metabolites of ethylene glycol monoalkyl ethers are reproductive and developmental toxins, but in general, these metabolites of concern are not expected to be formed in cosmetic formulations that contain polymers of ethylene glycol.<sup>11</sup>

## **CHEMISTRY**

### **Definition and Structure**

The ingredients in this report are related as copolymers that share in common trimellitic anhydride as a monomer. The monomers that comprise these copolymers are interconnected via ester bonds to form highly branched polymeric (polyester) networks. For example, Propylene Glycol/Sebacic Acid/Trimellitic Anhydride Copolymer is the result of the polymerization of propylene glycol, sebacic acid, and trimellitic anhydride. In this case, there are two acid monomers (sebacic acid and trimellitic anhydride) and one alcohol monomer (propylene glycol). This means that to form a polyester copolymer, every other repeat unit must be propylene glycol. Whether the repeat unit on either end of propylene glycol is the residue of sebacic acid or the residue of trimellitic acid is dependent on the polymerization conditions. Since trimellitic anhydride serves as a rigid, non-linear, tri-functional (trivalent) monomer, these polymers are branched, if not highly-branched, in a manner similar to dendrimers.



**Figure 1.** Propylene Glycol/Sebacic Acid/Trimellitic Anhydride Copolymer – the connectivity between alcohols (propylene glycol, in this case) and which acids (sebacic acid and trimellitic anhydride, in this case) can vary; this is just one theoretical example of a fragment within a polymeric network

The definitions and structures of the ingredients included in this review are provided in Table 1.

### Physical and Chemical Properties

Limited physical and chemical properties data on the trimellitic anhydride copolymers as cosmetic ingredients were found in the published literature, and unpublished data were not provided. The property information that was found is presented in Table 3.<sup>32-34</sup>

### Method of Manufacture

General polyester synthetic techniques common in the art can be described for the manufacture of trimellitic anhydride copolymers.<sup>35</sup> The manufacture of each of these trimellitic anhydride copolymers begins with trimellitic anhydride (an activated form of trimellitic acid). For example, synthesis would start by dissolving trimellitic anhydride in a dry solvent, such as dimethylformamide, under an inert gas, such as nitrogen. Next, the appropriate polyol monomer (e.g., propylene glycol, neopentyl glycol, cyclohexanedimethanol, trimethylolpropane, ethylene glycol, or trimethylpentanediol) would be added to the solution and distilled under reduced pressure. In a second step, the resultant terminal alcohol groups may be further esterified with appropriate mono- or multi-functional carboxylic acids (e.g., sebacic acid, adipic acid, maleic anhydride, isostearic acid, phthalic anhydride, sebacic acid, or isophthalic acid), and, likely, a catalyst. This two-step methodology would result in dendrimer-like copolymers, with trimellitic acid as the central core in each. Alternatively, trimellitic anhydride, a polyol, and an additional carboxylic acid of choice could be reacted together in one step, under similar conditions, to form more-randomly structured copolymers. Due to the trivalent nature of trimellitic acid, however, the resultant polymers from either of these two methodologies would be non-linear.

#### Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer

In the synthesis of Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer, the trifunctional glycol(s) and the di and tri basic acids are charged into a clean and dry reaction vessel.<sup>36</sup> Heat is applied to drive the polyester reaction, and water is generated as a by-product of the reaction; the rate of reaction is controlled by the heat applied. The reactant mixture is heated gradually to 200°C, and the in-process wet properties are measured. The reaction mixture is cooled and dissolved in the solvent; the final product is cooled further and packaged.

#### Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer

Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer results from condensation of phthalic anhydride, trimellitic anhydride, ethylene glycol, and neopentyl glycol monomers.<sup>37</sup>

### Impurities/Constituents

Limited impurities data on the trimellitic anhydride copolymers as cosmetic ingredients were found in the published literature, and unpublished data were not provided. The reactions used to manufacture the copolymers can be designed to result in little to no residual monomer, but information on the exact manufacturing process was not available for most of the polymers. Without having a precise manufacturing method, the amount of monomer present in the copolymer is unknown. Therefore, it is possible that residual amounts of the following monomers (used in the production of these copolymers) could be present in these ingredients: adipic acid, cyclohexanedimethanol, ethylene glycol, isophthalic acid, maleic anhydride (or maleic acid), neopentyl glycol, phthalic anhydride (or phthalic acid), trimellitic anhydride (or trimellitic acid), trimethylpentanediol, trimethylolpropane, and isostearic acid.

#### *Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer*

Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer is synthesized from adipic acid, neopentyl glycol, and trimellitic anhydride.<sup>36</sup> A quantitative <sup>3</sup>H nuclear magnetic resonance (NMR) study reported that approximately 1.5% residual glycol is present. Residual trimellitic anhydride and adipic acid concentrations were below the limit of detection (i.e., 50 ppm or 0.005%).

One supplier has reported that Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer is sold in butyl acetate (70-80% solids), and does not contain formaldehyde, toluene, or xylene.<sup>33</sup>

### USE

#### Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated based on data received from the U.S. Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by Industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to 2016 VCRP data, Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer is reported to be used in 471 cosmetic formulations, 470 of which are nail formulations, and Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer is reported to be used in 85 cosmetic formulations, 83 of which are nail formulations; the remaining uses reported to the VCRP indicated dermal exposure<sup>38</sup> (Table 4). However, the results of the concentration of use survey conducted by the Council in 2015 only report use in nail formulations. According to the Council survey, the highest maximum concentration of use for both of these ingredients is in nail polish and enamel; Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer is reported to be used at up to 32.8%, and Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer at up to 12%.<sup>39</sup>

The remaining trimellitic anhydride copolymers (i.e., Adipic Acid/CHDM/MA/Neopentyl Glycol/Trimellitic Anhydride Copolymer; Isostearyl Trimellitic Anhydride/Trimethylolpropane Copolymer; Propylene Glycol/Sebacic Acid/Trimellitic Anhydride Copolymer; or Trimethylpentanediol/Isophthalic Acid/Trimellitic Anhydride Copolymer) are not reported to be in use.

None of the trimellitic anhydride copolymers named in the report are restricted from use in any way under the rules governing cosmetic products in the European Union.<sup>40</sup> In Australia, according to a National Industrial Chemicals Notification and Assessment Scheme (NICNAS), Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer was determined to be a polymer of low concern, and it is not considered to pose an unreasonable risk to public health of workers and the public when used as a component of cosmetic nail products.<sup>41</sup>

#### Non-Cosmetic

Adipic Acid/CHDM/MA/Neopentyl Glycol/Trimellitic Anhydride Copolymer is used in preparation of glass fiber reinforced plastic.<sup>32</sup> Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer is used in the manufacture of dyes, pharmaceuticals, insecticides, and as a hardener for resins.<sup>42</sup>

### TOXICOKINETICS

#### Absorption, Distribution, Metabolism, and Excretion

Toxicokinetics studies on the trimellitic anhydride copolymers were not found in the published literature, and unpublished data were not provided.

### **TOXICOLOGICAL STUDIES**

Toxicological studies on the trimellitic anhydride copolymers were not found in the published literature, and unpublished data were not provided.

### **DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES**

Developmental and reproductive toxicity studies on the trimellitic anhydride copolymers were not found in the published literature, and unpublished data were not provided.

### **GENOTOXICITY STUDIES**

Genotoxicity studies on the trimellitic anhydride copolymers were not found in the published literature, and unpublished data were not provided.

### **CARCINOGENICITY STUDIES**

Carcinogenicity studies on the trimellitic anhydride copolymers were not found in the published literature, and unpublished data were not provided.

### **DERMAL IRRITATION AND SENSITIZATION STUDIES**

Human repeated insult patch tests (HRIPTs) were conducted with nail polish formulations containing up to 15% Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer<sup>43-48</sup> and up to 7.5% Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer<sup>49,50</sup> (Table 5). None of the formulations were sensitizers or irritants.

According to the NICNAS report, there is uncertainty regarding the potential sensitization of Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer, but the ingredient cannot be classified for sensitization.<sup>41</sup>

### **OCULAR IRRITATION STUDIES**

Ocular irritation studies on the trimellitic anhydride copolymers were not found in the published literature, and unpublished data were not provided.

### **CLINICAL REPORTS**

#### **Case Reports**

Several case reports describing allergic reactions to Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer in nail polish were available.<sup>37,42,51</sup> Details from these case reports are summarized in Table 6.

### **SUMMARY**

This report addresses the safety of 6 trimellitic anhydride copolymers as used in cosmetics. According to the *International Cosmetic Ingredient Dictionary and Handbook*, these ingredients are reported to function as film formers. The trimellitic anhydride copolymers are related as they all share a common monomer, i.e., trimellitic anhydride; each copolymer is also composed of another 1 to 4 monomers. The monomers that comprise these copolymers are interconnected via ester bonds to form highly branched polymeric (polyester) networks. Limited information on the amount of residual monomer in these copolymers was submitted.

VCRP data obtained from the FDA and data received in response to a survey of the maximum reported use concentration by product category conducted by the Council indicate that 2 of the 6 ingredients included in this safety assessment are used in cosmetic formulations. According to the VCRP, Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer is reported to be used in 471 cosmetic formulations, 470 of which are nail formulations, and Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer is reported to be used in 85 cosmetic formulations, 83 of which are nail formulations. Only uses in nail products were reported in response to the Council survey, and the highest maximum concentration of use for both of these ingredients is in nail polish and enamel; Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer is reported to be used at up to 32.8%, and Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer is reported to be used at up to 12%.

HRIPTs were conducted with nail polish formulations containing up to 15% Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer and up to 7.5% Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer. None of the formulations were sensitizers or irritants. Several case reports have, however, described allergic reactions to Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer in nail polish.

