Safety Assessment of Acrylamide/Acrylate Copolymers as Used in Cosmetics

Status:	Final Report for Panel Review
Release Date:	February 11, 2022
Panel Meeting Date:	March 7 – 8, 2022

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. Previous Panel member involved in this assessment: Lisa, A. Peterson, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Priya Cherian, Senior Scientific Analyst/Writer, CIR.

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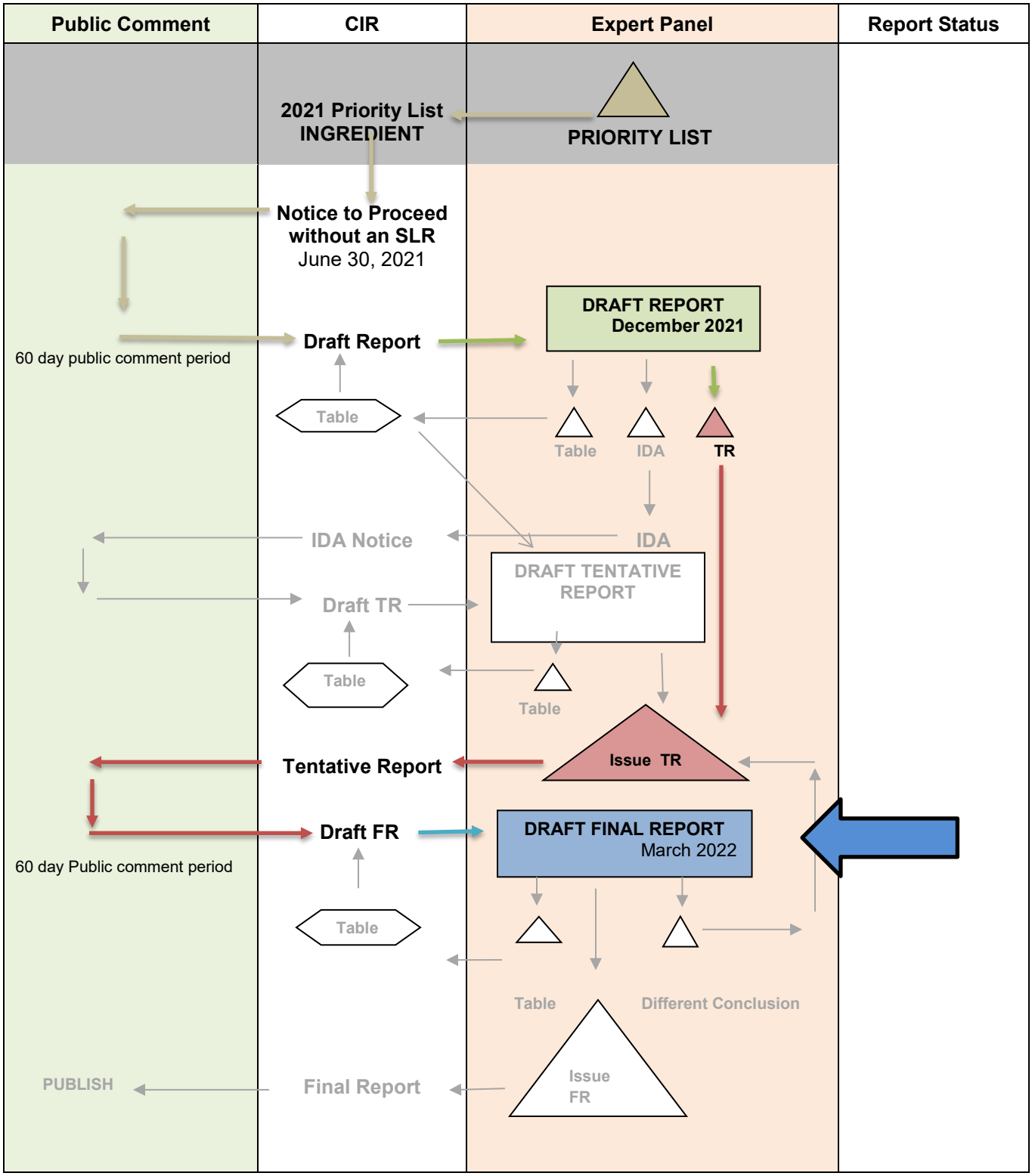
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Acrylamide/Acrylate Copolymers

MEETING March 2022



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Cherian, Senior Scientific Analyst/Writer, CIR
Date: February 11, 2022
Subject: Safety Assessment of Acrylamide/Acrylate Copolymer Ingredients

Enclosed is the Draft Final Report of the Safety Assessment of Acrylamide/Acrylate Copolymer Ingredients in Cosmetics (*report_AcrylamideAcrylatesCopolymers_032022*). At the December 2021 meeting, the Expert Panel for Cosmetic Ingredient Review Safety (Panel) issued a Tentative Report for public comment with the conclusion that the acrylamide/acrylate copolymer ingredients reviewed in the safety assessment are safe in the present practices of use and concentration.

Included in this packet are the report history (*history_ AcrylamideAcrylatesCopolymers_032022*), a data profile (*dataprofile_AcrylamideAcrylatesCopolymers_032022*), the search strategy (*search_AcrylamideAcrylatesCopolymers_032022*), transcripts of previous meeting (*transcripts_AcrylamideAcrylatesCopolymers_032022*), and flow chart (*flow_AcrylamideAcrylatesCopolymers_032022*).

Updated 2022 FDA VCRP data were received and incorporated into the report (*VCRP_AcrylamideAcrylatesCopolymers_032022*). These data were similar to 2021 FDA VCRP data; however, Potassium Acrylates/Acrylamide Copolymer is now reported to be in use. It should be noted that 3 of the 8 uses for this ingredient are reported to be in baby products.

In addition, attached are comments on the Tentative Report that were provided from Council (*PCPCcomments_AcrylamideAcrylatesCopolymers_032022*), as well as responses to these comments (*response-PCPCcomments_AcrylamideAcrylatesCopolymers_032022*).

The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. If these are satisfactory, the Panel should issue a Final Report.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: January 10, 2022

SUBJECT: Tentative Report: Safety Assessment of Acrylamide/Acrylate Copolymers as Used in Cosmetics (release date December 13, 2021)

The Personal Care Products Council respectfully submits the following comments on the tentative report, Safety Assessment of Acrylamide/Acrylate Copolymers as Used in Cosmetics.

Definition and Structure – The first sentence of the second paragraph ("According to a couple of suppliers, the acrylate/acrylamide copolymers reviewed in this report have large molecular weights ranging from 5000 to 250,000 g/mol.") suggests that the MW range of four ingredients applies to all ingredients in the report. This sentence should be revised to indicate that the stated MW range was for the four ingredients for which MW information was obtained.

Non-Cosmetic Use; Summary – Unless there is additional evidence that these polymers are used as food additives, it would be more accurate to state that they are permitted for use as food additives.

Acute – Please correct "Oral D_{50s}" to "Oral LD_{50s}"

Dermal Irritation and Sensitization – Please state the number of subjects used in the HRIPTs in the text.

Ocular Irritation; Summary – Please correct: "in an in *in vitro* ocular irritation assay" (delete duplicate "in")

Summary – Since acrylamide is the monomer of greatest concern, it would be helpful to state that for the copolymers for which information was available, acrylamide monomer was less than 2 ppm or not detectable. The general statement in the Summary that the four copolymers for which information is available contain less than 3000 ppm residual monomers may be misinterpreted as applying to the acrylamide monomer.

Discussion – It is misleading to state that these ingredients are used as "water additives". Based on the information in Table 5 Acrylamide/Sodium Acrylate Copolymer is permitted to be used as a boiler water additive in the preparation of steam that will contact food. It does not seem to be approved for direct addition to drinking water.

Discussion – The 13-week inhalation study on Acrylates/Octylacrylamide Copolymer in rats should be specifically mentioned in the Discussion. The inhalation data may haven been "limited" because it was only on one ingredient, but this 13-week study should be sufficient to support the inhalation safety of this ingredient.

Table 1, Potassium Acrylates/Acrylamide Copolymer – Perhaps the potassium ion should be shown in the structure of Potassium Acrylates/Acrylamide Copolymer in Table 1.

Table 6 – As all the values are either LD_{50} or LC_{50} values, the word "Results" can be deleted from the table column heading.

Table 7 – "(40% ethanolic solution)" needs to be added to AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer

Table 8 – Rather than "Not Reported", the Test Population for the *in vitro* assays should be stated as "Not Applicable (NA)". For the rabbit study, "irritation of the cornea, iris, and conjunctiva observed on days 1, 2, and 3 post-installation" needs to be moved from the Procedure column to the Results column.

Acrylamide/Acrylate Copolymers - March 2022 – Priya Cherian	
Comment Submitter: Personal Care Products Council **Date of Submission: January 10, 2022**	
Comment	**Response/Action**
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Non-Cosmetic Use; Summary – Unless there is additional evidence that these polymers are used as food additives, it would be more accurate to state that they are permitted for use as food additives.	Addressed
Acute – Please correct "Oral D50s" to "Oral LD50s"	Addressed
Dermal Irritation and Sensitization – Please state the number of subjects used in the HRIPTs in the text.	Addressed
Ocular Irritation; Summary – Please correct: "in an in in vitro ocular irritation assay" (delete duplicate "in")	Addressed
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Acrylamide-Acrylate Copolymer Ingredients – History

January 2021

- Updated concentration of use received

June 2021

- NTP issued

August 2021

The following data was received:

- Summary toxicity assays received for Acrylates/Octylacrylamide Copolymer
    - Acute dermal toxicity
    - Acute oral toxicity
    - Acute inhalation toxicity
    - Subchronic inhalation toxicity
    - Dermal irritation – animal
    - Dermal sensitization – animal
    - Dermal sensitization – human
    - Ocular irritation – animal
    - Ocular irritation (abraded and intact) – animal
- Summary data received for Dimethyl Acrylamide/ Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer
    - Chemistry
    - Impurities
    - Acute oral toxicity
    - Genotoxicity
    - Dermal irritation – animal
    - Dermal irritation (cumulative) – animal
    - Dermal irritation – human
    - In vitro dermal sensitization
    - Dermal sensitization – animal
    - In vitro ocular irritation
    - Ocular irritation – animal
- Summary data received for t-Butylacrylamide/ Dimethylacrylamide/PEG-14 Diacrylate Crosspolymer
    - Chemistry
- Summary data received for Acrylamide/Ammonium Acrylate Copolymer:
    - Chemistry
    - Impurities
    - Genotoxicity assay
    - Dermal irritation – human
    - Dermal sensitization – human

    - In vitro ocular irritation

- Summary data received for AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer
    - Chemistry
    - Impurities
    - Acute oral toxicity
    - Genotoxicity
    - Dermal irritation - animal
    - In vitro dermal sensitization
    - Dermal sensitization – animal
    - In vitro ocular irritation
    - Ocular irritation – animal

- Summary data received for AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer
    - Chemistry
    - Impurities
    - Acute oral toxicity
    - Dermal irritation – animal
    - Ocular irritation – ocular

- In vitro dermal irritation assay – Acrylamide/Ammonium Acrylate Copolymer
- Dermal sensitization assay – animal – Acrylamide/Ammonium Acrylate Copolymer
- Dermal sensitization assay – human – Acrylamide/Ammonium Acrylate Copolymer
- In vitro dermal irritation assay - Acrylates/t-Butylacrylamide Copolymer
- Dermal sensitization assay – human - Acrylates/t-Butylacrylamide Copolymer
- Genotoxicity assay – Ames - AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide /Hydroxyethylacrylate Copolymer
- Genotoxicity assay – micronucleus assay - AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide /Hydroxyethylacrylate Copolymer
- Subchronic dermal toxicity assay - AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide /Hydroxyethylacrylate Copolymer
- Dermal developmental assay - AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide /Hydroxyethylacrylate Copolymer
- Dermal sensitization assay – animal - AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide /Hydroxyethylacrylate Copolymer

December 2021

- Expert Panel reviews Draft Report and issues a Tentative Report for public comment

January 2022

- Council comments on Tentative Report received and addressed
- Updated 2022 FDA VCRP data received

- Data is similar to 2021 data; however, Potassium Acrylates/Acrylamide Copolymer is now reported to be in use, the majority of these uses being in baby products

March 2022

- Expert Panel reviews Draft Final Report

Acrylamide/Acrylate Copolymer Ingredients Profile – March 2022 – Writer, Priya Cherian																														
				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	Method of Mfg	Impurities	log P	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Acrylamide/Ammonium Acrylate Copolymer	x		x												x				x		x		x	x		x			
Acrylamide/Sodium Acrylate Copolymer	x																												
Acrylates/Acrylamide Copolymer	x																												
Acrylates/*t*-Butylacrylamide Copolymer	x																		x					x			x		
Acrylates/Methacrylamide Copolymer	x																												
Acrylates/Octylacrylamide Copolymer	x						x	x	x			x								x			x	x					
AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer	x	x	x					x							x					x		x	x			x			
AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer		x	x					x		x			x		x					x			x				x		
t-Butylacrylamide/Dimethylacrylamide/PEG-14 Diacrylate Crosspolymer		x																											
Butyl Acrylate/Isopropylacrylamide/ PEG-18 Dimethacrylate Crosspolymer:																													
Corn Starch/Acrylamide/Sodium Acrylate Copolymer	x																												
Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer	x	x	x					x							x					x	x	x	x			x	x		
Dimethylacrylamide/Lauryl Methacrylate Copolymer	x																												
Potassium Acrylates/Acrylamide Copolymer																													
Sodium Acrylate/Hydroxyethyl Acrylamide Copolymer																													
Starch/Acrylates/Acrylamide Copolymer																													

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

Acrylamide/Acrylate Copolymer Ingredients Search Strategy

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
Acrylamide/Ammonium Acrylate Copolymer	26100-47-0		x						x								
Acrylamide/Sodium Acrylate Copolymer	25085-02-3; 25987-30-8		x						x								
Acrylates/Acrylamide Copolymer	9003-06-9	x	x						x								
Acrylates/*t*-Butylacrylamide Copolymer									x								
Acrylates/Methacrylamide Copolymer									x								
Acrylates/Octylacrylamide Copolymer	129702-02-9	x							x								
AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer		x							x								
AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer		x							x								
t-Butylacrylamide/Dimethylacrylamide/PEG-14 Diacrylate Crosspolymer									x								
Butyl Acrylate/Isopropylacrylamide/ PEG-18 Dimethacrylate Crosspolymer:									x								
Corn Starch/Acrylamide/Sodium Acrylate Copolymer		x							x								
Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer	103479-14-7	x							x								
Dimethylacrylamide/Lauryl Methacrylate Copolymer									x								
Potassium Acrylates/Acrylamide Copolymer		x							x								
Sodium Acrylate/Hydroxyethyl Acrylamide Copolymer									x								

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
Starch/Acrylates/Acrylamide Copolymer									x								

Search Strategy

All search terms were searched in search engines without limiting parameters.

