Data Supplement

Acrylamide Acrylate Copolymers
Acryloyloxyethyl Phosphorylcholine Polymers
Barley
Fatty Ester Alkoxylates
Ginger
Glucosamine
Methacrylate Ester Monomers
Methicones
Portulaca Oleracea
Radish Root
Sage
Zeolites

EXPERT PANEL MEETING
DECEMBER 6-7, 2021

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: December 3, 2021

SUBJECT: Draft Report: Safety Assessment of Acrylamide/Acrylate Copolymer Ingredients as Used in Cosmetics (draft prepared for the December 6-7, 2021, meeting)

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

Introduction – As not all ingredients in the report have all the listed function, rather than stating "Other reported functions for this ingredient group" it would be clearer to state: "Other reported functions for ingredients in this group".

Chemical Properties – Please identify the copolymers for which the molecular weight information was received.

Method of Manufacture – Somewhere in the report it should be noted that 2-amino-2-methyl-1-propanol is another name for Aminomethyl Propanol which has a CIR safe conclusion (report published in 2009).

Cosmetic Use – In the description of the EU regulations, it should be made clear that the individual copolymers are not specifically listed in Annex III. Some of the copolymers are linked to Annex III entry 66, Polyacrylamide, and some of the copolymers are linked to Annex III entry 61, monoalkylamines, monoalkanolamines and their salts. The description for the monoalkylamines and monoalkanolamines needs to be corrected. The purity requirement is a "minimum" purity of 99% (it currently states "maximum"). It should be made clear that the secondary amine content of 0.5% applies to the finished product, not the ingredients.

Short-Term, Dermal – If microscopic examinations were completed, "pathological" should be corrected to "histopathological". As various endpoints were evaluated, the following sentence needs to be revised: "No relevant test item-related effects were evaluated throughout the study."

(please change “were evaluated” to “were observed”).

Genotoxicity, In Vitro, AMP-Acrylates/C1-18 Alkyl Acrylate/C1-8 Alkyl Acrylamide Copolymer – Please correct: “was performed was performed”

Ocular Irritation, Summary – Please add the word “assay” or “study” in the following (occurs in the Ocular Irritation section and the Summary) “ocular irritation performed in…”

Summary – It would be helpful if the Summary named the specific ingredients for which monomer levels were reported, and those that have limitations under the EU cosmetic regulations.

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

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

DATE: December 3, 2021

SUBJECT: Draft Tentative Report: Safety Assessment of Acryloyloxyethyl Phosphorylcholine Polymers as Used in Cosmetics (draft prepared for the December 6-7, 2021, meeting)

The Personal Care Products Council respectfully submits the following comments on the draft tentative report, Safety Assessment of Acryloyloxyethyl Phosphorylcholine Polymers as Used in Cosmetics.

Composition/Impurities, Polyphosphorylcholine Glycol Acrylate – "methyl (0.15%)" should be "methylparaben (0.15%)"

Cytotoxicity – If these studies concern anti-carcinogenicity, they should be presented in the Anti-Carcinogenicity section. The sentence under the Cytotoxicity heading is not needed if they are just studies of cytotoxicity.

Summary – Please revise "methyl p-hydroxybenzoate" to "methylparaben". Please correct: "Cytotoxicity as not observed" ("as" should be "was"). Please correct: "male 3 Wister rats".

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

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

DATE: December 3, 2021

SUBJECT: Draft Final Report: Safety Assessment of Barley-Derived Ingredients as Used in Cosmetics (draft prepared for the December 6-7, 2021, meeting)

The Personal Care Products Council respectfully submits the following comments on the draft final report, Safety Assessment of Barley-Derived Ingredients as Used in Cosmetics.

Key Issue
Discussion – The non-cosmetic use section indicates that malt extract from barley and other grains is GRAS. The Discussion incorrectly states that barley is GRAS. Generally, food ingredients/additives are considered GRAS, not food itself. The following sentence in the Discussion needs to be revised as it incorrectly indicates that food is GRAS: "While seeds of barley are generally recognized as safe (GRAS) for food use, other barley plant parts are not GRAS for food use, and safety test data are lacking"

Additional Considerations
Toxicological Studies – The following suggests that there are malt ingredients included in this report: "Many of the barley-derived seed and malt ingredients that are addressed in this safety assessment…"

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

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

DATE: December 3, 2021

SUBJECT: Draft Report: Safety Assessment of Fatty Ester End-Capped Alkoxylates as Used in Cosmetics (draft prepared for the December 6-7, 2021, meeting)

The Personal Care Products Council respectfully submits the following comments on the draft report, Safety Assessment of Fatty Ester End-Capped Alkoxylates as Used in Cosmetics.