Toxicokinetics, toxicological, genotoxicity, and ocular irritation data were not found in the published literature, and unpublished data were not provided.

## **DISCUSSION**

The Panel considered this safety assessment of 6 trimellitic anhydride copolymers as used in cosmetics; these ingredients are related in that they all include trimellitic anhydride (aka 1,2,4-benzenetricarboxylic acid anhydride) as a monomer. Because little data were available for use in determining the safety of these ingredients, the Panel issued an Insufficient Data Announcement (IDA) at its September 2015 meeting, notifying the public that the data on the trimellitic anhydride copolymers were insufficient to determine whether the ingredients, under each relevant condition of use as indicated in this assessment, are either safe or unsafe. Both the FDA VCRP data and the Council concentration of use survey report that these ingredients are used (or are likely to be used) in nail products, but only the VCRP data indicate that these ingredients are used in products that are intended to come into contact with the skin.

Dermal irritation and sensitization data on nail polish formulations were submitted to the CIR in response to the IDA; the test data were not at the maximum concentrations of use indicated in this assessment.

Despite the submission of irritation and sensitization data, the Panel expressed concern that these copolymers are essentially chemically undefined. The Panel stated that in the absence of fundamental data about the chemistry of these ingredients, safety cannot be evaluated for the use of these copolymers in any type of cosmetic formulation.

The following are needed to evaluate the safety of these ingredients in nail products:

- Method of manufacture; and
- Composition data.

In addition, the following data are needed to evaluate the safety of these ingredients in cosmetics other than nail products:

- Molecular weight;
- Impurities, specifically, the amount of residual monomer in each copolymer
- Metabolism, specifically, whether these ingredients are metabolized in the skin;
- Dermal absorption; if absorbed, then genotoxicity and reproductive toxicity data are needed; and
- Dermal irritation and sensitization data at maximum leave-on concentrations of use.

The Panel acknowledged that anhydride monomers (e.g., trimellitic anhydride) can be respiratory irritants and allergens, and exposures in the workplace to the anhydrides that are used in the production of these copolymers have resulted in numerous adverse effects. However, because the levels of residual monomer in nail products are expected to be minimal, exposure to trimellitic anhydride is not expected and is not of concern.

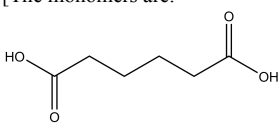
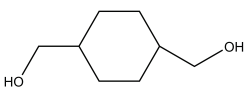
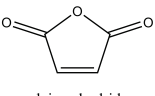
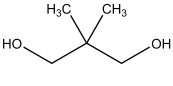
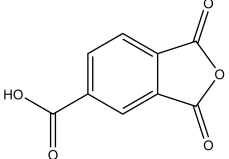
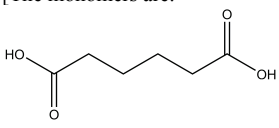
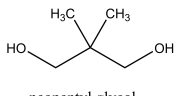
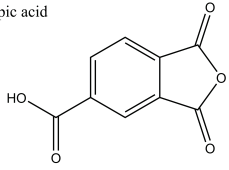
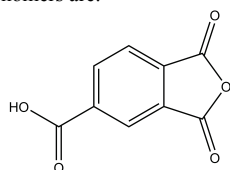
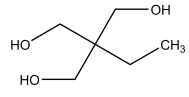
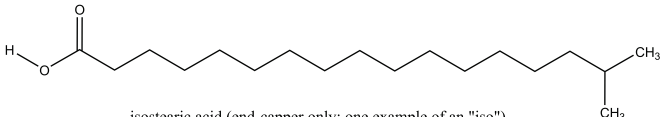
## **CONCLUSION**

The CIR Expert Panel concluded that the available data are insufficient to make a determination that the following 6 trimellitic anhydride copolymers are safe under the intended conditions of use in cosmetic formulations:

- Adipic Acid/CHDM/MA/Neopentyl Glycol/Trimellitic Anhydride Copolymer\*
- Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer
- Isostearoyl Trimellitic Anhydride/Trimethylolpropane Copolymer\*
- Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer
- Propylene Glycol/Sebacic Acid/Trimellitic Anhydride Copolymer\*
- Trimethylpentanediol/Isophthalic Acid/Trimellitic Anhydride Copolymer\*

*\* 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 safe for use in nail products at concentrations comparable to others in this group.*

**TABLES****Table 1. Definitions and Functions** <sup>1</sup>, CIR Staff

| Ingredient (CAS No., if available)                                                | Definition                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Function(s)                                                                                   |
|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Adipic Acid/CHDM/MA/Neopentyl Glycol/Trimellitic Anhydride Copolymer [67970-02-9] | <p>a copolymer of adipic acid, cyclohexanedimethanol (CHDM), maleic anhydride (MA), neopentyl glycol and trimellitic anhydride monomers</p> <p>[The monomers are:</p> <div style="display: flex; justify-content: space-around; align-items: flex-start;"> <div style="text-align: center;">  <p>adipic acid</p> </div> <div style="text-align: center;">  <p>cyclohexanedimethanol</p> </div> </div> <div style="display: flex; justify-content: space-around; align-items: flex-start;"> <div style="text-align: center;">  <p>maleic anhydride</p> </div> <div style="text-align: center;">  <p>neopentyl glycol</p> </div> <div style="text-align: center;">  <p>trimellitic anhydride</p> </div> </div> <p>]</p> | film former                                                                                   |
| Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer (28407-73-0)         | <p>a copolymer of adipic acid, neopentyl glycol and trimellitic anhydride monomers</p> <p>[The monomers are:</p> <div style="display: flex; justify-content: space-around; align-items: flex-start;"> <div style="text-align: center;">  <p>adipic acid</p> </div> <div style="text-align: center;">  <p>neopentyl glycol</p> </div> </div> <div style="text-align: center;">  <p>trimellitic anhydride</p> </div> <p>]</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                             | film former                                                                                   |
| Isostearoyl Trimellitic Anhydride/Trimethylolpropane Copolymer (1190965-82-2)     | <p>a copolymer of trimellitic anhydride and trimethylolpropane chain-terminated by isostearic acid.</p> <p>[The monomers are:</p> <div style="display: flex; justify-content: space-around; align-items: flex-start;"> <div style="text-align: center;">  <p>trimellitic anhydride</p> </div> <div style="text-align: center;">  <p>trimethylolpropane</p> </div> </div> <div style="text-align: center; margin-top: 20px;">  <p>isostearic acid (end-capper only; one example of an "iso")</p> </div> <p>]</p>                                                                                                                                                                                                                                                                                                                                                                   | skin protectant; skin-conditioning agent - emollient; skin-conditioning agent - miscellaneous |

**Table 1. Definitions and Functions** <sup>1</sup>, CIR Staff

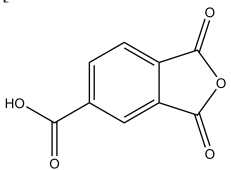
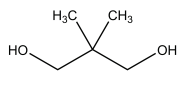
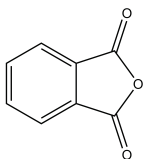
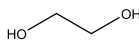
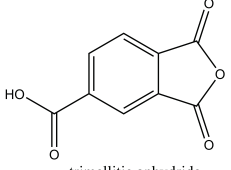
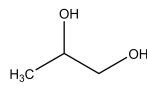
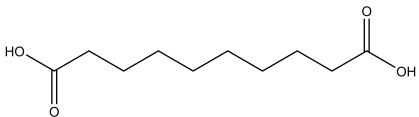
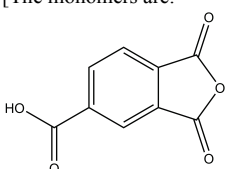
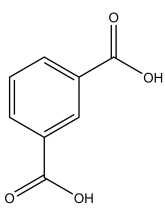
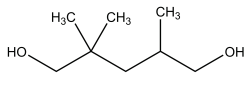
| Ingredient (CAS No., if available)                                          | Definition                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Function(s)                                           |
|-----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer<br>(186688-25-5) | <p>a copolymer of phthalic anhydride, trimellitic anhydride, ethylene glycol, and neopentyl glycol monomers</p> <p>[The monomers are:</p> <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p>trimellitic anhydride</p> </div> <div style="text-align: center;">  <p>neopentyl glycol</p> </div> </div> <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p>phthalic anhydride</p> </div> <div style="text-align: center;">  <p>ethylene glycol</p> </div> </div> <p>]</p> | film former; viscosity increasing agent – non-aqueous |
| Propylene Glycol/Sebacic Acid/Trimellitic Anhydride Copolymer               | <p>a copolymer of propylene glycol, sebacic acid and trimellitic anhydride</p> <p>[The monomers are:</p> <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p>trimellitic anhydride</p> </div> <div style="text-align: center;">  <p>propylene glycol</p> </div> </div> <div style="text-align: center; margin-top: 20px;">  <p>sebacic acid</p> </div> <p>]</p>                                                                                                                                                                                                                                                                | film former                                           |
| Trimethylpentanediol/Isophthalic Acid/Trimellitic Anhydride Copolymer       | <p>a copolymer of trimethylpentanediol, isophthalic acid and trimellitic anhydride monomers</p> <p>[The monomers are:</p> <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p>trimellitic anhydride</p> </div> <div style="text-align: center;">  <p>isophthalic acid</p> </div> </div> <div style="display: flex; justify-content: space-around; align-items: center; margin-top: 20px;"> <div style="text-align: center;">  <p>trimethylpentanediol</p> </div> </div> <p>]</p>                                                                                                                                          | film former; viscosity increasing agent – non-aqueous |