Typical Search Terms (this is informational – not for inclusion for search strategy that goes to the Panel)

- INCI names
- CAS numbers
- chemical/technical names
- additional terms will be used as appropriate

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)

appropriate qualifiers are used as necessary
search results are reviewed to identify relevant documents

Pertinent Websites

- wINCI - http://webdictionary.personalcarecouncil.org
- FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse
- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- Substances Added to Food (formerly, EAFUS): https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus
- GRAS listing: http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm
- SCOGS database: http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm
- Indirect Food Additives: http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives
- Drug Approvals and Database: http://www.fda.gov/Drugs/InformationOnDrugs/default.htm
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/
- HPVIS (EPA High-Production Volume Info Systems) - https://iaspub.epa.gov/oppthpv/public_search.html_page
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
  - technical reports search page: https://ntrl.ntis.gov/NTRL/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) GRAS: https://www.femaflavor.org/fema-gras
- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- AICIS (Australian Industrial Chemicals Introduction Scheme)- https://www.industrialchemicals.gov.au/

- International Programme on Chemical Safety http://www.inchem.org/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

Botanical Websites, if applicable

- Dr. Duke's - https://phytochem.nal.usda.gov/phytochem/search
- Taxonomy database - http://www.ncbi.nlm.nih.gov/taxonomy
- GRIN (U.S. National Plant Germplasm System) - https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
- Sigma Aldrich plant profiler- http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html
- American Herbal Products Association Botanical Safety Handbook (database) - http://www.ahpa.org/Resources/BotanicalSafetyHandbook.aspx
- National Agricultural Library NAL Catalog (AGRICOLA) https://agricola.nal.usda.gov/
- The Seasoning and Spice Association List of Culinary Herbs and Spices
- http://www.seasoningandspice.org.uk/ssa/background_culinary-herbs-spices.aspx

Fragrance Websites, if applicable

- IFRA (International Fragrance Association) – https://ifrafragrance.org/
- Research Institute for Fragrance Materials (RIFM) - https://www.rifm.org/#gsc.tab=0

DECEMBER 2021 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – December 6, 2021

DR. BELSITO: This is also again the first time we're looking at this, and we've gotten a whole bunch of data, which we need to look at. Sorry, the sun has just come out, and it blinded me. Okay. Okay, so acrylamide/acrylate copolymer. Okay. I presume here we're going to have to limit the acrylamide as well to less than five parts per million?

DR. SNYDER: We have purity data that says there is not greater than five parts per million.

DR. LIEBLER: Yeah.

DR. BELSITO: Okay. We don't have to specify since we have that.

DR. SNYDER: Correct. That's what my notes say.

DR. BELSITO: Okay, so we have composition and impurities for four ingredients. Do they cover the space, or do we need composition and impurities for all?

DR. LIEBLER: I thought that the table in the introductory memo from Priya was very helpful. We just need to update the chemistry sections with that information, and then I really thought that the data needs were met, at least particularly with respect to the chemistry content, composition, method of manufacture, composition impurities. I mean, these are high molecular weight polymers with no significant residual monomer, so they're not absorbed.

DR. BELSITO: Okay, so I guess I didn't follow your argument, Dan, why this table, you're talking about the table on PDF 9.

DR. LIEBLER: I'm talking about -- oh, no, I'm talking about PDF 3 in Priya's introductory memo, so PDF page 3.

DR. BELSITO: Okay.

DR. LIEBLER: There's a table that's a summary of all the data --

DR. BELSITO: Right.

DR. LIEBLER: -- provided by PCPC. I wasn't sure if none of that data was incorporated into the report yet, Priya?

DR. BELSITO: No, it has been.

DR. LIEBLER: Or it's all in the report now?

MS. CHERIAN: Yeah.

DR. LIEBLER: I thought the data looked fine.

DR. BELSITO: Okay, but, if you look at the composite table for page 9, we have method of manufacturing for only four of them and impurities for only three of them.

DR. SNYDER: Yeah, that was my comment, Don, to Dan, was that --

DR. BELSITO: We have 30 --

DR. SNYDER: -- most of the data we had were on three of them, the AMP, acrylates, C1 through 18, the C1 through 8 copolymer. If he thought that was a good read across, because there's really good data on three of those.

DR. BELSITO: Right. That's my comment. Do those three cover the space, Dan, or do we need additional information?

DR. LIEBLER: Oh, I thought -- I mean, the way you prepare these polymers, I mean, the chemistry of making the polymers is analogous across the entire family. Then, based on how they're going to be used, they have to be precipitated and washed. The monomers are highly volatile, so they're going to be gone whether they're washed out or whether they just evaporate.

DR. SNYDER: Then we have good tox data on those three, or at least one of the AMP acrylates, C1 through 18, a 28-day dermal with NOAEL of greater than a thousand milligrams per kilogram, and a developmental with a thousand milligrams per kilogram and NOAEL, and no genotox. As long as that was a good read across for all of them, I was fine with it.

DR. BELSITO: Great, okay, so, Dan, what I'm hearing is those are fine.

DR. LIEBLER: Yes. That's correct.

DR. BELSITO: Okay.

MR. GREMILLION: Can I ask a question about the -- this is Thomas, the CFA, sorry. Would residual acrylamide for the one ingredient on page 9, or sorry, page 16, where it says, "amounts may be present at levels of two parts per million." It's enough that you have that data on that impurity for that one ingredient? Is that -- am I understanding the conversation?

DR. BELSITO: The question that I asked before, Tom, was about the five parts per million, and we're told that that is a limit for all of these. That the level of acrylamide monomer in formulation is not to exceed five parts per million.

MR. GREMILLION: Okay, thank you.

DR. LIEBLER: Where does it say that?

DR. BELSITO: Well, that's a question I raised to begin with. It's on page 15.

DR. SNYDER: It was a previous report where we said that the monomer content is not greater than five parts per million.

DR. LIEBLER: Oh, I see. Yeah. That, oh, polyacrylamide. That doesn't refer to these ingredients.

DR. BELSITO: Okay.

DR. EISENMANN: Also, if you're referring to the final formulation.

DR. LIEBLER: Yeah, this paragraph, "Expert Panel... has previously reviewed several other polyacrylamides," and so these are chemically related ingredients that are not the ingredients in this report. So that reference to the five parts per million for polyacrylamide refers to polyacrylamide in another report. That's not a specification for the ingredients in this report.

DR. BELSITO: Okay, do we need that specification? That was my question.

DR. LIEBLER: Well, I don't know if there's a -- I mean, for this whole family of products, there probably isn't a uniform specification. For polyacrylamide, it was one ingredient with one specification.

DR. EISENMANN: And the value was for finished products, not the ingredient.

DR. SNYDER: I mean, we only have one here: three were negative, one was two parts per million.

DR. LIEBLER: Yeah, here are the weight for the first ingredient on PDF 16, the acrylamide ammonium acrylate copolymer. It says, "Residual acrylamide amounts may be present at levels of 2 ppm." I take that as an upper bound. If it's there, it's up to 2 parts per million, which is exceedingly low. And then the other three, it explicitly states that acrylamide was not detected.

DR. BELSITO: Okay.

DR. LIEBLER: Now, acrylamide itself is extremely volatile. So, if you had any acrylamide associated with this stuff after it was made, it would continue to lose any residual acrylamide through evaporation.

DR. BELSITO: All right.

DR. LIEBLER: That's its preparation and purification.

DR. HELDRETH: I can also tell you from my experience making some acrylate and acrylamide polymers in the lab when I was a grad student, these reactions are very exothermic. And so anything volatile that's left in there is basically getting boiled out of the situation.

DR. LIEBLER: Right, it releases a lot of heat, and that further evaporates any residual monomer.

DR. HELDRETH: Yes.

DR. BELSITO: Okay, and so, is this anything that needs to go in the discussion, or no?

DR. LIEBLER: No, I think we're making -- I mean, it explicitly says it's a low residual monomer or no detectable residual monomer. I think that settles it right there. I don't think this needs further elaboration.

DR. BELSITO: Okay. Any other comment? Go ahead.

DR. KLAASSEN: In regard to the toxicity, we can just watch Dan as he was just eating potato chips, and potato chips contain acrylamide.

DR. LIEBLER: Well, these were pita chips, Curt.

DR. KLAASSEN: Oh.

DR. LIEBLER: I don't know if we can read across from pita chips to potato chips.

DR. KLAASSEN: Well, probably.

DR. BELSITO: Are they fried?

DR. LIEBLER: They're pita chips. I don't know they make them. They're baked.

DR. BELSITO: Okay.

DR. LIEBLER: Or at least half-baked.

DR. BELSITO: Moving on to relevant discussion, PDF page 17, it says that there were restrictions with other related materials. The ingredients should not be used with nitrosating systems. Is that going to be a restriction that we want to add for these?

DR. LIEBLER: I don't really see -- now, this would be an interesting thing to ask Lisa because she's really the Panel expert on nitrosation chemistry. I mean, she's not just a Panel expert, she's a real card-carrying expert on this. But I would think that this is irrelevant due to the insolubility of these polymers in probably not being able to participate in this chemistry. That's the note I made here, and I think we can ask Lisa, or Lisa may bring it up. But my expectation is it's not significant enough. It's not a significant concern. I'd like --

DR. SNYDER: The composition impurity on the ammonium says no nitrosamines also to support that.

DR. BELSITO: I missed what you said, Paul.

DR. SNYDER: Under the composition impurities acrylamide ammonium acrylate copolymers, it says there, "Not expected to contain 1,4 dioxane, ethylene oxide, solvent residues (benzene), free amines, or nitrosamine."

DR. BELSITO: Okay. Okay. Go ahead.

MR. GREMILLION: Thanks. That's one of the 16 ingredients, or however many there are, and the fact that it's not expected to contain those impurities you can -- is that a read across issue?

DR. SNYDER: No, this is, I think, a summary of the European Union Inventory for these and what the European Commission says about these, about the --

MR. GREMILLION: Yeah, I didn't ask that question very well. I understand that because it says for acrylamide ammonium acrylate copolymer that it's not expected to contain one part dioxide and these other impurities, that's not an issue for this whole group of chemicals? Is that, or none of the other chemicals are expected to contain those impurities?

DR. SNYDER: I guess an answer would be unless a method of manufacture is significantly different, which I doubt they are. Then Dan could answer that.

DR. LIEBLER: Yeah, I think that this is more of a manufacturer labeling specification than a real chemical difference between the ingredients. I don't know why it's not mentioned in the others because really, if I look at these, they're very similar in their composition or the sort of the building blocks. I'm not sure why it would be mentioned in one and not the others except that it might be that the manufacturer of the first item simply has that as part of their labeling boilerplate. Tom, it kind of reads like a laundry list.

DR. BELSITO: Yeah. Thomas, if it helps you, you can look at the non-cosmetic use where these are used as indirect, direct, and secondary food additives. I think it's basically, as we've been discussing, they're not likely to be metabolized, and there's significant restrictions on impurities and the oligomers in them.

MR. GREMILLION: Yeah, I had that. I mean, I was looking at the acrylamide and, yeah, I wondered kind of the levels that is present in potato chips. Yeah, just two parts per million is pretty small.

DR. BELSITO: Yeah. Okay. In the DART study, it says that the NOAEL, the last sentence for maternal and fetal toxicity was a thousand milligrams per kilogram. Wasn't it greater than a thousand?

DR. SNYDER: They said they did see some pathological effects observed, so it must have been -- well, no, because it wasn't inept.

DR. LIEBLER: Yeah, they don't list any pathological.

DR. SNYDER: Yeah, so it should be greater than. It would be determined to be greater than, but it didn't see anything.

DR. BELSITO: Yeah, it says, "No adverse effects were observed."

DR. SNYDER: Yeah.

MS. CHERIAN: I just typed what the reference stated, which was up to a thousand milligrams per kilogram a day on PDF page 237.

DR. SNYDER: Yeah, that's not right.

DR. BELSITO: That means they could say no observed and no NOAEL at a thousand because there were some weight changes, but adverse was greater. It didn't say there was no adverse effect.

DR. SNYDER: Yeah, that would have to be greater than, yeah.

DR. BELSITO: Okay. The genotox, we're all okay with?

DR. SNYDER: Yeah, I was.

DR. BELSITO: I thought the sensitization and irritation was okay.

DR. SNYDER: It is used for mascara for seven percent.

DR. BELSITO: Yeah. In the ocular toxicity section, this is PDF page 19, the EpiSkin for the dermal irritation assay. The third line, it says, "Both test substances were considered to be non-sensitizing." That should be "non-irritating." Then, Paul, to answer your question, in the ocular irritation study they tested, the product's neat, and it had, "No ocular irritation was noted on New Zealand white rabbits using acrylates/Octylacrylamide Copolymer." That was a neat application.