Introduction; Chemistry; Summary – The Introduction and Chemistry sections suggest that all the ingredients in this report have a glycerin core. The Summary correctly states that most of the ingredients in this report "are glyceryl fatty acid esters with ethylene glycol repeat units:"

Chemistry – It would be helpful if the boundaries for the structures of the ingredients in this report were clearly stated. All but one of the ingredients have fatty acids with a chain length of 18. What are the smallest and largest fatty acid chain lengths of ingredients that could be considered for addition to this report?

Impurities – Please revise: "No further impurities data were not found in the published literature"

Cosmetic Use – Please complete the name of the ingredient used at 0.7% in eye lotion (it currently states "PEG-12 Glyceryl" it should be "PEG-12 Glyceryl Dimyristate").

Summary – The last paragraph states that minimal data on toxicokinetics were made available. There were no toxicokinetic data in the report. Only information on chemical and physical properties that indicate that dermal penetration would be minimal.

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Executive Director - Cosmetic Ingredient Review

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

DATE: December 3, 2021

SUBJECT: Draft Report: Safety Assessment of *Zingiber officinale* (Ginger) – Derived Ingredients as Used in Cosmetics (draft prepared for the December 6-7, 2021, meeting)

The Personal Care Products Council respectfully submits the following comments on the draft report, Safety Assessment of *Zingiber officinale* (Ginger) – Derived Ingredients as Used in Cosmetics.

Introduction – In the following statement: "the ingredient that is being tested in not clearly identified", please correct "in" to "is".

Cosmetic Use – The word "ingredients" is missing from the following: "some of these ginger-derived are used in cosmetic sprays". The word "in" is missing from the following: "Root Oil is reportedly used pump spray".

Chronic, Zingiber Officinale (Ginger) Root Powder – An observation period, which generally refers to a period after dosing has stopped, is not mentioned in the description of the 12-month study described in reference 42. If there was no observation period, it would be clearer to state "during the study" or "during the treatment period". Were the statistically significant differences observed in hemoglobin, white blood cell, neutrophil, lymphocyte, cholesterol, triglyceride, and glucose numbers increases or decreases?

Developmental and Reproductive Toxicity, Zingiber Officinale (Ginger) Rhizome Extract – Please check the time of exposure for the post-implantation study. It is unlikely that the post-implantation group of mice were treated 20 days before mating.

Immunomodulatory Effects – Please add the word "be" to the following: "they may helpful in addressing".

Dermal Irritation and Sensitization – Please identify the *in vitro* dermal irritation tests used in the text.

Ocular Irritation – Please correct “as” to “was” in the following: “The test article as considered to be non-irritating.”

Spice Allergy in Spice Sensitive Patients – Please correct “Aniseed” to “Anise seed”.

Summary – The first “these” in the following should be “the”: “these majority of these ingredients”. As there are two different ginger oils described in this report (fixed and essential) “fixed ginger essential oil” needs to be corrected to “fixed ginger oil”. Please provide the units for 2000 stated for the 28-day gavage study.

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Executive Director - Cosmetic Ingredient Review

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

DATE: December 3, 2021

SUBJECT: Draft Report: Safety Assessment of Glucosamine Ingredients as Used in Cosmetics (draft prepared for the December 6-7, 2021, meeting)

The Personal Care Products Council respectfully submits the following comments on the draft report, Safety Assessment of Glucosamine Ingredients as Used in Cosmetics.

Dermal Penetration, Glucosamine HCl – Did reference 24 provide any information as to why the flux of the cubic phase was greater than the other forms of Glucosamine HCl?

Dermal Penetration, Human, Glucosamine - The following is not a complete sentence: "The penetration of a 10% Glucosamine Sulfate cream into the synovial fluid of patients with knee osteoarthritis (134 subjects/group)."

ADME, Animal, Oral, Glucosamine HCl and Glucosamine Sulfate; Summary - Although the authors may have stated that "[^{14}C]Glucosamine quickly entered into all tissues", unless they did something to confirm it was glucosamine - all they should have said was that the ^{14}C from the labeled glucosamine entered all tissues including cartilage.

Short-Term, Oral, Glucosamine HCl – Please correct "8 rats/species/group" to "8 rats/strain/group"

Anti-Genotoxicity, In Vitro, Acetyl Glucosamine and Glucosamine – In the following sentence, please delete "control" after vehicle. "Control cells were treated with the vehicle control (PBS) and hydrogen peroxide."

Effects on Pigmentation, Human – Please revise: "By all parameters measured, the Acetyl Glucosamine and niacinamide formulation regimen was significantly ($p < 0.05$) caused a more pronounced decrease in detectable areas…"

Summary – In the third paragraph, delete “z” in “zwas”. In the description of the mouse DART study, please also indicate what happened with the 8-week-old mice. In the following, please change “on” to “with”: “The reduction of facial hyperpigmentation after topical treatment on Acetyl Glucosamine….”