Table 2. Monomer safety data

| Monomer (CAS No.)                   | Summary Information                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              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| trimellitic anhydride<br>(552-30-7) | <p><u>molecular weight</u>: 192.13 g/mol</p> <p><u>toxicokinetics</u>: rapidly converted to trimellitic acid in the body (complete hydrolysis likely occurs in &lt;10 min); in rats exposed to 0.95 mg/m<sup>3</sup> for 45 min and killed 3 hr or 1, 2, 4, 8, 16, and 32 days following exposure, in general, the highest tissue concentrations were obtained at the first time point (T-max&lt;3 hr), and a second T-max of 8 days was reported for lung lymph nodes in male rats, suggesting a possible role in the gender differences observed for lung toxicity; the biological half-life in the lungs was estimated to be 21 days in male rats and 16 days in female rats, and in lung associated lymph nodes, half-lives of 13 and 33 days were estimated for male and female rats, respectively; some of the rats became sensitized</p> <p><u>oral toxicity</u>: the oral LD<sub>50</sub> has been reported to range from 2,030 to 3,340 mg/kg in male and female rats, with stomach lesions appearing as the most consistent lesion upon necropsy; no adverse effects were observed in rats in a 90-day feed study with 1000- 10,000 ppm (50-500 mg/kg/day)</p> <p><u>dermal toxicity</u>: the dermal LD<sub>50</sub> was &gt;2000 mg/kg in rabbits after a 24-h occlusive application</p> <p><u>inhalation toxicity</u>: the LC<sub>50</sub> in rats was reported to exceed a concentration of 2,330 mg/m<sup>3</sup> (4-h exposure), with lung lesions appearing as the most consistent lesion upon necropsy</p> <p>numerous studies were conducted in rats, and in each of the following studies, the exposure was 6 h/day, 5 days/wk: in 2-wks studies, no adverse effects were observed with 0.3 mg/m<sup>3</sup>; in rats exposed to 0.1 mg/m<sup>3</sup>, lung injury was absent after 2 days of exposure, minimal after 6 days of exposure, and marked after 10 days of exposure; a dose-dependent increase in antibody levels and lung foci was observed in rats exposed to up to 0.30 mg/m<sup>3</sup> for 1-2 wks, and the lung foci completely resolved within 12 days after the last exposure, but reappeared following exposure to a single challenge concentration; exposure to 0.5 mg/m<sup>3</sup> produced hemorrhagic foci of the lung and increased antibody levels, and treatment with estrogen but not testosterone reduced the number of lung foci in both male and female rats; in a 13-wk study, a dose-dependent increase in lung lesions (hemorrhagic foci, inflammatory cell infiltration, bronchoalveolar pneumonia) and antibody levels was observed in rats exposed to ≤0.054 mg/m<sup>3</sup>, and these effects were more pronounced in rats following 6.5 weeks of exposure than observed in animals following 13 wks of exposure, and a NOEL was not identified</p> <p>in a 5-day inhalation study in mice with a 14-day recovery period, decreased time of inspiration and expiration and increased length of apneic periods were observed, and the LOEL was 0.01 mg/m<sup>3</sup></p> <p><u>reproductive and developmental toxicity</u>: no teratogenic effects or fetal deaths in rats or guinea pigs exposed to 500 µg/m<sup>3</sup> via inhalation on days 6-15 of gestation, however lung foci and TMA-specific antibody were observed in exposed dams and TMA-specific antibody was also noted in neonatal rats and in fetal but not neonatal guinea pigs, lung foci were only observed in the challenged offspring of rats whose mothers had not completely recovered from the original TMA exposure, but lung foci were not observed in adult rat offspring or in neonatal or adult guinea pig offspring; histopathological changes to reproductive tissues have not been observed in rats following subchronic exposures</p> <p><u>genotoxicity</u>: not genotoxic with or without metabolic activation in 2 Ames tests (≤10,000 µg/plate), in a CHO/HGPRT mutation assay (≤2000µg/ml), or a chromosomal aberration assay in CHO cells (≤2080 µg/ml)</p> <p><u>dermal irritation/sensitizer</u>: mild skin irritation potential; was a dermal sensitizer in guinea pigs with induction with a 30% solution in DMSO and challenge with 5% in acetone, but 300 mg of powder was not a sensitizer in guinea pigs; sensitizer in rats with 25-50% solutions in acetone/corn oil; sensitizer in mice with 10-50% solutions in acetone/olive oil</p> <p><u>ocular irritation</u>: highly irritating to rabbit eyes when instilled undiluted</p> <p><u>effects with occupational exposure</u>: may be a respiratory irritant and sensitizer; elevated antibody levels, asthma, allergic rhinitis, and a late respiratory systemic syndrome are associated with occupational exposures in some workers</p> <p><u>immunologic response</u>: TMA-induced syndromes are related to high chemical reactivity, which couples to human serum albumin and other proteins to form trimellitate protein conjugates, and some of the TMA syndromes have been correlated to immunologic responses to trimellitate haptenic groups; in TNF-α<sup>+/+</sup> mice, in the late phase of TMA-induced contact hypersensitivity, the peak of ear swelling responses occurred at 24 h with single challenge and at 8 h after repeated challenge</p> <p><u>recommended limits</u>: REL (U.S. NIOSH; exposure during a work week) – TWA 0.04 mg/m<sup>3</sup> (0.005 ppm)</p> | 2-7       |
| adipic acid<br>(124-04-9)           | <p><b>CIR Conclusion: safe in the present practices of use and concentration; reported to be used at a maximum of 0.000001% in leave-on formulations and 18% in rinse-off formulations</b></p> <p><u>molecular weight</u>: 146.14</p> <p><u>toxicokinetics</u>: under normal physiological conditions, dicarboxylic acids are rapidly β-oxidized, resulting in very low cellular concentrations and practically non-detectable concentrations in the plasma, and oxidation of odd- and even-numbered chains proceeds to different end points with even chains completely, and odd-number chains not completely, oxidized; most of a single oral dose administered to rats was exhaled as carbon dioxide, and adipic acid and its metabolites were recovered in the urine, while very little adipic acid was found in the tissues; recovered unchanged in the urine of rabbits: with oral and i.v. dosing, approximately 53-67% and 59-71% was recovered, respectively; in human studies using 1 subject per dose and various doses/durations, 6.76-61% was found in the urine after oral administration</p> <p><u>oral toxicity</u>: oral LD<sub>50</sub> in rats ranged from 0.94 g/kg to greater than the highest dose tested (11 g/kg); in feeding studies in rats, the NOAEL was &gt;435 mg/kg bw/day in a 4 wk study; with ≤34000 mg/kg bw/day sodium adipate in a protein-deficient diet, the NOAEL was 3333 mg/kg bw in a 19-wk study; 10/14 rats fed a diet containing 3200 mg/kg bw/day died during wks 0-4 of a 33 wk study, body weights of the surviving animals in that group were similar to controls at study termination, and slight effects were seen in the liver; in a 2-yr study, the NOAEL was 1%; slight decreases in weight gains were observed with 3 and 5%</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 8         |