DR. SNYDER: Okay.

DR. BELSITO: Okay. We don't have to mention acrylamides. We don't have to -- we're going to ask Lisa about nitrosation. How are we with the respiratory here?

DR. LIEBLER: We're all scrolling.

DR. SNYDER: Exactly. They're going to be large molecules, so they're not going to be respirable, right? They're going to be --

DR. BELSITO: Yeah, they're going to be used in hairsprays, which they --

DR. SNYDER: Right.

DR. BELSITO: Incidental inhalation spray.

DR. LIEBLER: And underarm deodorant.

DR. BELSITO: There's some powder use. Deodorant, underarm, no reported uses. No reported. No reported. There is a report of 0.05 for the AMP-acrylate. It doesn't say whether it's spray or -- so just one reported use there.

DR. LIEBLER: We've got the acrylates, octylacrylamide copolymer has the most -- looks like the most uses overall, and it does have incidental inhalation spray up to 3.2 percent. Then, yeah, and then hair, 3.2 percent, so that's probably this hairspray use.

DR. BELSITO: Right.

DR. LIEBLER: Now we have a little different variation of what we looked at previously, Paul, where we've got low toxicity, really no toxicity signals, but we have a more significant exposure burden. I mean it's single-digit percents.

DR. SNYDER: Yeah, but, again, I think the one of greatest concern is the aerosolized deodorant. Even if it was an aerosolized deodorant, it's not specified irritant, 0.05 percent, so that kind of mitigates that. The rest of them are sprays. It says two; we have one, the 3.9 percent and I don't know what that 7A is over on the dimethyl, seven with an A. Again, I think we just have to put it in there that with the particle size distribution associated with sprays, non-aerosolized, and --

DR. LIEBLER: It's hairspray.

DR. SNYDER: -- it's a low concentration of use, yeah, hairsprays, yeah.

DR. LIEBLER: Yeah, specifically with hairsprays, Priya, so, yeah.

MR. GREMILLION: This looks like the old inhalation boilerplate, right? I think this is what you're discussing. In practice, 95 to 99 percent of the droplets released from cosmetic sprays, on page 16 and 17.

DR. LIEBLER: It's true. That's true. All this additional data on the low, or the very small particles, is a very small percentage of distributions of the overall distributions.

MR. GREMILLION: Okay, so the inhalation boilerplate hasn't actually changed with respect to this language.

DR. LIEBLER: Yeah, right. We're tweaking this inhalation boilerplate a little bit to flesh out our justification and not just to fall back on an arbitrary number that we apply to everything, you know, 95 to 99 percent.

DR. BELSITO: In this case, we're keeping the standard respiratory boilerplate? Is that correct?

DR. KLAASSEN: Well, I don't know the boilerplates, do they have this 95 to 98 percent. I actually liked that statement in the boilerplate. Go ahead.

DR. LIEBLER: That's in it by default, Curt, and I think what would -- if I understand Paul correctly, he's arguing that we should flesh this out with a little bit of ingredient-specific information that's appropriate to our evaluation for this report, such as the low evidence, lack of evidence of any toxicity, and the use in a spray type that's associated with this distribution, in other words, hairsprays.

DR. KLAASSEN: Yeah, I would like both.

DR. EISENMANN: That deodorant is a non-spray.

DR. LIEBLER: Okay, thank you.

DR. BELSITO: Okay, so we'll add that, that it's a non-spray, and the boilerplate here, we're just fleshing out with lack of systemic tox and use in pumps or use in hairsprays.

DR. LIEBLER: Right.

DR. SNYDER: We may not know if these are pump sprays or, oh shoot, the other one.

DR. KLAASSEN: Aerosols.

DR. BELSITO: Aerosols.

DR. SNYDER: Aerosols, yeah, thank you.

DR. BELSITO: We know they're hair and not underarm. Okay. We'll add the usual respiratory boilerplate, but just flesh it out a little bit by the fact of lack of systemic toxicity and use of aerosols in hairsprays, but no reported underarm use. Correct?

DR. LIEBLER: Right.

DR. SNYDER: One reported underarm use, but it's not an aerosol, it's a spray, or not reported as a spray.

DR. BELSITO: Carol said it's not an aerosol.

DR. SNYDER: That's right.

DR. BELSITO: Not a spray.

DR. SNYDER: That's only 0.05 percent anyway.

DR. BELSITO: Right. Okay. Anything else? Okay, hearing nothing, we'll move on to methicones.

Cohen Team – December 6, 2021

DR. COHEN: All right. Acrylamide/acrylate copolymers. This is Priya's as well. It's a draft report. This is the first time we're reviewing it, and I must say there was a lot of data in here for a draft report to review. And this assessment is for 16 derived ingredients, and it's got a multiplicity of uses in addition to skin conditioning agents. We have frequency of use reported (audio skip 01:06:15). It's used for a number of them including the octylacrylamide copolymer 7 percent in leave-on formulation.

It has a potential for ingestion in a lipstick and a toothpaste, and it has max use in a toothpaste of the octylacrylamide copolymer at 19.4 percent. And it's used near the eye in an eye liner 4.6 percent and eye shadow at 0.001 percent and mascara at 7 percent. So, we do have -- I don't think we have much in method of manufacturing. We have a few of them.

DR. PETERSON: Yeah, there is some (audio skip 01:07:15). I felt since it was the first time through we should ask for method of manufacturing for --

DR. COHEN: The others.

DR. PETERSON: The others. I can list them all, but I just think it'll get lost. But everyone has not put the X on it. And then we need -- again, there might be some read across, but I think it's work asking for getting impurities for all the ones we don't have impurities for, particularly, the one of most use, which is the acrylates octylacrylamide. (audio skip 01:08:12).

DR. COHEN: We also had some mild eye irritation in the guinea pigs being used right around the eyes. I saw human sensitization data on 0.6 for ammonium acrylate copolymer and the 13 percent for the butylacrylamide copolymer. And there was a memo from the council (audio skip 01:09:13).

DR. SLAGA: I'd like to thank Priya. She put a Table 1 in there to summarize. It was very, very helpful and thank you very much. Number one, we had more data than we usually did for anything, and once again, that's very nice that industry supported all of this. I came up with -- I really didn't feel with potential read across and all that we could probably get away with -- I said that we could possibly go with safe. I'm stretching it right now, but I was impressed with trying to compare back and forth to various ingredients. And I wasn't sure if we really needed methods of manufacture.

We had a good bit of data there from some of them. I don't know. It's up to Lisa if she thinks that that's extremely important, but it is a nice body of data supporting its potential safety.

DR. PETERSON: Yeah, so I agree with you, and I thought that, like I said, there was potential for read across. It's just the first time through, so it's sort of this (inaudible).

DR. SLAGA: I understand that, too. That's why I said I'm stretching it because this is the point where we can possibly get more data, but the fact that we got so much, I doubt if we'll get anything else. I'm just --

DR. PETERSON: And I also agree that there's the safety issues suggests there's no concerns about any impurity, and the issues about impurity are actually discussed in the (audio skip 01:11:43) are discussed in the document about how acrylate

monomer needs to be at a minimum. And so that brings me to the point that I had a couple things that I thought were worth bringing into the discussion, and if we were to say we don't need anything, we could go safe as used, then I think the discussion -- so on PDF page 17, there's a statement about all of the acrylate/acrylamide copolymers named in this report are listed in the European Union inventory of cosmetic ingredients.

In that paragraph there's a sentence that says, "exceeds maximum residual acrylamide content at 0.1 milligrams per kilograms in the body." I guess there's something doesn't make -- in body care, leave-on products and 0.5 milligrams in other cosmetics and I thought that in our discussion we could just say, okay, we don't have impurities on these heavily used ones, but based on the data we're reading across from the others. Plus we have the safety issue which suggests that these chemicals, the monomers, which are the chemicals of concern are probably below a certain thing.

And we should say in the discussion that this is important that the concentration of the monomer would be below in something like what's here in this paragraph. And then there's another paragraph where they talk -- this gets to the nitrosamine issue which this is the document, and it has a statement that ingredients should not be used with -- nitrosating systems must have -- this all gets to the potential formation of nitrosamines which could be mutagenic in the cosmetic formulation. This is an issue with drugs. They have these trace amounts of nitrosamines.

There have been a bunch of drugs recalled because of this, and nitrosamines are bad. And so I think our discussion should say something similar to what the last few sentences of this paragraph have.

DR. SLAGA: I think the monomers that you mentioned, by discussing them and having -- which we put that in many reports. It should be in the discussion as well as the nitrosamines. I think that could handle those issues.

DR. BERGFELD: I think you need to note that it's a food additive and a water additive.

DR. SLAGA: Yeah.

DR. COHEN: For the discussion, Wilma?

DR. BERGFELD: Yes.

DR. SHANK: The only adverse toxic effect was in vitro studies on the eye, which at worse showed a possible mild irritation. I think that can be handled in the discussion.

DR. BERGFELD: Wasn't that at pretty high concentrations?

DR. SHANK: There were two tests. One was at 100 percent.

DR. SLAGA: Yeah.

DR. SHANK: This was in vitro now, and there was no irritation. Then there was another one at 15 percent that showed mild irritation.

DR. COHEN: Right.

DR. SHANK: I would say all of these ingredients are safe as used. If the Panel wants to put in "when formulated to be non-irritating to the eye," I wouldn't object, but I don't think it's necessary. And we have a lot of toxicity data overall, and it's negative. These are large molecules with the low probability of penetrating the stratum corneum. These are indirect food additives, so I think they're safe as used.

DR. SLAGA: I agree with Ron. I think that's the way to handle it.

DR. PETERSON: I'm on board.

DR. COHEN: One question. I didn't see -- maybe I missed it -- the HRIPT on 15 percent octylacrylamide copolymers. So, it's just summarized, but I didn't see the raw data where the majority of the reactions were -- 49 reactions in 50 people were classified as slight erythema and six being classified as mild erythema. So, I couldn't see the tables of when these were occurring, and I suppose I could get around that if we come out with a safe as formulated to be non-irritating. But wouldn't we want to see that before we go on? And we probably could get a copy of that full report.

MS. FIUME: Priya, did we ask for full data on the summary information? I can't remember.

MS. CHERIAN: I'm going to have to search through my emails and see if we did.

DR. COHEN: Because the ammonium acrylate copolymer at 0.6 percent was clean. But more importantly the butylacrylamide at 13.3 percent was clean. It was just zeros across the chart. But this summary seemed to suggest more action during the HRIPT than the others.

MS. FIUME: So, David, actually we have requested -- you're talking about the study from August 17th, the summary information?

DR. COHEN: Yes, yes.

MS. FIUME: So, we did ask Carol if we could get details, and she did not receive them. We were not able to -- at least when we asked the first time, were not able to get details from those studies. But I don't know if the Panel asks again if they'll be any other outcome.

DR. COHEN: That has happened before in the short time I'm here where, all of a sudden, we get even higher concentrations in HRIPT. Ron --

MS. FIUME: I just mean the details of the study we were told were not available to us.

DR. COHEN: So, Ron, I want to be differential to your comment before about going out as safe as used, so what do you think? Knowing there's some small signals -- there are some signals in this octylacrylamide HRIPT, do you still stick with safe as used? Do we do an IDA looking for more of that information to review or safe when formulated to be non-irritating? What do you think?

DR. SHANK: I accept all of the data including the sensitization data and the conclusions of the sensitization data that it was not a sensitize -- these aren't sensitizers. And the only concern I saw was a possible ocular irritation issue. I think I would say safe as used or safe as used when formulated to be non-irritating, and that would cover it. If you want more sensitization data, then we should certainly go ahead and ask for it. I was satisfied, but I'm not a dermatologist.

DR. COHEN: It was just more of an issue of having these slightly red or red reactions at times that are unclear to me.

DR. SHANK: Okay.

DR. COHEN: So, are we going out with an IDA looking for that or -- because I'm kind of stuck in the middle here. Safe as used when formulated to be non-irritating or an IDA, let's look at this, and then next time, we call it.

DR. BERGFELD: I wonder what they're doing with the in vitro testing that's in there on irritation and sensitization.

DR. COHEN: You mean that it's irritating, Wilma?

DR. BERGFELD: No, it's I'm doing off paper, so I can't give you exactly where I am. But it's before the discussion in the summary. The epi skin dermal irritation assays.

MS. FIUME: PDF page 29 is where it's at in the table.

DR. BERGFELD: Okay. This supports non-sensitizing and some non-irritating in guinea pig which is the next one, maximization test.

DR. COHEN: So, in the irritation animal there's a few there that says mildly irritating. And you see under humans under the ammonium acid mild patch test responses occasionally complicated accompanied by mild papular responses during the induction and the challenge phase. So, all of these just little comments here and there made me think that this has some irritation potential, that these weren't just completely clear, all of them.

DR. SLAGA: Formulated to be non-irritating.

DR. COHEN: Yeah, I think I could buy that.

DR. BERGFELD: Yeah.

DR. SHANK: I agree.

DR. COHEN: All right. So we'll go out safe as used when formulated to be non-irritating.

DR. SLAGA: Great.

MS. FIUME: David, can I just point out -- and this goes back to Lisa talking about the acrylamide, and she was referring to the European numbers. In I think it was 2005, polyacrylamide final report was published and that discussion -- I mean the conclusion -- actually, and I'm not saying this should be in the conclusion, but we do have history of indicating a maximum acrylamide monomer level in formulation, and it had stated not greater than five parts per million. So, we do also have CIR precedents.

DR. PETERSON: Yeah, I would do that because, I mean, that's a concern about the impurities is the monomer presence because it will be irritating.

DR. COHEN: So, Monice, we're going to actually put in a discussion that we want final monomer concentrations less than five parts per million.

MS. FIUME: I believe that's what Lisa said, and, as I said, we do have CIR precedents for doing that as well. So we do have a value that we can refer to.