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

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

DATE: December 3, 2021

SUBJECT: Re-review for Panel Consideration: Safety Assessment of Methacrylate Ester Monomers as Used in Cosmetics (draft prepared for the December 6-7, 2021, meeting)

The Personal Care Products Council respectfully submits the following comments on the re-review report, Safety Assessment of Methacrylate Ester Monomers as Used in Cosmetics.

In several places in this report the following is used: "Harlan Sprague-Dawley (C3H/HeNHsd strain) mice". Sprague-Dawley is an outbred rat strain. In this case "Harlan Sprague-Dawley" is describing the company from which the mice were purchased. It is not necessary to include this information in the CIR report. Only the strain should be stated. If it is left if the report, it should be made clear that "Harlan Sprague-Dawley" is the vendor.

Other Safety Assessments – This subsection does not belong under chemistry. The conclusion of the RIFM assessment should be stated: "All endpoints were cleared using target data, read-across, and/or TTC."

Acute, Dermal, Trimethylolpropane Trimethacrylate – Please revise: "All rats gained weight over of the study period."

Acute, Oral, Lauryl Methacrylate – The following is not a complete sentence: "Similar incidences of red and white foci on the lung surface of the experimental and control rats."

Short-Term, Dermal, Triethylene Glycol Dimethacrylate – Please describe the radioactive label used in the study in which autoradiography was completed.

Short-Term, Dermal, Triethylene Glycol Dimethacrylate – The study cited to reference 23 appears to be the same study as that described in reference 43.

Short-Term, Oral, Butyl Methacrylate – Please revise: “The animals were gavaged with Butyl Methacrylate” as the word “gavage” is not a verb. Please change “chlorine” to “chloride”.

Short-Term, Oral, Butyl Methacrylate, HEMA - Please change “chlorine” to “chloride”.

Short-Term, Oral, Isobornyl Methacrylate – Please correct the units for the NOAEL value, which is stated as “mg/kg bw/day”, while the units for the rest of the study are stated as “g/kg bw/day”.

Subchronic, Oral, Lauryl Methacrylate – This is the only OECD 422 study in the Subchronic section. The other OECD 422 studies are presented in the Short-Term section. All OECD 422 studies should be presented in the same section.

Genotoxicity – Please summarize the genotoxicity studies in a table.

Genotoxicity, In Vitro, Glycol Dimethacrylate – In the chromosomal aberrations assay in human lymphocytes, what was the highest concentration with metabolic activation that was negative?

Genotoxicity, In Vitro, HEMA – Please correct (or clarify) “8e10%”

Genotoxicity, In Vitro, HEMA Acetoacetate – Please revise: “in accordance with to OECD TG 471”

Cytotoxicity, Butyl Methacrylate, Glycol Dimethacrylate, HEMA, and Triethylene Glycol Dimethacrylate – The units should be stated once or with each value (currently they are stated with 3 of 5 values).

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

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

DATE: December 3, 2021

SUBJECT: Draft Final Amended Report: Amended Safety Assessment of Dimethicone, Methicone and Substituted Methicone Polymers as Used in Cosmetics (draft prepared for the December 6-7, 2021, meeting)

The Personal Care Products Council respectfully submits the following comments on the draft final amended report, Amended Safety Assessment of Dimethicone, Methicone and Substituted Methicone Polymers as Used in Cosmetics.

Cosmetic Use – It would be helpful to revise the following, so it is clearer that it is the maximum concentration in the product that has increased, not the exposure: "incidental ingestion via lipstick formulations increased from 20% in 1999 to 71.3% in 2019, and incidental inhalation increased from 16% (in perfume sprays) in 1999 to 85% (in moisturizing sprays) in 2019".

Short-term, Inhalation, old report summary – It should be noted that this study was presented under a dermal subheading in the original CIR report. As no exposure concentration or dose was stated, it would also be helpful to give the description of the exposure from the original CIR report: "but the atomizer output was described as a thick fog that settled rapidly on the animals and the cage. The treatment was repeated 29 days later". It is not clear from the original CIR report if this was a 29-day study (with daily exposure), or a study with 2 exposures separated by 29 days.

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Executive Director - Cosmetic Ingredient Review

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

DATE: December 3, 2021

SUBJECT: Draft Tentative Report: Safety Assessment of *Portulaca oleracea*-Derived Ingredients as Used in Cosmetics (draft prepared for the December 6-7, 2021, meeting)

The Personal Care Products Council respectfully submits the following comments on the draft tentative report, Safety Assessment of *Portulaca oleracea*-Derived Ingredients as Used in Cosmetics.