Table 2. Monomer safety data

| Monomer (CAS No.)                   | Summary Information                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Reference |
|-------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
|                                     | <p><u>inhalation toxicity</u>: in mice exposed to 13 or 129 mg/m<sup>3</sup> adipic acid via inhalation for 4 mos (details of exposure not provided), decreased weight gain, altered oxidase activity, and upper respiratory tract, liver, kidney, and central nervous system effects were observed</p> <p><u>reproductive and developmental toxicity</u>: NOAELs for maternal and developmental toxicity were 288 mg/kg bw in CD-1 mice (highest dose given orally on days 6-15 of gestation) and 288 mg/kg bw in Wistar rats (highest dose given orally on days 6-15 of gestation); NOAELs for maternal toxicity and developmental toxicity were ≥250 mg/kg bw and 250 mg/kg bw, respectively, in Dutch-belted rabbits (maximum dose given by gavage on days 6-18 of gestation)</p> <p><u>genotoxicity</u>: not genotoxic in vitro in the Ames tests (concentrations up to 10,000 mg/plate), yeast gene mutation assay (concentrations ≤200 mg/l), mouse lymphoma assay (concentrations of ≤2000 µg/plate), or cytogenetic assay (human embryonic lung fibroblast cells, ≤200 mg/l), or in vivo in a cytogenetics assay (chromosomes from rats dosed by gavage with 5000 mg/kg bw (single dose) or 2500 mg/kg bw (1x/day for 5 days) or in a dominant lethal assay (up to 5000 mg/kg bw); a significant increase in resorption per implant site was observed in hamsters with 205 mg/kg bw adipic acid, resulting in a decreased number of live fetuses (this decrease was not evaluated statistically, and no effects were reported at this or the other doses (≤44 mg/kg bw))</p> <p><u>carcinogenicity</u>: not carcinogenic in a 2-yr chronic study in rats fed up to 5% adipic acid</p> <p><u>dermal irritation</u>: occlusive application of a 50% aq. solution to intact and abraded rabbit skin for 24 h produced an erythema score of 2-3/4 for intact skin, with clearing by day 3, and mild to severe erythema and edema, for abraded skin, which cleared by day 7; when applied undiluted or as an 80% aq. paste to the backs or ears of rabbits for 24 h, no irritation was observed on the backs and erythema was observed on the ear, with clearing by 72 h; no irritation was observed with a 24 h application (no details provided; semi-occlusive application of a 50% paste in propylene glycol produced slight to mild irritation in 3/6 rabbits; a semi-occlusive application of undiluted adipic acid was not corrosive; 50% in propylene glycol, was not irritating to guinea pigs</p> <p><u>dermal sensitization</u>: not a sensitizer (1% for intradermal induction, up to 50% in propylene glycol for dermal challenge) and produced very mild or no irritation</p> <p><u>ocular irritation</u>: mild to severe ocular irritant in rabbit eyes; irritation was dose-dependent</p> <p><u>peroxisome proliferation</u>: did not induce peroxisome proliferation and did not affect relative liver to body weights in rats fed 2% dissolved in alcohol for 3 wks</p>                                                                                                                                                                                                                                                               | 9,10      |
| cyclohexanedimethanol<br>(105-08-8) | <p><u>molecular weight</u>: 144.21 g/mol</p> <p><u>toxicokinetics</u>: when rats were dosed by gavage with 40 or 400 mg/kg/bw (<sup>14</sup>C; 70% trans-, 30% cis-isomers), there was rapid absorption from the GI tract and after 48 hr, 95% of dose was excreted in urine, 2.5% in feces, 0.03% respired as <sup>14</sup>CO<sub>2</sub>, and 0.4% remained in carcass, recovery of radioactivity averaged 98.9% of dose, and the half-life in plasma from rats dosed with 400 mg/kg was about 13 min; the test article and 4-hydroxymethylcyclohexanecarboxylic acid were detected in plasma, unchanged test article was not detected in urine and the major metabolites identified in urine were cyclohexanedicarboxylic acid (68%) and 4-hydroxymethylcyclohexanecarboxylic acid (31%), &lt;2% of radioactivity in urine was not fully characterized, and the cis-trans ratio of metabolites excreted in urine was the same as that of original dose</p> <p><u>oral toxicity</u>: observations in rats given a single oral dose by gavage of 400-6400 mg/kg bw ranged from normal to very weak with prostration and vasodilatation; the oral LD<sub>50</sub> is reported to be &gt;3200-6400 mg/kg in rats; in a 13-wk study in which rats were given 4-12.5 mg/l (i.e., 256-861 mg./kg bw/day for males and 440-1754 mg/kg bw/day for females) in drinking water, the LOAELs were 861 and 1754 mg/kg bw/day for males and females, respectively, based on decreased survival, abnormal urine and feces, reduced body weights and weight gains, decreased feed consumption and increased urinary protein levels, and the NOAELs were 479 and 754 mg/kg bw/day for males and females, respectively</p> <p><u>reproductive and developmental toxicity</u>: male and female rats were given 4-12.5 mg/l (i.e., 256-861 mg./kg bw/day for males and 440-1754 mg/kg bw/day for females) in drinking water prior to and during mating and until day 4 of lactation, for systemic toxicity, the LOAELs were 861 and 1360 mg/kg bw/day (based on bloody or discolored urine, reductions in body weights and weight gains and decreased feed consumption) and the NOAELs were 479 and 854 mg/kg bw/day for males and females, respectively, for developmental toxicity the LOAEL was 1360 mg/kg bw/day (based on decreased fetal weight and postnatal survival) and the NOAEL was 854 mg/kg bw/day, and for reproductive toxicity the LOAEL was greater than the highest dose tested and the NOAEL was 1360 mg/kg bw/day</p> <p><u>genotoxicity</u>: not genotoxic in vitro in an Ames test at ≤5000 µg/plate without and with activation, in a chromosomal aberration assay in human lymphocytes at ≤10 mM with or without metabolic activation, or in vivo at doses up to 2000 mg/kg in a mammalian bone marrow chromosomal aberration test in rats or a micronucleus test in mice</p> <p><u>dermal irritation/sensitization</u>: not irritating to rat skin when applied undiluted with a semi-occlusive patch; not a sensitizer in a guinea pig maximization test with 1% at intradermal induction at neat, applied neat for topical induction, and neat and at 50% for challenge</p> <p><u>ocular irritation</u>: moderately irritating to rabbit eyes</p> | 11        |
| ethylene glycol<br>(107-21-1)       | <p><b>CIR Conclusion (Special Report on reproductive and developmental toxicity): the metabolites of ethylene glycol monoalkyl ethers are reproductive and developmental toxins, but in general, these metabolites of concern are not expected to be formed in cosmetic formulations that contain polymers of ethylene glycol</b></p> <p><u>molecular weight</u>: 62.07 g/mol</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |           |

Table 2. Monomer safety data

| Monomer (CAS No.)              | Summary Information                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Reference |
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| isophthalic acid<br>(121-91-5) | <p><u>molecular weight</u>: 166.13 g/mol</p> <p><u>toxicokinetics</u>: readily eliminated from the body, largely unchanged, through the urine; in a 13-wk feed study in rats, levels of test article in the blood increased in a dose-dependent manner, and 24-h urinary excretion samples collected on days 7, 30, 60, 90 indicate that urinary excretion, presumably as the unchanged chemical, is the primary route of excretion; exposure of rats to 10 mg/m<sup>3</sup> for 6 h/day resulted in immediate detection of the test article in the blood, serum levels were 5.3-9.3 µg/ml in females and 1.4-3.4 µg/ml for males, but no test article was detected in the blood 1 wk following exposure</p> <p><u>oral toxicity</u>: oral LD<sub>50</sub>s have been reported in the range &gt;5000 to 13,000 mg/kg in rats; in a 13-wk feeding study in rats with 800 mg/kg/day, a slight increase in the incidence of crystalluria and renal pathology (mild hydronephrosis, pelvic calcification) were observed, the NOAEL was 250 mg/kg/day, and the LOAEL was 800 mg/kg/day</p> <p><u>dermal toxicity</u>: no mortality was observed in rabbits following acute exposure to 23,000 mg/kg; in a study with a 24 h occlusive application, the oral LD<sub>50</sub> was &gt;2000 mg/kg bw</p> <p><u>inhalation toxicity</u>: no mortality was observed in rats following acute inhalation exposures to 11,400 mg/m<sup>3</sup>; in a 4-wk study in which rats were exposed 6h/day 5 days/wk, no significant effects were observed with up to 10 mg/m<sup>3</sup>, and the NOAEL was 10 mg/m<sup>3</sup></p> <p><u>reproductive and developmental toxicity</u>: no maternal or developmental toxicity at inhalation exposures up to 10 mg/m<sup>3</sup> in rats on days 6-15 of gestation</p> <p><u>genotoxicity</u>: mixed results were reported in 3 Ames tests; negative in a chromosomal aberration assay in CHO cells at up to 5000 µg/ml with and without metabolic activation, in an HGPRT assay, and a mouse lymphoma mutation assay (with metabolic activation)</p> <p><u>dermal irritation/sensitization</u>: no dermal irritation with application of a single dermal dose to rabbits; a 4-h semi-occlusive application and a 24-h occlusive application of undiluted test material was not irritating to rabbit skin; mild dermal irritation with application of 2000 mg/kg; a 30% solution was not a skin sensitizer in guinea pigs (a reaction were observed in 1/10 of the guinea pigs)</p> <p><u>ocular irritation</u>: 0.1 g, undiluted, was non- to slightly irritating to rabbit eyes</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 12-14     |
| maleic anhydride<br>(108-31-6) | <p><u>toxicokinetics</u>: readily hydrolyzed to maleic acid under aqueous conditions</p> <p><u>oral toxicity</u>: according to the OECD summary, relatively low acute toxicity, with the oral LD<sub>50</sub> of about 1.0 g/kg in rats, but according to the EPA summary, acute oral studies in rats, mice, rabbits, and guinea pigs have demonstrated moderate to high acute toxicity by ingestion; oral feeding studies have resulted in kidney damage in rats at relatively high doses (&gt; 100 mg/kg/day after 90 days of exposure), with the effects (which were more severe in males than in females) likely due to maleic acid; no kidney effects were observed in rats that were fed diets containing 32 and 100 mg/kg/day maleic anhydride for 2 yrs; a dietary study in dogs dosed with up to 60 mg/kg for 7days/wk for 90 days, showed no adverse effects related to maleic anhydride exposure</p> <p><u>dermal toxicity</u>: according to the OECD summary, relatively low acute toxicity, with a dermal LD<sub>50</sub> in the range of 1.6 - 2.6 g/kg in rabbit, but according to the EPA summary, moderate acute dermal toxicity</p> <p><u>inhalation toxicity</u>: bronchial asthma was observed with acute exposure in guinea pigs; possible respiratory sensitizer to rats; repeated exposure by inhalation to rats, hamsters, and monkeys resulted in effects that were limited to the respiratory tract and eye irritation; in a 4-wk study in rats exposed 6 hours/day to up to 84 mg/m<sup>3</sup> (21 ppm), evidence of nasal, trachea, and lung irritation was observed at all exposure levels, and the effects were concentration-related and included epithelial hyperplasia and the presence of inflammatory exudates in the nasal turbinates and trachea; and epithelia hyperplasia, squamous metaplasia, and intra-alveolar hemorrhage in the lung, with a LOAEL of 12 mg/m<sup>3</sup> (3 ppm); in a 6-month inhalation study in which rats, hamsters, and monkeys were exposed to up to 9.8 mg/m<sup>3</sup> (2.4 ppm), respiratory tract and eye irritation were observed, hyperplastic and metaplastic changes in the nasal passages were considered indicative of irritation and judged to be reversible, and the NOAEL for rats was 3.3 mg/m<sup>3</sup> (0.8 ppm) and the NOAEL for hamsters and monkeys was 9.8 mg/m<sup>3</sup> (2.4 ppm)</p> <p><u>reproductive and developmental toxicity</u>: in a 2-generation reproductive toxicity study in which rats were dosed via gavage with up to 150 mg/kg/day, the NOAEL for reproductive effects was 55 mg/kg/day (highest dose tested due to parental death at 150 mg/kg/day), but in the parental group adverse effects (mortality, body weight changes, and respiratory irritation) were observed at 150 mg/kg/day and there were histopathological effects in the kidneys and bladder of the parental animals (first generation only) in all treated dose groups, and the LOAEL for parental effects was 20 mg/kg/day; no developmental toxicity was observed when pregnant rats were dosed via gavage with up to 140 mg/kg/day, but the dams in all dose groups either lost weight or failed to gain weight between days 6 and 9 of gestation (effect was not statistically significant at any interval and was reversible), and the NOAEL (maternal) was determined to be 140 mg/kg/day</p> <p><u>genotoxicity</u>: negative in bacterial gene mutation tests; a single in vitro chromosomal aberration test with and without S-9 was positive (due to inadequate documentation on this study, it is unclear whether the results were due to the test material itself or a change in pH to an acidic environment, which could have resulted in a non-specific effect); exposure of Sprague-Dawley rats of up to 100 mg/m<sup>3</sup> (25 ppm) did not increase chromosomal aberrations in the bone marrow</p> <p><u>carcinogenicity</u>: not carcinogenic when given to rats in their diets for 2 yrs at doses up to 100 mg/kg/day; the EPA has not classified maleic anhydride for carcinogenicity</p> <p><u>dermal irritation/sensitization</u>: severely irritating to the skin of rabbits after application of 0.5 g to the skin for 4 hours (mean irritation score of 3.67 – 4.00 during the 7-day observation period); shown to be a skin sensitizer to guinea pigs</p> <p><u>ocular irritation</u>: severely irritating to the eyes of rabbits (eye irritation score was 106.7/110); in humans,</p> | 15-18     |