DR. COHEN: And that was from a polyacrylamide?

MS. FIUME: The polyacrylamide final report, which was published in 2005.

DR. COHEN: Got it. That's good.

DR. SLAGA: Good discussion.

DR. COHEN: Yeah, and I think we came to a good conclusion. We'll hear what the other team has to say tomorrow.

DR. PETERSON: Yeah. Would it be possible to take a five-minute break?

DR. COHEN: Sure. Let's see, what time is it? It's 9:57, just like two minutes after 10:00?

DR. PETERSON: Yeah, just a short break.

DR. COHEN: Got it. See you in a sec.

DR. PETERSON: Okey-doke.

DR. BERGFELD: That's good to do it before inhalation.

Full Panel – December 7, 2021

DR. COHEN: Yes. So this is a draft report for acrylamide/acrylate copolymers. It's the first time we're reviewing this, and this was a very data dense draft report. So thank you, Priya, for putting this together. It was a lot of material. The safety assessment is for 16 derived ingredients. It has a multiplicity of uses, and octylacrylamide copolymer is reported to be used in 160 formulations and the others less so. We have max use reported. These are large molecular weight molecules. Our motion is safe as used when formulated to be non-sensitizing.

DR. BERGFELD: That's a motion?

DR. COHEN: Yes.

DR. BERGFELD: Any discussion or second?

DR. BELSITO: Yeah. We had safe as used. We didn't have the non-sensitizing restriction. Where did that come from, David?

DR. COHEN: Thank you, Don. It went back in forth in my head between sensitizing and irritating, but the memo from August 12th from the council had an HRIPT with 15 percent octylacrylamide copolymer. I didn't see the full report, but it said 30 subjects reacted one or more times to the application of the test material. The majority of the reactions, 49, were classified as very slight erythema and six being classified as mild erythema. There was no evidence of skin sensitization mentioned in that, and the other reactions were classified as transient irritant. We certainly had in the discussion that we'd want monomer to be low, less than five parts per million like the final report for polyacrylamide. So open for discussion and your comments about it.

DR. BELSITO: I mean, you're applying these materials under occlusion. You're pulling it off and putting it on nine times over the course of three weeks. I mean, I think these kinds of minor transient erythema reactions are usually for these HRIPTs discounted, and that's what I did. I don't have any strong objection to formulated to be non-sensitizing, but I didn't think it was needed.

DR. BERGFELD: Any response of any type?

DR. COHEN: Anyone else from your team, Don, who would want to persuade us to just drop the non-sensitizing component? In the discussion, you're okay with the concentration of the monomer being low?

DR. BELSITO: Yes.

DR. SNYDER: We didn't have a non-sensitizing clip on ours yesterday, so I'm still in that field.

DR. LIEBLER: I defer to Don and David on that.

DR. BELSITO: I mean, these are big molecules, and in the absence of any significant monomer they're not going to be sensitizing.

DR. COHEN: Yeah. Don, I'm okay. If we're having our discussion that we're keeping the monomer low, I'm okay with that. I could revise my motion to safe as used.

DR. BERGFELD: Okay.

DR. COHEN: And in the discussion have a low monomer content.

DR. BERGFELD: And, Don, you seconded before. Will you second this?

DR. BELSITO: Yeah. I didn't second before. I will second this, yes.

DR. BERGFELD: Okay. All right. Any further discussion or clarifications?

DR. BELSITO: Yeah. Our team wanted to bounce back to Lisa. On one of the prior reviews we had restricted nitrosation. Dan looked at the current document and didn't feel that we needed to put that in the discussion but would cede to Lisa because she's apparently the expert on this.

DR. LIEBLER: I'm referring to PDF 17, bottom of the second paragraph, and my thinking was it these aren't even soluble I don't know if that chemistry is really practically possible. But I said this is an "ask Lisa" situation.

DR. PETERSON: Yeah. Well, you're talking to somebody who's a bit risk averse, so I'm always for including to cover the base because it's not in sort of the discussion. I mean, I agree with you. It's probably another huge -- but I don't know what it hurts to leave it in on page 17.

DR. LIEBLER: I'm fine with it.

DR. COHEN: There was some additional comments from our team in the discussion of these chemicals being used in food and water additives, and there was some irritation in the eyes of guinea pigs when used around the eyes. That was all we had.

DR. BERGFELD: Any other comments? So, Dr. Cohen, will you restate your conclusion?

DR. COHEN: The conclusion is safe as used.

DR. BERGFELD: And it was seconded by Don. I'm going to call the question. Opposed? Abstaining? Unanimously approved. Okay. Moving on to other items. This is a big one. Dr. Belsito, we've been discussing it through all these documents.

Safety Assessment of Acrylamide/Acrylate Copolymers as Used in Cosmetics

Status: Final Report for Panel Review
Release Date: February 11, 2022
Panel Meeting Date: March 7 – 8, 2022

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. Previous Panel member involved in this assessment: Lisa, A. Peterson, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Priya Cherian, Senior Scientific Analyst/Writer, CIR.

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ABBREVIATIONS

AMP	adenosine monophosphate
CAS	Chemical Abstracts Service
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
Da	Daltons
DART	developmental and reproductive toxicity
DMSO	dimethyl sulfoxide
Dictionary	*International Cosmetic Ingredient Dictionary and Handbook*
EU	European Union
FDA	Food and Drug Administration
GD	gestation days
GRAS	generally recognized as safe
HCE	human corneal epithelium
HET-CAM	hen's egg test-chorioallantoic membrane
HRIPT	human repeat insult patch test
LC_{50}	lethal concentration 50
LD_{50}	median lethal dose
NOAEL	no-observable-adverse-effect-level
NR	not reported
OECD	Organisation for Economic Cooperation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
ppm	parts per million
TG	test guidelines
US	United States
VCRP	Voluntary Cosmetic Registration Program

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 16 acrylamide/acrylate copolymers, most of which are reported to function in cosmetics as binders, film formers, and hair fixatives. The Panel reviewed the available data to determine the safety of these ingredients. The Panel stated that industry should continue to use good manufacturing practices to ensure that the concentration of acrylamide monomer in cosmetic formulations does not exceed 5 ppm, and concluded that the acrylamide/acrylate copolymers are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

This assessment reviews the safety of the following 16 acrylamide/acrylate copolymer ingredients as used in cosmetic formulations:

- Acrylamide/Ammonium Acrylate Copolymer
- Acrylamide/Sodium Acrylate Copolymer
- Acrylates/Acrylamide Copolymer
- Acrylates/*t*-Butylacrylamide Copolymer
- Acrylates/Methacrylamide Copolymer
- Acrylates/Octylacrylamide Copolymer
- AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer
- AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer
- *t*-Butylacrylamide/Dimethylacrylamide/PEG-14 Diacrylate Crosspolymer
- Butyl Acrylate/Isopropylacrylamide/PEG-18 Dimethacrylate Crosspolymer
- Corn Starch/Acrylamide/Sodium Acrylate Copolymer
- Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer
- Dimethylacrylamide/Lauryl Methacrylate Copolymer
- Potassium Acrylates/Acrylamide Copolymer
- Sodium Acrylate/Hydroxyethyl Acrylamide Copolymer
- Starch/Acrylates/Acrylamide Copolymer

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook (*wINCI *Dictionary)*, the majority of these ingredients are reported to function in cosmetics as binders, film formers, and hair fixatives (Table 1).[1] Other reported functions for ingredients in this group include viscosity-increasing agent, hair-waving/straightening agent, emulsion stabilizer, skin-conditioning agent – miscellaneous, dispersing agent – non-surfactant, antistatic agent, and hair conditioning agent.

These ingredients are being reviewed together as they share structural similarities. Specifically, each of these ingredients comprise a copolymer, polymerized from at least 1 acrylamide monomer and 1 acrylate monomer. The Expert Panel for Cosmetic Ingredient Safety (Panel) has previously reviewed the safety of several other polyacrylamides (Polyacrylate 2, Polyacrylamide, and Acrylamide/Sodium Acryloyldimethyltaurate Copolymer). Polyacrylate 2 and Acrylamide/Sodium Acryloyldimethyltaurate Copolymer were considered safe as used in the present practices of use and concentration (as described in that safety assessment).[2,3] Polyacrylamide was considered safe as used in the present practices of use and concentration (as described in that safety assessment), if the level of acrylamide monomer in formulation is not greater than 5 ppm.[4] In addition, aminomethyl propanol, an ingredient used in the neutralization process in the manufacturing of two of the acrylamide/acrylate copolymers, has previously been reviewed, and was considered safe as used in the present practices of use and concentration (as described in that safety assessment).[5] The full reports on these ingredients can be accessed on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/ingredients).

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the CIR website (https://www.cir-safety.org/supplementaldoc/ preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

CHEMISTRY

Definition and Structure

All ingredients reviewed in this report comprise a copolymer, polymerized from at least 1 acrylamide monomer and 1 acrylate monomer. Acrylate monomers may comprise acrylic acid, methacrylic acid, or one of their esters.[1] For example, Acrylates/Methacrylamide Copolymer is a copolymer comprising methacrylamide and acrylate monomers, as demonstrated in idealized Figure 1. Two ingredients in this report, *t*-Butylacrylamide/Dimethylacrylamide/PEG-14 Diacrylate Crosspolymer and Butyl Acrylate/Isopropylacrylamide/PEG-18 Dimethacrylate Crosspolymer, are crosspolymers formed by crosslinking copolymer chains. The definitions and structures of all the ingredients are provided in Table 1.

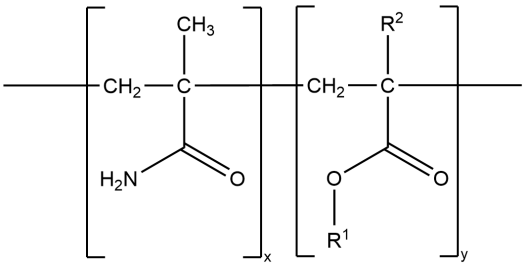


Figure 1. Acrylates/Methacrylamide Copolymer, wherein R^1 may be hydrogen, methyl, ethyl, propyl, or butyl; R^2 may be hydrogen or methyl; and, x and y are undefined.

Molecular weights have been reported for 4 of the acrylate/acrylamide copolymers , ranging from 5000 to 250,000 g/mol.[6,7] Approximate molecular weights for AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer, AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer, *t*-Butylacrylamide/Dimethylacrylamide/PEG-14 Diacrylate Crosspolymer, and Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer can be found in Table 2. Mean molecular weights, related weight distributions, and degrees of polymerization were neither found in the available literature nor submitted as unpublished data, for many of these ingredients.

Method of Manufacture

According to unpublished summary manufacturing data, the starting monomers of several of these ingredients (AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer, AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer, Dimethyl Acrylamide/ Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer, and *t*-Butylacrylamide/ Dimethylacrylamide/PEG-14 Diacrylate Crosspolymer) are polymerized in ethanol, and then refined.[6-9] AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer and AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer solutions are reported to be neutralized with 2-amino-2-methyl-1-propanol (aka aminomethyl propanol).

Composition and Impurities

Acrylamide/Ammonium Acrylate Copolymer

For Acrylamide/Ammonium Acrylate Copolymer, less than 2% of oligomers are < 500 Da.[10] In addition, this ingredient is not expected to contain 1,4-dioxane, ethylene oxide, solvent residues (e.g., benzene), free amines, or nitrosamines. Residual acrylamide amounts may be present at levels of 2 ppm.

AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer

According to a manufacturer, less than 2000 ppm residual monomers were present in AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer.[9] Acrylamide was not detected as an impurity.

AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer

Residual monomers were present in amounts of less than 3000 ppm in AMP-Acrylate/C1-18 Alkyl Acrylate/C1-8 Acrylamide/Hydroxyethylacrylate Copolymer.[8] Acrylamide was not detected as an impurity.

Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer

Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer contains less than 200 ppm residual monomers.[6] Acrylamide was not detected as an impurity.

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US 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 the FDA Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetic industry in response to a survey, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to 2022 VCRP survey data, the ingredient with the highest number of uses, Acrylates/Octylacrylamide Copolymer, is reported to be used in 117 formulations; all other in-use ingredients are reported to be used in 14 formulations or less (Table 3).[11] The results of the concentration of use survey conducted by the Council in 2020 indicate that Acrylates/

t-Butylacrylamide Copolymer, Acrylates/Octylacrylamide Copolymer, and Dimethyl Acrylamide/Hydroxyethyl Acrylate/ Methoxyethyl Acrylate Copolymer are each used at up to 7% in leave-on formulations (i.e., aerosol hair sprays, mascaras, and tonics, dressings, and other hair grooming aids, respectively).[12] Use concentration data were reported for Dimethylacrylamide/Lauryl Methacrylate Copolymer, but no uses were received in the VCRP; it should be presumed that there is at least one use in every category for which a concentration is reported. The 5 ingredients not in use, according to the VCRP data and industry survey, are listed in Table 4.

Two ingredients are used in products that can potentially be ingested (Acrylamide/Sodium Acrylate Copolymer, used in lipstick (concentration not reported), and Acrylates/Octylacrylamide Copolymer, used in dentifrices (toothpaste) at up to 19.4%). Acrylates/Octylacrylamide Copolymer is also used in products used near the eye (i.e., eyeliners up to 4.6%, eye shadows up to 0.001%, and mascaras at up to 7%). In addition, mucous membrane exposure to these ingredients may occur (Acrylates/Acrylamide Copolymer is used in bath soaps and detergents (concentration not reported), and Corn Starch/ Acrylamide/Sodium Acrylate Copolymer is used in bath oils, tablets, and salts at up to 2%). Potassium Acrylates/Acrylamide Copolymer is reported to be used in baby shampoos and other baby products. Furthermore, some of these ingredients are used in cosmetic sprays and could possibly be inhaled; for example, Acrylates/ *t*-Butylacrylamide Copolymer is reported to be used at 7% in aerosol hair sprays and Acrylates/Octylacrylamide Copolymer is reportedly used in face powders (concentration not reported).