Table 2. Monomer safety data

| Monomer (CAS No.)               | Summary Information                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Reference |
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|                                 | <p>exposure to 0.25 - 0.38 ppm (1- 1.6 mg/m<sup>3</sup>) produced eye irritation, no irritation was reported at 0.22 ppm</p> <p><u>respiratory effects (human)</u>: exposure to 0.25 - 0.38 ppm (1- 1.6 mg/m<sup>3</sup>) produced respiratory tract irritation, no irritation was reported at 0.22 ppm</p> <p><u>effects with occupational exposure</u>: according to the OECD summary, there have been a few published human cases suggesting that maleic anhydride provokes asthma in a relatively small proportion of exposed workers, however, questions have been raised whether the asthma was actually related to maleic anhydride exposure; according to the EPA summary, chronic (long-term) exposure has been observed to cause chronic bronchitis, asthma-like attacks, and upper respiratory tract and eye irritation in workers, and in some people, allergies have developed so that lower concentrations can no longer be tolerated</p> <p><u>recommended limits</u>: the EPA RfD is 0.1 mg/kg bw/d based on renal lesions in rats (the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious noncancer effects during a lifetime; it is not a direct estimator of risk but rather a reference point to gauge the potential effects); OEHHA inhalation REL (chronic exposure level, exposure 24 h/day for a lifetime) is 0.7 µg/m<sup>3</sup> (2.5 ppb)</p> <p><b>Maleic Acid - CIR Conclusion: safe for use in cosmetic formulations as a pH adjustor in the practices of use described in the safety assessment (only use as a pH adjustor was evaluated) ; was reported to be used at 0.004% in "other" bath products; used in hair straighteners, other hair-coloring preparations, and shaving cream according to VCRP data, but no concentration data were reported for these uses</b></p> <p>according to the Discussion of the report, the Panel recognized that maleic acid itself may be a dermal and/or ocular irritant, but its use as a pH adjustor in cosmetic formulations dictates that most of the acid would be neutralized into various maleate salts; additionally, the concentration of maleic acid would be dependent on the alkaline content of the formulation; the Panel also stated that safety of maleic acid as a pH adjustor should be based on the amount of free maleic acid remaining after neutralizing the formulations</p>                    | 19        |
| neopentyl glycol<br>(126-30-7)  | <p><u>molecular weight</u>: 104.15</p> <p><u>toxicokinetics</u>: after rabbits were dosed with 1-1.5 g/kg bw (unlabeled) by gavage, 62% of the dose was found in the 24-h urine as the conjugate of glucuronic acid, indicating rapid absorption, 1.9% was recovered as the metabolite 3-hydroxy-2,2-dimethylpropionic acid, and only 0.7% of the dose was present unchanged</p> <p><u>oral toxicity</u>: oral LD<sub>50</sub> in rats reported as 3200 mg/kg to 6920 mg/kg; with repeated dosing with up to 1000 mg/kg/day by gavage, the NOAEL for males and females were 300 and 1000 mg/kg/day, respectively; in a 90-day gavage study, no adverse effects were observed at doses up to 1000 mg/kg</p> <p><u>dermal toxicity</u>: the dermal LD<sub>50</sub> was &gt;4000 mg/kg bw in guinea pigs with a 24-h occlusive application to a 20% solution in acetone/corn oil vehicle</p> <p><u>inhalation toxicity</u>: there was no mortality in rats exposed to a saturated vapor for 8 h (the calculated nominal concentration was 140 mg/m<sup>3</sup>); rats exposed for 6 h to 39,400 ppm (168 mg/l) showed symptoms of irritation of the respiratory tract, 1/3 died within 24 h; 3 rats were exposed to 4000 ppm, 6 h/day for 10 days, and irritation of the respiratory tract and dilatation of the skin blood vessels were detected, but no evidence of toxic effects on internal organs was observed at necropsy</p> <p><u>reproductive and developmental toxicity</u>: the NOAEL for maternal and prenatal developmental toxicity was 1000 mg/kg with dosing with ≤1000 mg/kg on days 6-19 of gestation; in a reproductive toxicity study in which rats were dosed with up to 1000 mg/kg/day by gavage before and during mating and through day 3 of lactation, the NOAEL was 1000 mg/kg for the parent and F<sub>1</sub> generation</p> <p><u>genotoxicity</u>: not genotoxic in an Ames test (up to 5000 µg/plate) or to Chinese hamster ovary cells (up to 1 mg/ml)</p> <p><u>dermal irritation/sensitization</u>: an 80% aq. solution was not an irritant to rabbit skin with a 20-h -occlusive exposure; slightly irritating to rabbit skin with a 4-h exposure to undiluted test material; not a sensitizer in a mouse LLNA (60% in propylene glycol)</p> <p><u>ocular irritation</u>: instillation of crystalline test substance resulted in serious damage to rabbit eyes in one study, and instillation of neat test article in rabbit eyes resulted in irreversible damage in one study and slight to moderate irritation in another study</p> | 20,21     |
| phthalic anhydride<br>(85-44-9) | <p><u>molecular weight</u>: 148.12 g/mol</p> <p><u>stability</u>: rapidly hydrolyzed to phthalic acid upon contact with water</p> <p><u>toxicokinetics</u>: unconjugated compound was found in the urine of humans exposed by inhalation, demonstrating systemic absorption and elimination via the urine and the existence as a hydrolysis product in vivo</p> <p><u>oral toxicity</u>: oral LD<sub>50</sub> of 1530 mg/kg bw in rats; low repeated dose toxicity in rats; in a 7-wk feed study in which mice were given up to 7140 and rats up to 3330 mg/kg bw/day, there were no effects in mice, but there was a significant reduction in body weight gains in rats of the high dose group and centrilobular cytoplasmic vacuolation were seen in the livers in most of the male rats fed 1660 mg/kg bw/day; in male and female mice fed 4670 and 3430 mg/kg bw/day, respectively, for 105 wks, significantly increased incidences of lung and kidney lymphocytosis in the low- and high-dose males and females, chronic bile duct inflammation in the high-dose males and females, and dose-related adrenal atrophy and mineralization of the thalamus in the low-and high-dose males were observed, and the time weighted LOAELs were approximately 1717 and 2340 mg/kg bw/day in female and male mice, respectively, and no NOAEL was obtained</p> <p><u>dermal toxicity</u>: the dermal LD<sub>50</sub> was &gt;10,000 mg/kg bw in rabbits</p> <p><u>inhalation toxicity</u>: the LC<sub>50</sub> was &gt;2.14 mg/l following a 4-h nose-only exposure; respiratory sensitization potential in guinea pigs, and animals exposed to and challenged with 5.0 mg/m<sup>3</sup> phthalic anhydride dust had</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 22,23     |