All of the acrylate/acrylamide copolymers named in this report are listed in the European Union inventory of cosmetic ingredients.[13] According to the European Commission, several of these ingredients (Acrylamide/Ammonium Acrylate Copolymer, Acrylamide/Sodium Acrylate Copolymer, Acrylates/Acrylamide Copolymer, AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer, Corn Starch/Acrylamide/Sodium Acrylate Copolymer, Dimethyl Acrylamide/ Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer, Potassium Acrylates/Acrylamide Copolymer and Starch/ Acrylates/Acrylamide Copolymer) are linked to the entry for polyacrylamide, which states that the maximum residual acrylamide content in final formulations must not exceed 0.1 mg/kg in body care leave-on products and 0.5 mg/kg in other cosmetic products.[14] AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer and Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer are linked to the entry of monoalkylamines, monoalkanolamines, and their salts, which states that these substances should not be used with nitrosating systems, must have a minimum purity of 99%, must not exceed a nitrosamine content of 50 µg/kg, and must be kept in nitrite-free containers. In addition, finished products containing these ingredients should not exceed a secondary amine content of 0.5%.

Non-Cosmetic

Acrylate/Acrylamide Copolymer and Acrylamide/Sodium Acrylate Copolymer

Acrylate/Acrylamide Copolymer and Acrylamide/Sodium Acrylate Copolymer are permitted for use as indirect, direct, and secondary food additives. CFR citation details regarding these uses and relevant limitations can be found in Table 5.

TOXICOKINETIC STUDIES

Toxicokinetics studies were not found in the published literature, and unpublished data were not submitted.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

The acute dermal, oral, and inhalation studies summarized below can be found in Table 6.

The acute dermal LD_{50} was reported to be greater than 2000 mg/kg in rabbits dosed with Acrylates/Octylacrylamide Copolymer.[15] Acute oral toxicity assays were performed in rats using several test substances (Acrylates/Octylacrylamide Copolymer (15% solids), a 40% ethanolic solution of AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer, a 40% ethanolic solution of AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer, and a 70% ethanol solution of Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer).[6,8,9,15] Oral LD_{50}s reported for these assays were greater than 2000 mg/kg, excluding Acrylates/Octylacrylamide Copolymer, in which the reported LD_{50} was greater than 2300 mg solids/kg bw. An LC_{50} of greater than 3.4 mg/l was reported in an acute inhalation toxicity assay performed in rats exposed to Acrylates/Octylacrylamide Copolymer.[15]

Short-Term Toxicity Studies

Dermal

AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer

A 28-d dermal toxicity assay was performed in Wistar Han rats (5/sex/group).[16] The test substance (38% AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer in water; 2 ml/kg) was applied to the skin at doses of 0, 100, 300, and 1000 mg/kg bw/d, under semi-occlusive conditions, for 6 h/d. Clinical, hematological, urinary, and histopathological parameters were evaluated. Very slight erythema was observed between days 26 and 29 in two females dosed with 1000 mg/kg of the test substance. No other skin reactions were observed. No relevant adverse test item-

related effects were observed throughout the study. The no-observed-adverse-effect level (NOAEL) was determined to be 1000 mg/kg bw/d.

Subchronic Toxicity Studies

Inhalation

Acrylates/Octylacrylamide Copolymer

Sprague-Dawley rats (10/sex/group) were exposed to 0, 199, 491, or 828 µg/m^3 Acrylates/Octylacrylamide Copolymer in ethanol (mean particle aerodynamic diameter of 1.9 µ), via a full body chamber, for 4 h/d, 7 d/wk, for 13 wk.[15] Clinical, hematological, and histopathological parameters were observed. The test substance did not produce any adverse effects.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer

A dermal prenatal development toxicity assay was performed in pregnant female Wistar rats (24/group).[17] The test substance (38% AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer in water; 2 ml/kg) was applied to the skin, in doses of 0, 100, 300, and 1000 mg/kg bw/d, under semi-occlusive conditions, on gestation days 5 to 19. Each application lasted for a duration of 6 h. Maternal skin reactions, body weight, clinical parameters, and gross pathological effects were observed. In addition, litter parameters and external, visceral, and skeletal observations of fetuses were performed. No adverse effects were observed for any of the evaluated parameters. The NOAEL for maternal and fetal toxicity was determined to be greater than 1000 mg/kg bw/d.

GENOTOXICITY

In Vitro

Acrylamide/Ammonium Acrylate Copolymer

The potential genotoxicity of Acrylamide/Ammonium Acrylate Copolymer (up to 5000 µg/plate) was evaluated via an Ames test *(Salmonella typhimurium* (strains not specified) and *Escherichia coli* WP2 (uvrA-)).[10] No other details regarding this study were provided. The test substance was considered to be non-genotoxic.

AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer

A 40% ethanolic solution of AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer was used in an Ames assay to determine potential genotoxicity.[9] No other details regarding this study were provided. The test substance was considered to be non-genotoxic.

AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer

An Ames assay was performed with and without metabolic activation using a mixture containing 38% AMP-Acrylates/C1-18 Alkyl Acrylate/C1-18 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer (5, 15.81, 50, 158.1, 500, 1581, and 5000 µg/plate; dissolved in dimethyl sulfoxide (DMSO)) in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102.[18] Negative (DMSO) and positive controls (2-nitrofluorene, sodium azide, 9-aminoacridine, mitomycin c, benzo[a]pyrene, 2-aminoanthracene) were used, and yielded expected results. The test substance was not considered to be mutagenic.

The same test substance (up to 300 µg/ml; dissolved in DMSO) was evaluated in an in vitro mammalian cell micronucleus assay using human peripheral blood lymphocytes, with and without metabolic activation.[19] Negative (DMSO) and positive controls (mitomycin C, cyclophosphamide, vinblastine) were used, and yielded expected results. The test substance did not induce micronuclei in cultured human peripheral blood lymphocytes.

Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer

The genotoxic potential of a 70% ethanolic solution of Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer was evaluated via an Ames assay.[6] No details regarding this assay were provided. The test material was considered to be non-genotoxic.

CARCINOGENICITY STUDIES

Carcinogenicity studies were not found in the published literature, and unpublished data were not submitted.

DERMAL IRRITATION AND SENSITIZATION

Details regarding the irritation and sensitization studies summarized below can be found in Table 7.

Reconstructed human epidermis cytotoxicity assays were performed using a mixture containing 32% Acrylamide/ Ammonium Acrylate Copolymer and undiluted *t*-Butylacrylamide Copolymer.[20] Both test substances were considered to be

non-irritating. In an animal assay, a neutralized, aqueous solution of Acrylates/Octylacrylamide Copolymer (15% solids) was applied to intact and abraded skin sites on New Zealand White rabbits, under occlusive conditions.[15] The test substance was considered to be mildly irritating. A primary skin irritation assay performed in rabbits using AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer (40% ethanolic solution) yielded negative results.[9] Mild irritation was noted in a primary skin assay performed in rabbits using a 10% aqueous solution of Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer; however the same test substance was non-irritating in a cumulative irritation assay performed in guinea pigs.[6] Mild irritation was also noted in a primary irritation assay performed in rabbits using a 40% ethanolic solution of AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer.[8] No irritation was noted in a human dermal irritation assay using a 5% aqueous solution of Acrylamide/Ammonium Acrylate Copolymer.[10] A human dermal irritation assay performed using a 50% aqueous solution of Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer yielded negative results.[6]

In vitro EpiSkin® dermal sensitization assays were performed on AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer and a 50% aqueous solution of Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer.[6,9] Both test substances were considered to be non-sensitizing. The skin sensitization potential of a mixture containing 32% Acrylamide/Ammonium Acrylate Copolymer was evaluated in guinea pigs (tested undiluted under occlusive conditions).[21] No signs of sensitization were observed. Guinea pig maximization assays were performed to evaluate the potential sensitization of Acrylates/Octylacrylamide Copolymer (5 - 100%), a 40% ethanolic solution of AMP-Acrylates/ C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer, and a 70% ethanolic solution Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer.[6,9,15] All test substances were considered to be non-sensitizing. Similarly, no signs of sensitization were observed in a local lymph node assay performed in mice using a mixture containing 38% AMP-Acrylates/C1-18 Alkyl Acrylate/C1-18 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer (5, 10, 25, and 50% in dimethylformamide).[22] Several test substances (mixture containing 0.66% Acrylamide/Ammonium Acrylate Copolymer (n = 109), aqueous solution of Acrylamide/Ammonium Acrylate Copolymer (5%; n = 50), aqueous solution of neutralized Acrylates/Octylacrylamide Copolymer (15% solids; n = 25), and a formula containing 13.34% Acrylates/*t*-Butylacrylamide Copolymer (n = 96)) were evaluated for potential sensitization via human repeat insult patch tests (HRIPTs).[10,15,23] All test substances evaluated were considered to be non-irritating and non-sensitizing.

OCULAR IRRITATION STUDIES

The ocular irritation studies summarized below can be found in Table 8.

In vitro ocular irritation assays performed using a 3% solution of Acrylamide/Ammonium Acrylate Copolymer, AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer, and a 50% aqueous solution of Dimethyl Acrylamide/ Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer yielded negative results.[6,9,10] Mild irritation was noted in an in in vitro ocular irritation assay performed using a 40% ethanolic solution of AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer.[6] No ocular irritation was noted in an ocular irritation assay performed on New Zealand White rabbits using Acrylates/Octylacrylamide Copolymer (tested at 100%).[15] However, mild ocular irritation was observed in an ocular irritation assay performed in New Zealand white rabbits using a neutralized, aqueous solution of Acrylates/Octylacrylamide Copolymer (15% solids). Slight irritation was observed in an ocular irritation assay performed on rabbits using a 40% ethanolic solution of AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer.[8] No irritation was noted in an ocular irritation assay performed in rabbits using a 10% aqueous solution of Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer.[6]

SUMMARY

The majority of the acrylamide/acrylate copolymers reviewed in this report are reported to function as binders, film formers, and hair fixatives. According to manufacturers, the acrylamide monomer concentration for Acrylamide/Ammonium Acrylate Copolymer, AMP-Acrylates/ C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer, AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/ Hydroxyethylacrylate Copolymer, and Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer was either less than 2% or undetectable.

Based on 2022 FDA VCRP and data, Acrylates/Octylacrylamide Copolymer is reported to be used in 117 formulations. All other in-use formulations are reported to be used in 14 formulations or less. The results of the concentration of use survey conducted by the Council indicate that Acrylates/*t*-Butylacrylamide Copolymer, Acrylates/Octylacrylamide Copolymer, and Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer are used at up to 7% in leave-on formulations (i.e., aerosol hair sprays, mascaras, and tonics, dressings, and other hair grooming aids, respectively). According to the European Commission, several of the ingredients reviewed in this report are linked to entries for substances that may be used in cosmetics under certain restrictions. In addition, Acrylate/Acrylamide Copolymer and Acrylamide/ Sodium Acrylate Copolymer are used as indirect, direct, and secondary food additives.

The acute dermal LD_{50} was reported to be greater than 2000 mg/kg in rabbits dosed with Acrylates/Octylacrylamide Copolymer. Acute oral toxicity assays were performed in rats using several test substances (Acrylates/Octylacrylamide Copolymer (15% solids), a 40% ethanolic solution of AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide

Copolymer, a 40% ethanolic solution of AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer, and a 70% Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer). LD_{50}s reported for these assays were greater than 2000 mg/kg, excluding Acrylates/Octylacrylamide Copolymer, in which the reported LD_{50} was greater than 2300 mg solids/kg bw. An LC_{50} of greater than 3.4 mg/l was reported in an acute inhalation toxicity assay performed in rats exposed to Acrylates/Octylacrylamide Copolymer.

In a 28-d dermal toxicity assay, Wistar rats were given 38% AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer in water in doses of up to 1000 mg/kg bw/d. The NOAEL was determined to be 1000 mg/kg bw/d. The potential subchronic inhalation toxicity of Acrylates/Octylacrylamide Copolymer in ethanol (up to 828 $\mu g/m^3$) was evaluated in Sprague-Dawley rats, for 13 wks. No adverse effects were observed.

Potential dermal developmental toxicity of 38% AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/ Hydroxyethylacrylate Copolymer in water (up to 1000 mg/kg bw/d; semi-occlusive conditions; gestation days 5 - 19) was evaluated in pregnant female Wistar rats. The NOAEL for maternal and fetal toxicity was determined to be greater than 1000 mg/kg bw/d.

Ames assays were performed on several test substances (Acrylamide/Ammonium Acrylate Copolymer, a 40% ethanolic solution of AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer, a mixture containing 38% AMP-Acrylates/C1-18 Alkyl Acrylate/C1-18 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer, and a 70% ethanolic solution of Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer). All test substances were considered to be non-genotoxic. In addition, negative results were obtained in an in vitro mammalian cell micronucleus assay performed in human peripheral blood lymphocytes using a mixture containing 38% AMP-Acrylates/C1-18 Alkyl Acrylate/C1-18 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer.

Reconstructed human epidermis cytotoxicity assays were performed using a mixture containing 32% Acrylamide/ Ammonium Acrylate Copolymer and undiluted *t*-Butylacrylamide Copolymer. Both test substances were considered to be non-irritating. In an animal assay, a neutralized, aqueous solution of Acrylates/Octylacrylamide Copolymer (15% solids) was applied to intact and abraded skin sites on New Zealand White rabbits, under occlusive conditions. The test substance was considered to be mildly irritating. A primary skin irritation assay performed in rabbits using AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer (40% ethanolic solution) yielded negative results. Mild irritation was noted in a primary skin assay performed in rabbits using a 10% aqueous solution of Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer; however, the same test substance was non-irritating in a cumulative irritation assay performed in guinea pigs. Mild irritation was also noted in a primary irritation assay performed in rabbits using a 40% ethanolic solution of AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer. No irritation was noted in a human dermal irritation assay using a 5% aqueous solution of Acrylamide/Ammonium Acrylate Copolymer.[10] A human dermal irritation assay performed using a 50% aqueous solution of Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer yielded negative results.

In vitro EpiSkin® dermal sensitization assays were performed on AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer and a 50% aqueous solution of Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer. Both test substances were considered to be non-sensitizing. The skin sensitization potential of a mixture containing 32% Acrylamide/Ammonium Acrylate Copolymer was evaluated in guinea pigs (tested undiluted under occlusive conditions). No signs of sensitization were observed. Guinea pig maximization assays were performed to evaluate the potential sensitization of Acrylates/Octylacrylamide Copolymer (5 - 100%), a 40% ethanolic solution of AMP-Acrylates/ C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer, and a 70% ethanolic solution Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer. All test substances were considered to be non-sensitizing. Similarly, no signs of sensitization were observed in a local lymph node assay performed in mice using a mixture containing 38% AMP-Acrylates/C1-18 Alkyl Acrylate/C1-18 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer (up to 50% in dimethyl-formamide). Several test substances (mixture containing 0.66% Acrylamide/Ammonium Acrylate Copolymer, aqueous solution of Acrylamide/Ammonium Acrylate Copolymer (5%), aqueous solution of neutralized Acrylates/Octylacrylamide Copolymer (15% solids), and a formula containing 13.34% Acrylates/ *t*-Butylacrylamide Copolymer) were evaluated for potential sensitization via HRIPTs. All test substances evaluated were considered to be non-irritating and non-sensitizing.

In vitro ocular irritation assays performed using a 3% solution of Acrylamide/Ammonium Acrylate Copolymer, AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer, and a 50% aqueous solution of Dimethyl Acrylamide/ Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer yielded negative results. Mild irritation was noted in an in vitro ocular irritation assay performed using a 40% ethanolic solution of AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer. No ocular irritation was noted in an ocular irritation assay performed on New Zealand White rabbits using Acrylates/Octylacrylamide Copolymer. However, mild ocular irritation was observed in an ocular irritation assay performed in New Zealand white rabbits using a neutralized, aqueous solution of Acrylates/Octylacrylamide Copolymer (15% solids). Slight irritation was observed in an ocular irritation assay performed on rabbits using a 40% ethanolic solution of AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer. No irritation was noted in an ocular irritation assay performed in rabbits using a 10% aqueous solution of Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer.

DISCUSSION

This assessment reviews the safety of 16 acrylamide/acrylate copolymers as used in cosmetic formulations. The Panel reviewed the available data and concluded that these ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment. Formulators of these ingredients should ensure that the concentration of acrylamide monomer in cosmetic formulations does not exceed 5 ppm.

The Panel determined that the available chemistry, method of manufacturing, composition and impurities, systemic toxicity, and dermal irritation/sensitization data were sufficient to support the safety of these ingredients. Safety was further supported by the large molecular weights of these ingredients, which precludes dermal absorption, and the permitted use of these ingredients as food additives. The possibility of the presence of residual monomers in these ingredients was noted, and the Panel stated that formulators should minimize the presences of residual monomer, and ensure that the concentration of acrylamide monomer in cosmetic formulations does not exceed 5 ppm. In addition, it should be noted that these ingredients are insoluble and are unlikely to form nitrosamines or nitrosamides.

The Panel discussed the fact that some of these ingredients are used in formulations that could result in incidental inhalation (e.g., Acrylates/ *t*-Butylacrylamide Copolymer is used at up to 7% in aerosol and pump hair sprays). An acute and a subchronic toxicity study were available for Acrylates/Octylacrylamide Copolymer; in a 13-wk study performed in rats, full-body exposure of up to 828 μg/m^3 Acrylates/Octylacrylamide Copolymer in ethanol did not produce any adverse effects. Additionally, the Panel noted that in aerosol products, 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone, the concentrations at which the ingredients are used, the large, irrespirable molecule sizes, negative inhalation toxicity data, and a lack of systemic toxicity, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 16 acrylamide/acrylate copolymers are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

Acrylamide/Ammonium Acrylate Copolymer
Acrylamide/Sodium Acrylate Copolymer
Acrylates/Acrylamide Copolymer
Acrylates/*t*-Butylacrylamide Copolymer
Acrylates/Methacrylamide Copolymer
Acrylates/Octylacrylamide Copolymer
AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer
AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer*
t-Butylacrylamide/Dimethylacrylamide/PEG-14 Diacrylate Crosspolymer*
Butyl Acrylate/Isopropylacrylamide/PEG-18 Dimethacrylate Crosspolymer*
Corn Starch/Acrylamide/Sodium Acrylate Copolymer
Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer
Dimethylacrylamide/Lauryl Methacrylate Copolymer
Potassium Acrylates/Acrylamide Copolymer*
Sodium Acrylate/Hydroxyethyl Acrylamide Copolymer*
Starch/Acrylates/Acrylamide 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 used in product categories and at concentrations comparable to others in this group.*

TABLES

Table 1. INCI names, definitions, and reported functions of the Acrylamide/Acrylate Copolymer ingredients in this safety assessment[1, CIR Staff]

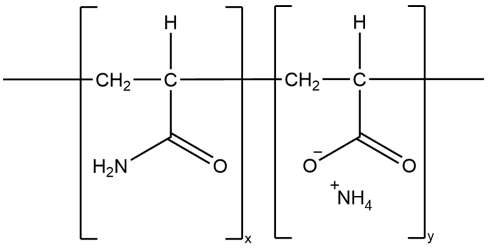
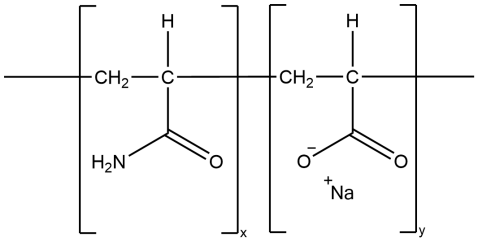
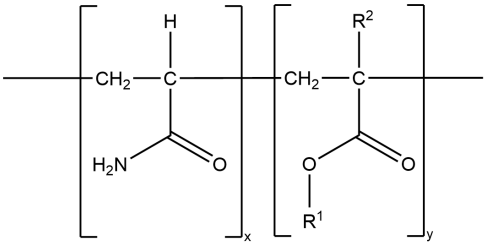
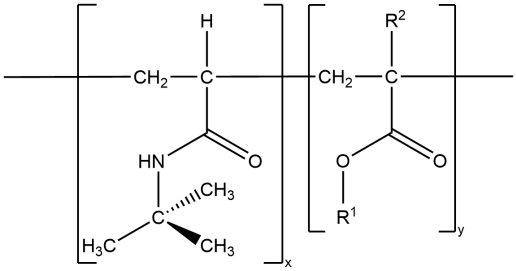
Ingredient (CAS No.)	Definition	Function
Acrylamide/Ammonium Acrylate Copolymer [26100-47-0]	Acrylamide/Ammonium Acrylate Copolymer is a copolymer of Acrylamide and Ammonium Acrylate monomers. 	Binders; Film Formers; Hair Fixatives
Acrylamide/Sodium Acrylate Copolymer [25085-02-3; 25987-30-8]	Acrylamide/Sodium Acrylate Copolymer is a copolymer of Acrylamide and sodium acrylate monomers. 	Binders; Film Formers; Viscosity Increasing Agents - Aqueous
Acrylates/Acrylamide Copolymer [9003-06-9]	Acrylates/Acrylamide Copolymer is a copolymer of Acrylamide and one or more monomers of Acrylic Acid, Methacrylic Acid or one of their simple esters. 	Binders; Film Formers; Hair Fixatives
Acrylates/*t*-Butylacrylamide Copolymer	Acrylates/t-Butylacrylamide Copolymer is a copolymer of t-Butylacrylamide and one or more monomers of Acrylic Acid, Methacrylic Acid, or one of their simple esters.  **wherein R^1 may be hydrogen, methyl, ethyl, propyl, or butyl; and R^2 may be hydrogen or methyl**	Binders; Film Formers; Hair Fixatives

Table 1. INCI names, definitions, and reported functions of the Acrylamide/Acrylate Copolymer ingredients in this safety assessment[1, CIR Staff]

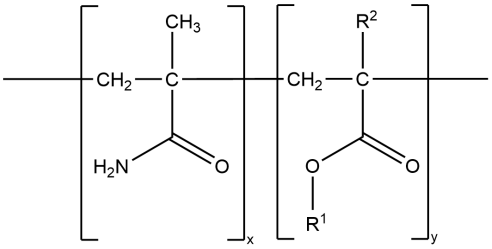
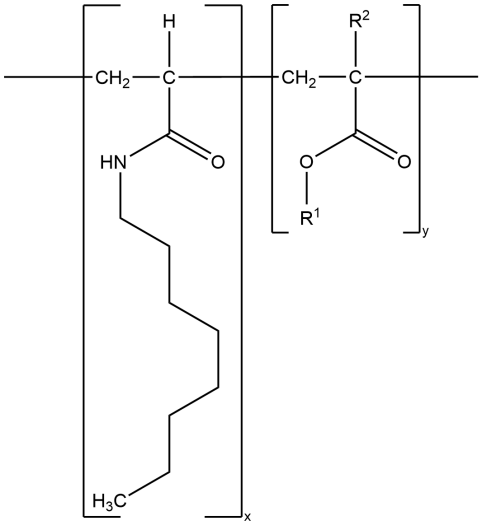
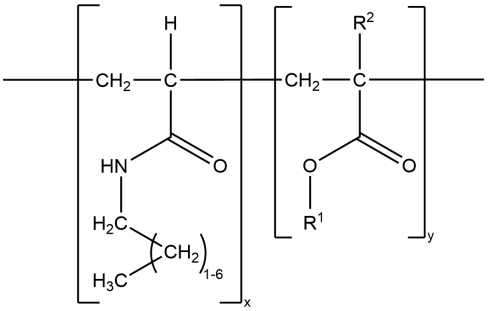
Ingredient (CAS No.)	Definition	Function
Acrylates/Methacrylamide Copolymer	Acrylates/Methacrylamide Copolymer is a copolymer of Methacrylamide and one or more monomers of Acrylic Acid, Methacrylic Acid or one of their simple esters.  **wherein R^1 may be hydrogen, methyl, ethyl, propyl, or butyl; and R^2 may be hydrogen or methyl**	Film Formers; Hair Fixatives
Acrylates/Octylacrylamide Copolymer [129702-02-9]	Acrylates/Octylacrylamide Copolymer is a copolymer of octylacrylamide and one or more monomers consisting of Acrylic Acid, Methacrylic Acid or one of their simple esters. 	Film Formers; Hair Fixatives
AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer	AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer is a polymer of C1-18 Alkyl Acrylate, C1-8 Alkyl Acrylamide and the aminomethylpropanol salt of a monomer consisting of Acrylic Acid, Methacrylic Acid or one of their simple esters.  **wherein R^1 may be hydrogen, C1-18-alkyl, or a salt of 3-aminopropanol; and R^2 may be hydrogen or methyl**	Film Formers; Hair Fixatives

Table 1. INCI names, definitions, and reported functions of the Acrylamide/Acrylate Copolymer ingredients in this safety assessment[1, CIR Staff]

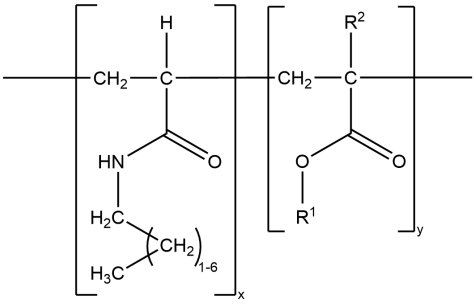
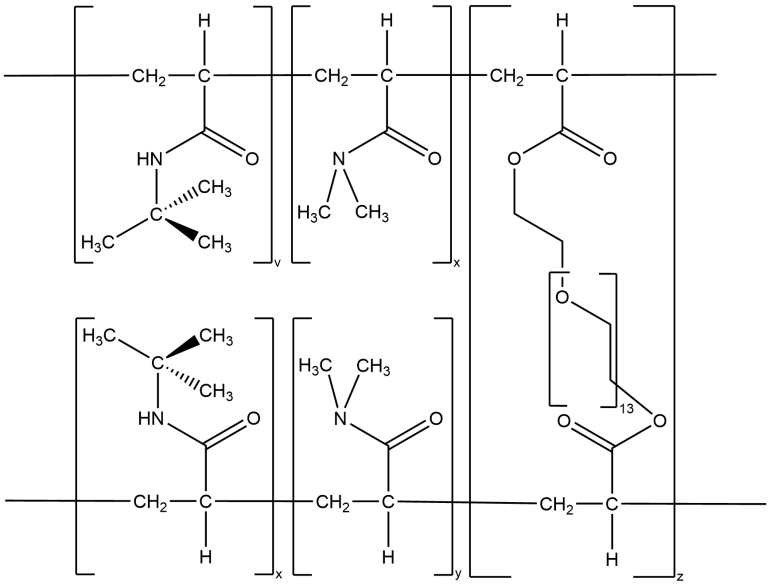
Ingredient (CAS No.)	Definition	Function
AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer	AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer is a polymer of C1-18 Alkyl Acrylate or C1-18 alkyl methacrylate, C1-8 Alkyl Acrylamide, 2-Hydroxyethyl Acrylate, and the aminomethylpropanol salt of a monomer consisting of Acrylic Acid, Methacrylic Acid or one of their simple esters.  **wherein R^1 may be hydrogen, C1-18-alkyl, 2-hydroxyethyl, or a salt of 3-aminopropanol; and R^2 may be hydrogen or methyl**	Hair-Waving/Straightening Agents
t-Butylacrylamide/Dimethylacrylamide/PEG-14 Diacrylate Crosspolymer	t-Butylacrylamide/Dimethylacrylamide/PEG-14 Diacrylate Crosspolymer is a copolymer of t-Butylacrylamide and Dimethylacrylamide, cross-linked with PEG-14 diacrylate. 	Hair Fixatives