Table 2. Monomer safety data

| Monomer (CAS No.)             | Summary Information                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Reference |
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|                               | <p>significant numbers of hemorrhagic lung foci</p> <p><u>reproductive and developmental toxicity</u>: no evidence of toxicity to reproductive organs was observed in comprehensive carcinogenicity studies in rats and mice, as no treatment-related changes were observed for any reproductive organ investigated during macroscopic and microscopic examination; decreased sperm motility time was reported in a study in which male rats were exposed via inhalation at 0.2 mg/m<sup>3</sup> and no effects were observed at 0.02 mg/m<sup>3</sup> (it was noted that confidence in this study was limited because of the small sample size of 6/group, poor documentation, and lack of data on the biological and statistical relevance of the observed effects)</p> <p><u>genotoxicity</u>: not mutagenic in the Ames test (up to 5000 µg/plate); induced chromosomal aberrations in mammalian cells only at the high concentration of 10 mM without metabolic activation; not genotoxic in a sister chromatid exchange assay (10-300 µg/ml with and without metabolic activation)</p> <p><u>carcinogenicity</u>: no evidence of carcinogenicity in rats fed 1000 mg/kg bw/day or in in male and female mice fed 4670 and 3430 mg/kg bw/day, respectively, 105 wks</p> <p><u>dermal irritation/sensitization (animal)</u>: mild irritation was observed when 550 mg of flakes were applied to rabbits for 4 h, the average dermal irritation index after semi-occlusive exposure was 1.21/8, and observed effects were reversible; semi-occlusive application of 500 mg (moistened with water) on the ear for 24 h was not an irritant; sensitizer in the GPMT and at a concentration of 10% in the LLNA in mice</p> <p><u>dermal irritation (humans)</u>: contact with either the solid or a vapor has been reported to cause skin irritation after occupational exposure; erythema, blistering, ulceration and necrosis have been reported following skin contact</p> <p><u>ocular irritation</u>: irritating to rabbit eyes (undiluted)</p> <p><u>mucous membrane irritation</u>: a primary irritant in humans when in the form of vapor, fumes, or dust</p> <p><u>respiratory effects (humans)</u>: a primary irritant to the upper respiratory tract when in the form of vapor, fumes, or dust</p> <p><u>effects with occupational exposure</u>: conjunctivitis, rhinitis, rhinoconjunctivitis, bronchitis, and irritation of the skin and mucous membranes of the respiratory tract have been observed in exposed workers; initial exposure produces coughing, sneezing, burning sensations in the nose and throat, and increased mucous secretion; occasional bloody sputum, emphysema, lower blood pressure, and minor signs of central nervous system excitation has been observed in chronically-exposed workers</p> <p><u>recommended limits</u>: the EPA has calculated a provisional RfC of 0.12 mg/m<sup>3</sup> (the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious noncancer effects during a lifetime. It is not a direct estimator of risk but rather a reference point to gauge the potential effects); the EPA has established a RfD of 2.0 mg/kg bw/day</p>                                                                                                                                                                                                                        |           |
| propylene glycol<br>(57-55-6) | <p><b>CIR Conclusion: safe in the present practices of use and concentration when formulated to be non-irritating; reported to be used at up to 73% in leave-on formulations</b></p> <p><u>molecular weight</u>: 76.09 g/mol</p> <p><u>toxicokinetics</u>: the major route of metabolism is to lactaldehyde and then lactate via hepatic alcohol and aldehyde dehydrogenases</p> <p><u>dermal absorption</u>: penetration from a ternary cosolvent solution through hairless mouse skin was 57% over a 24-h period, and it appears that it does not reach the dermis; it can act as a penetration enhancer</p> <p><u>oral toxicity</u>: the oral LD<sub>50</sub> was 21 g/kg in rats; no mortality in mice given 10% in drinking water for 14 days; lesions were not observed in rats that were fed diets containing 50,000 ppm (2.5 g/kg/day) for 15 wks or up to 50,000 ppm in the diet for 2 yrs; similar results were reported in a study in which dogs were fed 2 or 5 g/kg in the diet for 103 wks; in dogs given 5% in drinking water for 5-9 mos, no hepatic or renal impairment was noted</p> <p><u>inhalation toxicity</u>: some effects in rats due to exposure of 2.2 mg/L air for 6 h/day, 5 days/wk, for 13 wks, but these effects were inconsistent and without dose-response trends</p> <p><u>reproductive and developmental toxicity</u>: not teratogenic in female CD-1 mice when administered orally at a concentration of 10,000 ppm (vehicle not specified) on days 8-12 of gestation; no reproductive effects in a continuous breeding reproduction study in albino mice with up to 5% administered in feed or water; no adverse effects on reproduction or development when given orally at doses up to 1600 mg/kg in mice and rats, 1230 mg/kg in rabbits, or 1550 mg/kg in hamsters</p> <p><u>genotoxicity</u>: not mutagenic in an Ames test at up to 10,000 µg/plate with or without metabolic activation; caused a dose-dependent increase in the frequency of SCEs in a Chinese hamster cell line and was classified as a weak inducer of SCEs, but in another SCE study, it was not genotoxic in human cultured fibroblasts or a cultured Chinese hamster cell line with or without metabolic activation; chromosomal aberrations were induced in Chinese hamster fibroblasts in another assay; was not genotoxic in additional tests for chromosomal aberrations, mitotic recombination, or basepair substitution, or DNA damage or a micronucleus test</p> <p><u>carcinogenicity</u>: not carcinogenic in a 2-yr feeding study at up to 50,000 ppm in rats; did not induce skin tumors and was not carcinogenic in a lifetime dermal study at concentrations up to 100% in mice</p> <p><u>dermal irritation/sensitization (animal)</u>: 10% was not a dermal irritant in a 24-h test in nude mice, but hypertrophy, dermal inflammation, and proliferation were observed at a concentration of 50%; not an irritant to intact or abraded skin of rabbits in a Draize test, to guinea pig or rabbit skin when applied for 48 h using open and occlusive patches, or to swine skin in 48-h and 21-day open and occlusive patch tests; not a sensitizer in a mouse external ear swelling sensitization test undiluted), in a GPMT, OET, or chamber (Finn chamber) test (at 70%); was a potentially weak sensitizer in one maximization test, but the results of 6 other guinea pig sensitization indicated it was not an allergen</p> <p><u>dermal irritation/sensitization (human)</u>: induced skin irritation and sensitization reactions in normal subjects and</p> | 26,27     |

Table 2. Monomer safety data

| Monomer (CAS No.)                  | Summary Information                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Reference |
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|                                    | <p>patients in studies with test concentrations ranged from 2 - 100%, and reactions were observed at concentrations as low as 10% in predictive tests and as low as 2% in provocative tests; however, the dermal irritation potentials of deodorant formulations containing 68.06% or 69.15% were evaluated in an SIOPT and compared to a reference in-use control formulation, and the formulations containing propylene glycol were no more irritating or even less irritating than the reference control; use studies of deodorant formulations containing 35%-73% did not report any potential for eliciting irritation or sensitization; deodorant formulations containing 69.15% or 86% did not induce sensitization reactions; questionable results were obtained in an RIPT of a deodorant containing 73%; retrospective analysis of pools of patient patch test data indicated that ≤6.0% of patients tested had positive reactions to a 30% aq. solution; increased the allergic responses in 43 patients patch tested with 50 µg 1% nickel sulfate solution</p> <p><u>photoallergenicity</u>: did not produce a photoallergic response in a provocative photopatch test (concentration not specified)</p> <p><u>ocular irritation</u>: did not induce corneal damage in rabbit eyes in one study; was a slight ocular irritant in another</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |           |
| sebacic acid<br>(111-20-6)         | <p><b>CIR Conclusion: safe in the present practices of use and concentration; reported to be used at a maximum of 0.03% in leave-on formulations and 1% in rinse-off formulations</b></p> <p><u>molecular weight</u>: 202.25</p> <p><u>toxicokinetics</u>: oxidized to water and carbon dioxide, passing through acetyl-CoA and succinyl-CoA formation; under normal physiological conditions, dicarboxylic acids are rapidly β-oxidized, resulting in very low cellular concentrations and practically non-detectable concentrations in the plasma, and oxidation of even-numbered chains is complete; recovered unchanged in the urine of rats: with i.v. dosing, approximately 35% sebacate was recovered</p> <p><u>oral toxicity</u>: disodium sebacate was not toxic to rats or rabbits fed up to 1000 mg/kg bw for 6 mos</p> <p><u>reproductive and developmental toxicity</u>: in dietary studies, disodium sebacate was not a developmental toxicant in rats (500 mg/kg bw day; days of dosing not stated) or rabbits (1000 mg/kg bw)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 8         |
| trimethylpentanediol<br>(144-19-4) | <p><u>molecular weight</u>: 146.23</p> <p><u>oral toxicity</u>: oral LD<sub>50</sub> was 1800 mg/kg bw and &gt;2000 mg/kg bw in male mice and female rats, respectively; in rats fed ≤2% for 57 days, the NOAEL for males and females was 0.5% (376 mg/kg bw/day) because of changes in organ wts at higher doses</p> <p><u>dermal toxicity</u>: in a study in guinea pigs (1 animal/dose), the dermal LD<sub>50</sub> was &gt;1 g/kg bw</p> <p><u>inhalation toxicity</u>: the LC<sub>50</sub> was &gt;4.5 mg/l in rats with a 6-h exposure period (the respirable concentration of the test substance was 1.43 mg/l and the calculated exposure to the respirable portion of the test substance was 2.8 g/kg bw)</p> <p><u>reproductive and developmental toxicity</u>: in a 3-generation dietary study in rats at concentrations up to 1% in feed, the NOAEL was 1% for both parental and for reproductive and developmental toxicity</p> <p><u>genotoxicity</u>: not genotoxic, with or without metabolic activation, in an Ames test at concentrations up to 5000 µg/plate, in a mammalian cell assay at concentrations up to 1462.3 µg/mL in mouse lymphoma cells, or in a chromosomal aberration assay at concentrations up to 1500 µg/ml in CHO cells</p> <p><u>irritation/sensitization</u>: an occlusive 4-h exposure was not irritating to intact or abraded rabbit skin; 0.1 M was not a sensitizer in guinea pigs</p> <p><u>ocular irritation</u>: undiluted test material was a slight irritant to rabbit eyes</p>                                                                                                                                                                                                                                                                                                                                                                               | 28,29     |
| trimethylolpropane<br>(77-99-6)    | <p><u>molecular weight</u>: 134.17 g/mol</p> <p><u>oral toxicity</u>: in a gavage study, the LD<sub>50</sub> was ~14,700 mg/kg in male rats; in a 90 day feeding study with up to 1.0% (667 mg/kg bw/d) in rats, the NOAEL was 0.1% (67 mg/kg bw/d) based on significant changes of clinical chemistry or hematological data (at ≥0.3 %) and histopathological changes, mainly in liver and spleen (at 1%)</p> <p><u>dermal toxicity</u>: the dermal LD<sub>50</sub> was &gt;10,000 mg/kg bw in rabbits with a 24-h occlusive application</p> <p><u>inhalation toxicity</u>: the LC<sub>50</sub> was &gt;850 mg/m<sup>3</sup> (vehicle, ethanol/lutrol 1:1) in rats with a 4-h exposure period</p> <p><u>reproductive and developmental toxicity</u>: in rats dosed by gavage with up to 1000 mg/kg/day on days 6-20 of gestation, the NOAEL was 100 mg/kg bw/day for developmental toxicity due to decreases in fetal weight and 100 mg/kg bw/day for maternal toxicity due to decreased body weight and weight gains; in a study in which male and female rats were dosed by gavage with up to 800 mg/kg bw/day before, during, and after mating, the NOAEL was 800 mg/kg bw/day for reproductive and developmental toxicity and 200 mg/kg bw/day for general toxicity</p> <p><u>genotoxicity</u>: not genotoxic, with or without metabolic activation, in an Ames test at concentrations up to 5000 µg/plate, in a mammalian cell assay at concentrations up to 1400 µg/mL in Chinese hamster lung fibroblasts, or in a chromosomal aberration assay at concentrations up to 1340 µg/ml in Chinese hamster lung cells</p> <p><u>dermal irritation/sensitization</u>: application to the inner ear of rabbits did not produce irritation; no sensitization in a mouse LLNA at concentrations up to 50%</p> <p><u>ocular irritation</u>: not irritating to rabbit eyes when instilled undiluted or melted</p> | 30,31     |