Table 1. INCI names, definitions, and reported functions of the Acrylamide/Acrylate Copolymer ingredients in this safety assessment[1, CIR Staff]

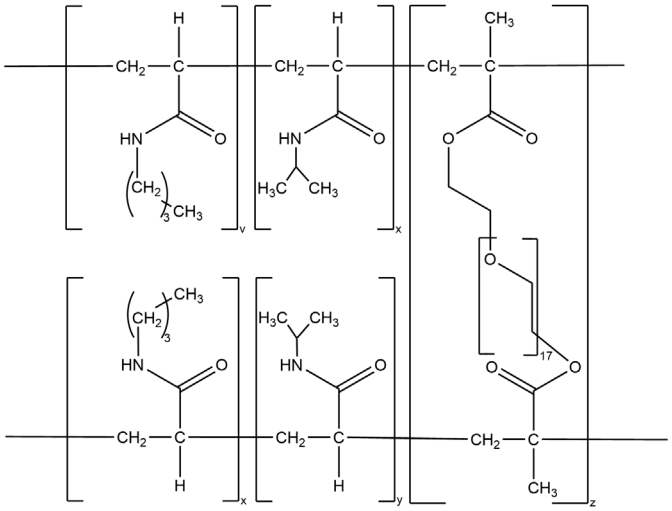
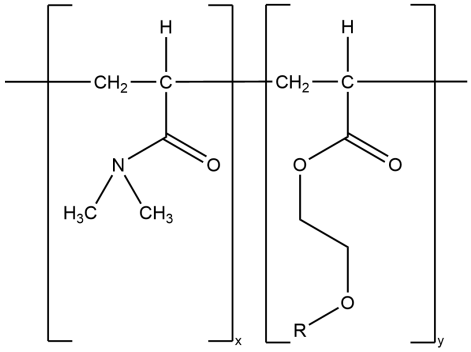
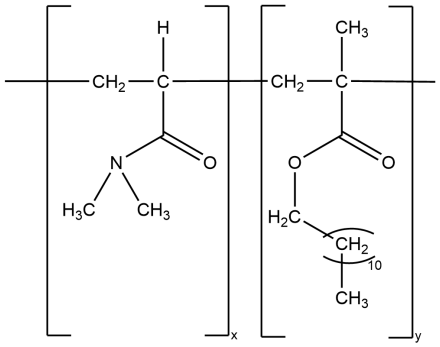
Ingredient (CAS No.)	Definition	Function
Butyl Acrylate/Isopropylacrylamide/PEG-18 Dimethacrylate Crosspolymer	Butyl Acrylate/Isopropylacrylamide/PEG-18 Dimethacrylate Crosspolymer is a crosslinked copolymer of Butyl Acrylate, Isopropylacrylamide and PEG-18 dimethacrylate monomers.	Emulsion Stabilizers; Film Formers; Skin-Conditioning Agents - Miscellaneous
		
Corn Starch/Acrylamide/Sodium Acrylate Copolymer	Corn Starch/Acrylamide/Sodium Acrylate Copolymer is a polymer of Zea Mays (Corn) Starch, Acrylamide and sodium acrylate monomers.	Dispersing Agents - Nonsurfactant; Emulsion Stabilizers; Film Formers; Hair Fixatives
Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer	Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer is a copolymer of Dimethylacrylamide, 2-Hydroxyethyl Acrylate and Methoxyethyl Acrylate monomers.  wherein R may be hydrogen or methyl	Hair Fixatives
Dimethylacrylamide/Lauryl Methacrylate Copolymer [103479-14-7]	Dimethylacrylamide/Lauryl Methacrylate Copolymer is a copolymer of Dimethylacrylamide and Lauryl Methacrylate. 	Binders; Film Formers; Hair Fixatives

Table 1. INCI names, definitions, and reported functions of the Acrylamide/Acrylate Copolymer ingredients in this safety assessment[1, CIR Staff]

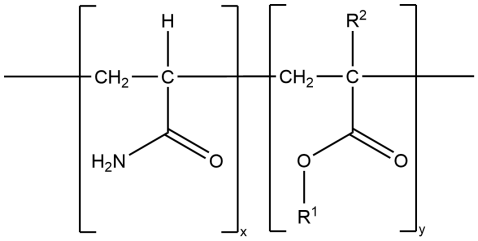
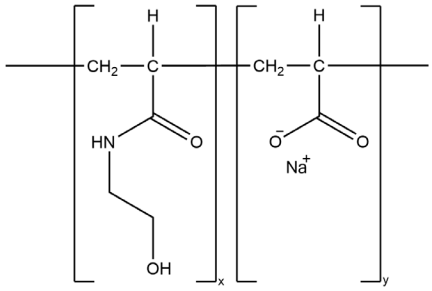
Ingredient (CAS No.)	Definition	Function
Potassium Acrylates/Acrylamide Copolymer	Potassium Acrylates/Acrylamide Copolymer is the potassium salt of Acrylates/Acrylamide Copolymer.  **wherein R^1 may be hydrogen, methyl, ethyl, propyl, butyl or potassium; and R^2 may be hydrogen or methyl**	Film Formers
Sodium Acrylate/Hydroxyethyl Acrylamide Copolymer	Sodium Acrylate/Hydroxyethyl Acrylamide Copolymer is a copolymer of sodium acrylate and Hydroxyethyl Acrylamide that conforms generally to the formula: 	Antistatic Agents; Film Formers; Hair Conditioning Agents; Hair Fixatives
Starch/Acrylates/Acrylamide Copolymer	Starch/Acrylates/Acrylamide Copolymer is a polymer of starch, Acrylamide and a monomer consisting of Acrylic Acid, Methacrylic Acid or one of their simple ester.	Film Formers; Viscosity Increasing Agents - Aqueous

Table 2. Molecular weights of the acrylamide/acrylate copolymers

Ingredient	Approximate Molecular Weight (g/mol)	Reference
AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer	24,000 (percent molecular weight less than 500 Da: 0.0001%)	[9]
AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer	250,000 (percent molecular weight less than 500 Da: 0%)	[8]
t-Butylacrylamide/Dimethylacrylamide/PEG-14 Diacrylate Crosspolymer	5000 (percent molecular weight less than 500 Da: < 0.0005%)	[7]
Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer	10,000 (percent molecular weight less than 500 Da: 0.0124%)	[6]

Da = Daltons

Table 3. Frequency (2022) and concentration (2020) of use according to duration and exposure[11,12]

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Acrylamide/Ammonium Acrylate Copolymer		**Acrylamide/Sodium Acrylate Copolymer**		**Acrylates/Acrylamide Copolymer**	
Totals*	**1**	**NR**	**14**	**0.5 – 2.8**	**8**	**0.41**
Duration of Use						
Leave-On	*1*	*NR*	*13*	*NR*	*5*	*0.41*
Rinse-Off	*NR*	*NR*	*1*	*NR*	*3*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	2	NR	NR	NR
Incidental Inhalation-Spray	1[a]	NR	6[a]; 5[b]	2.8[a]	3[b]	NR
Incidental Inhalation-Powder	NR	NR	5[b]	0.5[c]	3[b]	NR
Dermal Contact	1	NR	10	0.5 – 2.8	8	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	2	2.8	NR	0.41
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	2	NR	3	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Acrylates/*t*-Butylacrylamide Copolymer		**Acrylates/Methacrylamide Copolymer**		**Acrylates/Octylacrylamide Copolymer**	
Totals*	**5**	**0.06 – 7**	**2**	**NR**	**117**	**0.00097 – 19.4**
Duration of Use						
Leave-On	*5*	*0.06 – 7*	*NR*	*NR*	*116*	*0.00097 – 7*
Rinse Off	*NR*	*NR*	*2*	*NR*	*1*	*4.9 – 19.4*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	17	0.00097 – 7
Incidental Ingestion	NR	NR	NR	NR	1	19.4
Incidental Inhalation-Spray	2	0.06 – 7; 5[a]	NR	NR	81; 6[a]	0.5 – 3.2
Incidental Inhalation-Powder	NR	NR	NR	NR	3	NR
Dermal Contact	NR	NR	NR	NR	95	0.00097 – 4.9
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	5	0.06 – 7	2	NR	15	0.5 – 3.2
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	2	NR
Mucous Membrane	NR	NR	NR	NR	1	19.4
Baby Products	NR	NR	NR	NR	NR	NR
	AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer		**Corn Starch/Acrylamide/Sodium Acrylate Copolymer**		**Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer**	
Totals*	**4**	**0.032 – 5**	**6**	**0.002 – 2**	**8**	**0.26 – 7**
Duration of Use						
Leave-On	*4*	*0.032 – 5*	2	*0.002*	8	*0.26 – 7*
Rinse Off	*NR*	*NR*	NR	*NR*	NR	*NR*
Diluted for (Bath) Use	*NR*	*NR*	4	*2*	NR	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	2	1.3 – 3.9; 0.032 – 5[a]	1[b]	NR	2	0.26; 7[a]
Incidental Inhalation-Powder	NR	NR	1[b]	0.002[c]	NR	NR
Dermal Contact	2	0.032 – 0.05	6	0.002 – 2	NR	NR
Deodorant (underarm)	NR	0.05	NR	NR	NR	NR
Hair - Non-Coloring	2	0.3 – 5	NR	NR	6	0.26 – 7
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	2	NR
Mucous Membrane	NR	NR	4	2	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

Table 3. Frequency (2022) and concentration (2020) of use according to duration and exposure[11,12]

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Dimethylacrylamide/Lauryl Methacrylate Copolymer		Potassium Acrylates/Acrylamide Copolymer			
Totals*	**NR**	**0.5**	**8**	**NR**		
Duration of Use						
Leave-On	*NR*	*NR*	*2*	*NR*		
Rinse Off	*NR*	*0.5*	*6*	*NR*		
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*		
Exposure Type						
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	NR	0.5	7	NR		
Deodorant (underarm)	NR	NR	NR	NR		
Hair - Non-Coloring	NR	NR	1	NR		
Hair-Coloring	NR	NR	NR	NR		
Nail	NR	NR	NR	NR		
Mucous Membrane	NR	0.5	1	NR		
Baby Products	NR	NR	3	NR		

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders
NR – not reported

Table 4. Acrylate/Acrylamide Copolymers with no reported uses, according to the VCRP and Council survey

AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer
t-Butylacrylamide/Dimethylacrylamide/PEG-14 Diacrylate Crosspolymer
Butyl Acrylate/Isopropylacrylamide/PEG-18 Dimethacrylate Crosspolymer
Sodium Acrylates/Hydroxyethyl Acrylamide Copolymer
Starch/Acrylates/Acrylamide Copolymer

Table 5. CFR Citations for Acrylate/Acrylamide Copolymer and Acrylamide/Sodium Acrylate Copolymer

CFR Citation	Limitations
	Acrylate/Acrylamide Copolymer
21CFR176.110 Indirect food additives: paper and paperboard components	Acrylamide-acrylic acid resins may be safely used as components of articles in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food under the following limitations: -acrylamide-acrylic acid resins are produced by the polymerization of acrylamide with partial hydrolysis or by the copolymerization of acrylamide and acrylic acid -the acrylamide-acrylic acid resins contain less than 0.2% residual monomer -the resins are used as adjuvants in the manufacture of paper and paperboard in amounts not to exceed that necessary to accomplish the technical effect and not to exceed 2% by weight of the paper or paperboard
21CFR573.120 Food additives permitted in feed and drinking water of animals	Acrylamide-acrylic acid resin may be used safely under the following limitations: -the additive is produced by polymerization of acrylamide with partial hydrolysis, or by copolymerization of acrylamide and acrylic acid with the greater part of the polymer being composed of acrylamide units -the additive meets the following specifications: a) a minimum molecular weight of 3 million b) viscosity range: 3000 to 6000 centipoises at 77° F in a 1% aqueous solution as determined by LVF Brookfield Viscometer or equivalent using a number 6 spindle at 20 rpm c) residual acrylamide: not more than 0.05% -it is used as a thickener and suspending agent in non-medicated aqueous suspensions intended for addition to animal feeds
21CFR173.357 Secondary direct food additives permitted in food for human consumption	May be used as a fixing material in the immobilization of glucose isomerase enzyme preparations for use in the manufacture of high fructose corn syrup in accordance with CFR 184.1372

Table 5. CFR Citations for Acrylate/Acrylamide Copolymer and Acrylamide/Sodium Acrylate Copolymer

CFR Citation	Limitations
	Acrylamide/Sodium Acrylate Copolymer
21CFR172.710 Food additives permitted for direct addition to food for human consumption	Sodium acrylate and acrylamide copolymer with a minimum average molecular weight of 10,000,000 in which 30% of the polymer is comprised of acrylate units and acrylamide units, for use as a drift control agent in herbicide formulations applied to crops at a level not to exceed 0.5 oz of the additive per acre
21CFR173.310 Secondary direct food additives permitted in food for human consumption	Boiler water additives may be safely used in the preparation of steam that will contact food under the following conditions: -the amount of additive is not in excess of that required for its functional purposed, and the amount of steam in contact with food does not exceed that required to produce the intended effect in or on food -acrylamide-sodium acrylate resin may not contain more that 0.05% by weight of acrylamide monomer
40CFR180.960 Polymers; exemptions from the requirement of a tolerance	Exempted from the requirement of a tolerance under FFDCA section 408
	Acrylate/Acrylamide Copolymer and Acrylamide/Sodium Acrylate Copolymer
21CFR173.5 Secondary direct food additives permitted in food for human consumption	Acrylate-acrylamide resins may be safely used in food under the following conditions: 1. the additive consists of one of the following: a. acrylamide-acrylic resin (hydrolyzed polyacrylamide) is produced by the polymerization of acrylamide with partial hydrolysis, or by copolymerization of acrylamide and acrylic acid, with the greater part of the polymer being composed of acrylamide units b. sodium polyacrylate-acrylamide resin is produced by the polymerization and subsequent hydrolysis of acrylonitrile in a sodium silicate-sodium hydroxide aqueous solution, with the greater part of the polymer being composed of acrylate units 2. the additive contains not more than 0.05% of residual monomer calculated as acrylamide 3. the additive is used or intended for use as follows: a. the additive is used as a flocculent in the clarification of beet sugar juice and liquor of cane sugar juice and liquor or corn starch hydrolysate in an amount not to exceed 5 ppm by weight of the juice or 10 ppm by weight of liquor or the corn starch hydrolysate b. the additive is used to control organic and mineral scale in beet sugar juice and liquor or cane sugar juice and liquor in an amount not to exceed 2.5 ppm by the weight of the juice or liquor