Abbreviations: DMSO – dimethyl sulfoxide; EPA – Environmental Protection Agency; CHO – Chinese hamster ovary; GPMT – guinea pig maximization test; HGPRT - hypoxanthine-guanine phosphoribosyltransferase; LLNA – local lymph node assay; LOAEL – lowest observable adverse effect level; NIOSH – National Institute for Occupational Safety and Health; NOAEL – no-observable adverse effect level; OECD – Organisation for Economic Co-operation and Development; OEHA - Office of Environmental Health Hazard Assessment (California); OET – open epicutaneous test; NIOSH REL – recommended exposure limit; OEHA REL – reference exposure level; RfC – reference concentration; RfD - reference dose; RIPT – repeated insult patch test; SCE – sister chromatid exchange; SIOPT – single insult occlusive patch test; TMA – trimellitic anhydride; TWA – time-weighted average

**Table 3. Physical and chemical properties**

| Property                                                                                | Description                                                    | Reference     |
|-----------------------------------------------------------------------------------------|----------------------------------------------------------------|---------------|
| <b>Adipic Acid/CHDM/MA/Neopentyl Glycol/ Trimellitic Anhydride Copolymer</b>            |                                                                |               |
| physical characteristics                                                                | liquid or solid                                                | <sup>32</sup> |
| solubility                                                                              | insoluble in water                                             | <sup>32</sup> |
| <b>Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer</b>                     |                                                                |               |
| physical characteristics                                                                | clear liquid                                                   | <sup>33</sup> |
| avg molecular weight                                                                    | 8999 Da                                                        | <sup>36</sup> |
| solid content                                                                           | 70-80% (in butyl acetate)                                      | <sup>33</sup> |
| solubility                                                                              | low solubility in cold water; soluble in all "common solvents" | <sup>33</sup> |
| acid number                                                                             | 10-20 mg KOH/g                                                 | <sup>33</sup> |
| <b>Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer</b>                       |                                                                |               |
| number avg molecular weight (Mn)                                                        | >1000 Da                                                       | <sup>41</sup> |
| water solubility                                                                        | insoluble                                                      | <sup>41</sup> |
| dissociation constant                                                                   | expected to be ionized under environmental conditions (pH 4-9) | <sup>41</sup> |
| <b>70% Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer/30% butyl acetate</b> |                                                                |               |
| physical characteristics (20°C)                                                         | light yellow liquid                                            | <sup>41</sup> |
| density                                                                                 | 1091 kg/m                                                      | <sup>41</sup> |

**Table 4. Frequency and concentration of use according to duration and type of exposure**

|                              | # of Uses <sup>38</sup>                                             | Max Conc of Use (%) <sup>39</sup> | # of Uses <sup>38</sup>                                            | Max Conc of Use (%) <sup>39</sup> |  |
|------------------------------|---------------------------------------------------------------------|-----------------------------------|--------------------------------------------------------------------|-----------------------------------|--|
|                              | <b>Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer</b> |                                   | <b>Phthalic Anhydride/ Trimellitic Anhydride/Glycols Copolymer</b> |                                   |  |
| <b>Totals*</b>               | <b>471</b>                                                          | <b>5.4-32.8</b>                   | <b>85</b>                                                          | <b>1.8-12</b>                     |  |
| <b>Duration of Use</b>       |                                                                     |                                   |                                                                    |                                   |  |
| Leave-On                     | 470                                                                 | 5.4-32.8                          | 85                                                                 | 1.8-12                            |  |
| Rinse-Off                    | 1                                                                   | NR                                | NR                                                                 | NR                                |  |
| Diluted for (Bath) Use       | NR                                                                  | NR                                | NR                                                                 | NR                                |  |
| <b>Exposure Type</b>         |                                                                     |                                   |                                                                    |                                   |  |
| Eye Area                     | NR                                                                  | NR                                | NR                                                                 | NR                                |  |
| Incidental Ingestion         | NR                                                                  | NR                                | NR                                                                 | NR                                |  |
| Incidental Inhalation-Spray  | NR                                                                  | NR                                | NR                                                                 | NR                                |  |
| Incidental Inhalation-Powder | NR                                                                  | NR                                | NR                                                                 | NR                                |  |
| Dermal Contact               | 1                                                                   | NR                                | 2                                                                  | NR                                |  |
| Deodorant (underarm)         | NR                                                                  | NR                                | NR                                                                 | NR                                |  |
| Hair - Non-Coloring          | NR                                                                  | NR                                | NR                                                                 | NR                                |  |
| Hair-Coloring                | NR                                                                  | NR                                | NR                                                                 | NR                                |  |
| Nail                         | 470                                                                 | 5.4-32.8                          | 83                                                                 | 1.8-12                            |  |
| Mucous Membrane              | NR                                                                  | NR                                | NR                                                                 | NR                                |  |
| Baby Products                | NR                                                                  | NR                                | NR                                                                 | NR                                |  |

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

NR – not reported

**Table 5. Human repeated insult patch tests of nail polish formulations**

| Concentration in Formulation                                         | Concentration/Dose                                                           | Test Population | Procedure                                                                                                                                                                                                                   | Results                                                                                                                                                         | Reference |
|----------------------------------------------------------------------|------------------------------------------------------------------------------|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| <b>ADIPIIC ACID/NEOPENTYL GLYCOL/TRIMELLITIC ANHYDRIDE COPOLYMER</b> |                                                                              |                 |                                                                                                                                                                                                                             |                                                                                                                                                                 |           |
| 3.85%                                                                | undiluted                                                                    | 52 subjects     | $\frac{3}{4}$ " x $\frac{3}{4}$ " patches applied to the back<br>no other details provided                                                                                                                                  | no irritation or sensitization                                                                                                                                  | 43        |
| 7.98%                                                                | undiluted; 0.2 ml<br>volatilized for 30-60 min<br>prior to patch application | 113 subjects    | 24-h semi-occlusive induction patches were applied to the back<br>3x/wk for 3 wks; 24-h challenge patches were applied after a 2-<br>wk non-treatment period to previously untreated sites                                  | not an irritant or sensitizer<br>sporadic generally transient, barely perceptible (0.5)<br>response were observed in some subjects                              | 44        |
| 10%                                                                  | undiluted; test material was<br>volatilized                                  | 213 subjects    | 24-h semi-occlusive induction patches were applied to the back<br>3x/wk for 3 wks; 24-h challenge patches were applied after a 2-<br>wk non-treatment period to previously untreated site                                   | not an irritant or sensitizer                                                                                                                                   | 45        |
| 10.5%                                                                | undiluted                                                                    | 107 subjects    | 1" x 1" patches applied to the upper back<br>no other details provided                                                                                                                                                      | no irritation or sensitization                                                                                                                                  | 46        |
| 13.9%                                                                | undiluted; 0.2 ml<br>dried to touch before<br>application                    | 213 subjects    | 24-h semi-occlusive induction patches (2cm x 2 cm) were<br>applied to the back or upper arm 3x/wk for 3 wks; 24-h<br>challenge patches were applied after a 10-15 day non-treatment<br>period to previously untreated sites | no irritation or sensitization                                                                                                                                  | 47        |
| 15%                                                                  | undiluted; test material was<br>allowed to air dry on patch                  | 108 subjects    | 24-h semi-occlusive induction patches were applied to the upper<br>back 3x/wk for 3 wks; 24-h challenge patches were applied<br>after a 2-wk non-treatment period to previously untreated sites                             | not an irritant or sensitizer                                                                                                                                   | 48        |
| <b>PHTHALIC ANHYDRIDE/TRIMELLITIC ANHYDRIDE/GLYCOLS COPOLYMER</b>    |                                                                              |                 |                                                                                                                                                                                                                             |                                                                                                                                                                 |           |
| 7%                                                                   | undiluted; 0.2 ml<br>volatilized for 30-60 min<br>prior to patch application | 53 subjects     | 24-h semi-occlusive induction patches were applied to the back<br>3x/wk for 3 wks; 24-h challenge patches were applied after a 2-<br>wk non-treatment period to previously untreated sites                                  | not an irritant or sensitizer                                                                                                                                   | 49        |
| 7.5%                                                                 | undiluted; 0.2 ml<br>volatilized for 15 min prior<br>to patch application    | 103 subjects    | 9, 24-h semi-occlusive induction patches; 1 challenge patch<br>was applied after a 10-15 day non-treatment period                                                                                                           | One subject had minimal or definite erythema, often<br>with itching, at all but 2 of the induction readings<br>and at challenge; no other reactions were noted. | 50        |

**Table 6. Case reports with Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer in nail polish**

| Case History                                                                                                                                                                                                                                                                    | Patch Testing                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Reference |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| a female subject had a 2-mo history of an intermittent itchy rash on the neck and around the eyes, associated with episodes of swelling of the eyelids; mild erythema and scaling were present the upper eyelids and neck                                                       | <ul style="list-style-type: none"> <li>- Patch testing was performed with the British standard series, a modified cosmetic series, a modified plant series, with her cosmetics, and her nail varnish (which was applied to a Finn Chamber and allowed to dry before application); a positive reaction (+) was observed with the nail varnish at days 2 and 4; there was no reaction to tosylamide/formaldehyde resin</li> <li>- Patch testing with the nail varnish components resulted in a positive reaction (++) to 1% Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer in petrolatum was observed at days 2 and 4; a + reaction was also observed to the 5 coloring bases that contained this ingredient</li> <li>- testing in 12 control subjects had negative results</li> </ul> | 51        |
| a female subject had a 12-mo history of periorbital and fingertip eczema                                                                                                                                                                                                        | <ul style="list-style-type: none"> <li>- the subject was patch-tested with the BCDSB, a cosmetic and medicament series, and her own cosmetics; a positive reaction (+) was observed with her nail varnish (which was applied to a Finn Chamber and allowed to dry before application) on day 4</li> <li>- Patch testing with the nail varnish components resulted in a positive reaction (++) to 1% Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer in petrolatum at day 4</li> </ul>                                                                                                                                                                                                                                                                                                 | 42        |
| a female subject had a 6-mo history of perioral eczema and dry, fissured lips                                                                                                                                                                                                   | <ul style="list-style-type: none"> <li>- the subject was patch-tested with the BCDSB, a cosmetic and dental series, and her own cosmetics; a positive reaction (+) was observed with her nail varnish (which was applied to a Finn Chamber and allowed to dry before application) on day 4</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 42        |
| a female subject had a 6-mo history of intermittent eczema of her face and fingers                                                                                                                                                                                              | <ul style="list-style-type: none"> <li>- the subject was patch-tested with the BCDSB, a cosmetic series, and her own cosmetics; positive reactions (+) were observed with her nail varnish (which was applied to a Finn Chamber and allowed to dry before application) on days 2 and 4</li> <li>- patch testing with the nail varnish components resulted in a positive reaction (+) to 1% Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer in butyl acetate on day 4</li> </ul>                                                                                                                                                                                                                                                                                                       | 42        |
| a female subject had periungual dermatitis affecting all her fingers; she had been wearing nail varnish and acrylic nails for several years                                                                                                                                     | <ul style="list-style-type: none"> <li>- the subject was patch-tested with the BCDSB and acrylic series; she had positive reactions to several compounds, including 1% Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer in butyl acetate on days 2 and 4</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 42        |
| Three case reports were described:<br>an atopic female subject presented with generalized eczema and major lichenification of lips and eyelids progressively worsening during the past 4 yrs; recent patch testing with the standard ICDRG series (2) was negative              | <ul style="list-style-type: none"> <li>- patch testing with all nail polish formulations resulted in positive reactions to a few of the polishes; patch testing with toluene sulfonamide formaldehyde resin was negative</li> <li>- patch testing with the nail varnish components Identified Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer (tested at 1% and 5% in petrolatum) as the allergen in all 3 subjects</li> </ul>                                                                                                                                                                                                                                                                                                                                                        | 37        |
| a female subject had recurrent eyelid and neck dermatitis, with severe nail dystrophy; patch testing with a standard series, toluene sulfonamide formaldehyde resin, and her own nail polishes were negative; the lesions persisted for several mos, and she was referred again | <ul style="list-style-type: none"> <li>- subsequent patch testing with the raw monomers, i.e. phthalic anhydride, trimellitic anhydride and glycols was performed in 2 subjects; the results were negative</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |           |
| a female subject had a history of occupational contact dermatitis and asthma due to glutaraldehyde presented with head and neck eczema lasting for 3 mos                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |           |

Abbreviations: BCDSB - British Contact Dermatitis Society Standard Battery; ICDRG - International Contact Dermatitis Research Group

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|                                                                                                    |     |
|----------------------------------------------------------------------------------------------------|-----|
| ADIPIC ACID/NEOPENTYL GLYCOL/TRIMELLITIC ANHYDRIDE COPOLYMER 07F - Makeup Bases                    | 1   |
| ADIPIC ACID/NEOPENTYL GLYCOL/TRIMELLITIC ANHYDRIDE COPOLYMER 08A - Basecoats and Undercoats        | 42  |
| ADIPIC ACID/NEOPENTYL GLYCOL/TRIMELLITIC ANHYDRIDE COPOLYMER 08C - Nail Creams and Lotions         | 4   |
| ADIPIC ACID/NEOPENTYL GLYCOL/TRIMELLITIC ANHYDRIDE COPOLYMER 08D - Nail Extenders                  | 1   |
| ADIPIC ACID/NEOPENTYL GLYCOL/TRIMELLITIC ANHYDRIDE COPOLYMER 08E - Nail Polish and Enamel          | 398 |
| ADIPIC ACID/NEOPENTYL GLYCOL/TRIMELLITIC ANHYDRIDE COPOLYMER 08F - Nail Polish and Enamel Removers | 1   |
| ADIPIC ACID/NEOPENTYL GLYCOL/TRIMELLITIC ANHYDRIDE COPOLYMER 08G - Other Manicuring Preparations   | 24  |
|                                                                                                    |     |
| PHTHALIC ANHYDRIDE/TRIMELLITIC ANHYDRIDE/GLYCOLS COPOLYMER 07I - Other Makeup Preparations         | 2   |
| PHTHALIC ANHYDRIDE/TRIMELLITIC ANHYDRIDE/GLYCOLS COPOLYMER 08A - Basecoats and Undercoats          | 14  |
| PHTHALIC ANHYDRIDE/TRIMELLITIC ANHYDRIDE/GLYCOLS COPOLYMER 08C - Nail Creams and Lotions           | 1   |
| PHTHALIC ANHYDRIDE/TRIMELLITIC ANHYDRIDE/GLYCOLS COPOLYMER 08D - Nail Extenders                    | 1   |
| PHTHALIC ANHYDRIDE/TRIMELLITIC ANHYDRIDE/GLYCOLS COPOLYMER 08E - Nail Polish and Enamel            | 55  |
| PHTHALIC ANHYDRIDE/TRIMELLITIC ANHYDRIDE/GLYCOLS COPOLYMER 08G - Other Manicuring Preparations     | 12  |



## Memorandum

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

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

**DATE:** August 17, 2016

**SUBJECT:** Information Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer

Anonymous. 2016. Method of manufacture and composition of Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer.

August 2016

## **Method of Manufacture and Composition of Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer**

### **Product Synthesis**

Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer is synthesized as follows:

The trifunctional glycol(s) and the di and tri basic acids are charged into a clean and dry reaction vessel. Heat is applied to drive the polyester reaction; water is generated as a by-product of this reaction. The rate of reaction is controlled by the heat applied and the reaction water that is generated. The reactant mixture is heated gradually to 200°C and the in-process wet properties are measured. Once the reactants reach defined in-process wet properties, the reaction is deemed to be completed. The reaction mixture is cooled and dissolved in solvent. The final product is further cooled and then packaged in appropriate containers.

### **Product Composition**

Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer is a polyester resin composed of adipic acid, neopentyl glycol, and trimellitic anhydride. According to a quantitative  $^1\text{H}$  NMR study, residual neopentyl glycol is present at a concentration of approximately 1.5%. Residual trimellitic anhydride and adipic acid concentrations are below the level of detection (50 ppm or 0.005%) of this method.

### **Product Molecular Weight**

The average molecular weight of Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer is 8999 Daltons.



**Memorandum**

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

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

**DATE:** March 23, 2016

**SUBJECT:** Comments on the Draft Final Report: Safety Assessment of Trimellitic Anhydride Copolymers as Used in Cosmetics (prepared for the March 31-April 1, 2016 CIR Expert Panel meeting)

As no additional information has been received, the following should be deleted from the Introduction of the final report; "(If data are submitted to show no residual monomers are present, or that those residual monomers are entrapped in such a way that they cannot have an effect, then these data will be deleted.)".



## Memorandum

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

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

**DATE:** April 21, 2016

**SUBJECT:** Comments on the Revised Tentative Report: Safety Assessment of Trimellitic Anhydride Copolymers as Used in Cosmetics (posted April 7, 2016)

Reference 33 indicates that Adipic Acid Neopentyl Glycol/Trimellitic Anhydride Copolymer is sold at a solids concentration of 70-80% in Butyl Acetate. This is clear in the safety data sheet from the same company found from <http://lpt.lanxess.com/en/industries/energy-nuclear/energy-nuclear/uniplex-670p/> that indicates that this ingredient contains 20-30% n-Butyl Acetate. This information should be added to the CIR report.