Table 6. Acute toxicity studies

Test Substance	Animals	No./Group	Concentration/Dose/Protocol	LD_{50}/LC_{50}	Reference
			DERMAL		
Acrylates/Octylacrylamide Copolymer	albino rabbits (strain not reported)	10	2000 mg/kg; occlusion not reported; animals observed for 14 d	greater than 2000 mg/kg	[15]
			ORAL		
Acrylates/Octylacrylamide Copolymer (aqueous solution ; 15% solids)	Charles River albino rats	2/sex/group	1000, 1500, 2300 mg solids/kg bw; method of oral administration not reported	greater than 2300 mg/kg	[15]
AMP-Acrylates/C1-18 Alkyl Acrylate/ C1-8 Alkyl Acrylamide Copolymer (40% ethanol solution)	rats (strain not reported)	NR	2000 mg/kg	greater than 2000 mg/kg	[9]
AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/ Hydroxyethylacrylate Copolymer (40% ethanol solution)	rats (strain not reported)	NR	2000 mg/kg	greater than 2000 mg/kg	[8]
Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer (70% ethanol solution)	rats (strain not reported)	NR	2000 mg/kg	greater than 2000 mg/kg	[6]
			INHALATION		
Acrylates/Octylacrylamide Copolymer (aqueous solution; 10% solids)	Sprague-Dawley rats	5/sex	whole body chamber (exposure concentration of 3.4 mg polymer/l; particle size 5.5 µm; 84% of the aerosol was less than 10 µ in size); animals observed for 14 d	greater than 3.4 mg/l	[15]

NR = not reported

Table 7. Dermal irritation and sensitization

Test Article	Dose/Concentration	Test Population	Procedure	Results	Reference
IRRITATION					
In Vitro					
Acrylamide/Ammonium Acrylate Copolymer (mixture containing 32%)	10 µl; administered neat	reconstructed human epidermis	reconstructed human epidermis cytotoxicity assay; application time 15 min; incubation time 42 h	non-irritating	[20]
Acrylates/t-Butylacrylamide Copolymer	10 mg; 100%	reconstructed human epidermis	reconstructed human epidermis cytotoxicity assay; application time 15 min; incubation time 42 h	non-irritating	[20]
Animal					
Acrylates/Octylacrylamide Copolymer (neutralized, aqueous solution ; 15% solids)	0.5 ml; applied neat	6 New Zealand White rabbits (sex not reported)	test substance applied to intact and abraded skin sites; occlusive conditions; duration of application was not reported.	erythema observed 24 and 72 h after application, in both intact and abraded sites; test substance considered to be mildly irritating; primarily irritation score of 2.9	[15]
AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer (40% ethanol solution)	NR	rabbits (strain and number of animals not reported)	primary skin irritation assay; Draize method; details not provided	non-irritating	[9]
AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer (40% ethanol solution)	NR	rabbits (strain and number of animals not reported)	primary skin irritation assay; Draize method; details not provided	mildly irritating; PII = 0	[8]
Dimethyl Acrylamide/Hydroxyethyl Acrylate/ Methoxyethyl Acrylate Copolymer (10% aqueous solution)	applied neat	rabbits (strain and number of animals not reported)	primary skin irritation assay; Draize method; details not provided	mildly irritating; PII = 0	[6]
Dimethyl Acrylamide/Hydroxyethyl Acrylate/ Methoxyethyl Acrylate Copolymer (10% aqueous solution)	applied neat	guinea pigs (strain and number of animals not reported)	cumulative skin irritation assay; details not provided	non-irritating	[6]
Human					
Acrylamide/Ammonium Acrylate Copolymer (5% aqueous solution)	applied neat	20 subjects	test substance applied to skin, under occlusive conditions, for 48 h	non-irritating	[10]
Dimethyl Acrylamide/Hydroxyethyl Acrylate/ Methoxyethyl Acrylate Copolymer (50% aqueous solution)	applied neat	40 subjects	patch test; no other details reported	non-irritating	[6]
SENSITIZATION					
In Vitro					
AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer	NR	reconstructed human epidermis	EpiSkin® method	non-sensitizing	[9]
Dimethyl Acrylamide/Hydroxyethyl Acrylate/ Methoxyethyl Acrylate Copolymer (50% aqueous solution)	applied neat	reconstructed human epidermis	EpiSkin® method	non-sensitizing	[6]
Animal					
Acrylamide/Ammonium Acrylate Copolymer (mixture containing 32%)	applied neat; 0.5 ml (dermal induction); 0.25 ml (dermal challenge)	22 female Dunkin-Hartley guinea pigs	For the intradermal induction, animals were treated with an injection of Freund's Complete Adjuvant and 0.9 % saline. Animals then received a dermal induction application of the test substance, under occlusive conditions for 48 h. A challenge patch was performed 29 d later, using the undiluted test material, under occlusive conditions, for 48 h	non-sensitizing	[21]

Table 7. Dermal irritation and sensitization

Test Article	Dose/Concentration	Test Population	Procedure	Results	Reference
Acrylates/Octylacrylamide Copolymer (aqueous solution and powder form)	intradermal induction: 5% aqueous solution; dermal induction: powder applied neat ; dermal challenge: aqueous solution (100% solids and 50% solids)	20 female guinea pigs/group (strain not reported)	guinea pig maximization assay; animals were exposed to a two-part induction phase: -part 1: injection with of solution containing Acrylates/Octylacrylamide Copolymer (5%) with and without Freund's Complete Adjuvant) -part 2: dermal induction with Acrylates/Octylacrylamide Copolymer powder (8 cm^2 patch; moistened) for 48 h; use of occlusion not reported Animals were then exposed to a challenge phase: -1 saturated, occlusive patch (4 cm^2) of an aqueous solution of Acrylates/Octylacrylamide Copolymer (100% solids) and 1 saturated, occlusive patch (4 cm^2) of an aqueous solution of Acrylates/Octylacrylamide Copolymer (50% solids); both patches were left on for 24 h	non-irritating and non-sensitizing	[15]
AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer (40% ethanol solution)	applied neat	guinea pigs (strain not reported)	guinea pig maximization assay; no other details provided	non-sensitizing	[9]
AMP-Acrylates/C1-18 Alkyl Acrylate/C1-18 Alkyl Acrylamide/ Hydroxyethylacrylate Copolymer in dimethylformamide (mixture containing 38%)	25 µl; 5, 10, 25, 50, and 75%	female CBA/J mice (4/group)	LLNA in accordance with OECD TG 429; positive control: α-hexylcinnamaldehyde in acetone/olive oil; negative control: *N,N*-dimethylformamide; 3-d applications	non-sensitizing; stimulation index: 0.8 – 1.5% (comparable to negative control); no local ear skin irritation; EC3 value was not calculable	[22]
Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer (70% ethanolic solution)	applied neat	guinea pig (strain not reported)	guinea pig maximization assay; no other details provided	non-sensitizing	[7]
Human					
Acrylamide/Ammonium Acrylate Copolymer (mixture containing 0.66%)	applied neat	109 subjects	HRIPT; induction phase consisted of 3 applications of the test substance, under occlusive conditions, each wk, for 3 wk; after a 2-wk rest period, challenge patch was applied to an untreated skin site, under occlusive conditions; all patches were applied for 48 h	Mild patch test responses occasionally accompanied by mild papular responses were observed in 28 subjects during the induction and/or challenge phase. The test substance was considered to be non-irritating and non-sensitizing.	[24]
Acrylamide/Ammonium Acrylate Copolymer (5% aqueous solution)	applied neat	50 subjects	HRIPT; details not provided	non-irritating and non-sensitizing	[10]
Acrylates/Octylacrylamide Copolymer (neutralized, aqueous solution; 15% solids)	applied neat	25 subjects/sex	HRIPT; use of occlusion not reported; 24-h patch application	Thirty subjects responded to the application of the test material with very slight to mild erythema. The test substance as considered to be non-irritating and non-sensitizing.	[15]
Acrylates/ *t*-Butylacrylamide Copolymer (formula containing 13.34%)	applied neat; 0.2 ml	96 subjects	HRIPT; semi-occlusive conditions; 2 cm x 2 cm patch	non-irritating and non-sensitizing	[23]

HRIPT: human repeat insult patch test; LLNA: local lymph node assay; NR = not reported; OECD TG: Organisation for Economic Co-operation and Development Test Guidelines

Table 8. Ocular irritation studies

Test Article	Concentration	Test Population	Procedure	Results	Reference
			IN VITRO		
Acrylamide/Ammonium Acrylate Copolymer (3% in water and 0.5% sodium chloride)	applied neat	NA	HET-CAM assay	non-irritating	[10]
AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer	100%	NA	SkinEthic™ HCE (human corneal epithelium) assay	non-irritating	[9]
Dimethyl Acrylamide/ Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer (50% aqueous solution)	applied neat	NA	SkinEthic™ HCE (human corneal epithelium) assay	non-irritating	[6]
			ANIMAL		
Acrylates/Octylacrylamide Copolymer	100%	6 New Zealand White rabbits	ocular irritation assay; irritation of cornea, iris, and conjunctiva observed on days 1, 2, and 3 post-instillation	Non-irritating	[15]
Acrylates/Octylacrylamide Copolymer (neutralized, aqueous solution ; 15% solids)	applied neat	6 New Zealand White rabbits	ocular irritation assay	Iritis and mild conjunctival irritation were noted in 3/6 and 6/6 animals, respectively. Effects were fully reversible within 24 h. The test substance was considered to be mildly irritating.	[15]
AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer (40% ethanolic solution)	applied neat	NR	ocular irritation assay performed according to the Draize method	slightly irritating	[9]
AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/ Hydroxyethylacrylate Copolymer (40% ethanol solution)	applied neat	rabbits (strain and number of animals not reported)	ocular irritation assay performed according to the Draize method	Slightly irritating	[8]
Dimethyl Acrylamide/ Hydroxyethyl Acrylate/ Methoxyethyl Acrylate Copolymer (10% aqueous solution)	applied neat	rabbits (strain and number of animals not specified)	ocular irritation assay performed according to the Draize method	Non-irritating	[6]

HET-CAM = hen's egg test chorioallantoic membrane; NA = not applicable; NR = not reported

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Acrylamide/Ammonium Acrylate Copolymer

Moisturizing	1

Total: 1

Acrylamide/Sodium Acrylate Copolymer

Shampoos	1
Tonics, Dressings, and Other Hair Grooming Aids	1
Lipstick	2
Face and Neck (exc shave)	4
Body and Hand (exc shave)	1
Moisturizing	4
Suntan Gels, Creams, and Liquids	1

Total: 14

Acrylates/Acrylamide Copolymer

Bath Soaps and Detergents	3
Face and Neck (exc shave)	3
Other Skin Care Preps	2

Total: 8

Acrylates/*t*-Butylacrylamide Copolymer

Hair Spray (aerosol fixatives)	2
Other Hair Preparations	3

Total: 5

Acrylates/Methacrylamide Copolymer

Shampoos (non-coloring)	2

Total: 2

Acrylates/Octylacrylamide Copolymer

Eyeliner	13
Mascara	4

Cologne and Toilet waters	48
Perfumes	19
Other Fragrance Preparation	4
Hair Spray (aerosol fixatives)	10
Tonics, Dressings, and Other Hair Grooming Aids	4
Other Hair Preparations	1
Blushers (all types)	2
Face Powders	3
Other Makeup Preparations	1
Basecoats and Undercoats	1
Nail Polish and Enamel	1
Other Oral Hygiene Products	1
Aftershave Lotion	3
Other Suntan Preparations	2

Total: 117

AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer

Hair Spray (aerosol fixatives)	2
Makeup Fixatives	2

Total: 4

AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide/Hydroxyethylacrylate Copolymer

Total: 0

***t*-Butylacrylamide/Dimethylacrylamide/PEG-14 Diacrylate Crosspolymer**

Total: 0

Butyl Acrylate/Isopropylacrylamide/PEG-18 Dimethacrylate Crosspolymer

Total: 0

Corn Starch/Acrylamide/Sodium Acrylate Copolymer

Other Bath Preparations	4
Face and Neck (exc shave)	1
Moisturizing	1

Total: 6

Dimethyl Acrylamide/Hydroxyethyl Acrylate/Methoxyethyl Acrylate Copolymer

Hair Spray (aerosol fixatives)	2
Other Hair Preparations	4
Nail Polish and Enamel	1
Other Manicuring Preparations	1

Total: 8

Dimethylacrylamide/Lauryl Methacrylate Copolymer

Total: 0

Potassium Acrylates/Acrylamide Copolymer

Baby Shampoos	1
Other Baby Products	2
Other Personal Cleanliness Products	1
Cleansing	4

Total: 8

Sodium Acrylate/Hydroxyethyl Acrylamide Copolymer

Total: 0

Starch/Acrylates/Acrylamide Copolymer

Total: 0