Composition and Impurities – Reference 34 is not a correct citation for oxalate poisoning of sheep and goats eating *Portulaca oleracea*. The article is about nitrate/nitrite poisoning of sheep and goats that ate *Portulaca oleracea.* The ASPCA purslane page (reference 35) does not describe oxalate poisoning in dogs, cats and horses, it just cautions that because this plant species contains soluble calcium oxalates it would be toxic to dogs, cats and horses.

Acute; Table 4 – The information concerning the lack of sensitization in rabbits should be presented in the sensitization section.

Short-Term – In the description of the studies, it would be helpful to state all the endpoints that were examined not just the endpoints for which there were negative observations. Which hematological endpoints were increased (whether an increase is good or bad is dependent on the endpoint)?

Developmental and Reproductive Toxicity; Summary – Please be specific and state the days during gestation the rats were treated. Stating "at three different time frames during 21 d of gestation" is not sufficient.

Discussion – Rather than stating "anomalies" were observed, please be more specific. There were three studies that looked at testosterone levels in animals treated with *Portulaca oleracea*, no change was observed in one study and decreases in testosterone were observed in two studies.

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

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

DATE: December 3, 2021

SUBJECT: Draft Report: Safety Assessment of Radish Root-Derived Ingredients as Used in Cosmetics (draft prepared for the December 6-7, 2021, meeting)

The Personal Care Products Council respectfully submits the following comments on the draft report, Safety Assessment of Radish Root-Derived Ingredients as Used in Cosmetics.

Introduction – Please make it clear that not all the ingredients in the report have the listed functions. For example, only Leuconostoc/Radish Root Ferment Filtrate has preservative listed as a function.

Introduction – Please correct: "the terminology the International Nomenclature Committee (INC) terminology"

Method of Manufacture – As the definitions from the Dictionary are presented in this section, it is inappropriate to imply that "it is unknown if they apply to cosmetic ingredient manufacturing."

Photosensitization/Phototoxicity; Summary – The study described in reference 36 is an *in vitro* photoirritation study. The conclusion should state Leuconostoc/Radish Root Ferment Filtrate was not considered a "photoirritant" (in currently says "photosensitizer"). It should also state that the report indicated that the 11% concentration was considered significantly higher than use levels.

Summary – Please correct: "Most of the other reported are not considered cosmetic functions in the US". Please mention the genera of bacteria used for lactic fermentation that have GRAS status.

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

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

DATE: December 3, 2021

SUBJECT: Draft Tentative Report: Safety Assessment of *Salvia officinalis* (Sage)-Derived Ingredients as Used in Cosmetics (draft prepared for the December 6-7, 2021, meeting)

The Personal Care Products Council respectfully submits the following comments on the draft tentative report, Safety Assessment of *Salvia officinalis* (Sage)-Derived Ingredients as Used in Cosmetics.

Key Issue

It is not clear why the studies from the ECHA dossier are being presented under a "water". The composition section of the dossier states: "Essential oil of Salvia officinalis (Lamiaceae) obtained from leaves, flowers and stalks by steam distillation." It also states the 14 major constituents found in the oil:

1-isopropyl-4-methylbicyclo[3.1.0]hexan-3-one
DL-bornan-2-one
Cineole
(1S, 4S, 5R)-4-Methyl-1-(1-methylethyl)bicyclo[3.1.0]hexan-3-one
Camphene
Humulene
Pin-2(3)-ene
Caryophyllene
(1S-endo)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol
Pin-2(10)-ene
p-mentha-1,4-diene
Dipentene
L-born-2-yl acetate
7-methyl-3-methyleneocta-1,6-diene

Additional Considerations

Introduction – Please provide a reference for the neurotoxic potential of thujone.

Acute, Oral, Salvia Officinalis (Sage) Extract; Summary – Please check the LD_{50} value of 44,760 mg/kg. It is so much larger than the highest tested dose (5000 mg/kg), a dose that resulted in one death, if it is correct, it should be made clear that the LD_{50} is an extrapolation.

Anti-carcinogenicity – The materials and methods section of reference 46 indicates that the dose of 3 mg/kg was selected. This dose should replace "(concentration not provided)".

Summary – In the description of the 14-day reproductive toxicity study, please state the gestation day the embryos were collected (day 4).

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Executive Director - Cosmetic Ingredient Review

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

DATE: December 3, 2021

SUBJECT: Draft Tentative Amended Report: Safety Assessment of Zeolites as Used in Cosmetics (draft prepared for the December 6-7, 2021, meeting)

The Personal Care Products Council respectfully submits the following comments on the draft tentative amended report, Safety Assessment of Zeolites as Used in Cosmetics.

Composition/Impurities – Please correct: “are reported to be are very similar”

Cosmetic Use – Please correct: “indicate Zeolite is the only with reported concentration of use data”

Non-Cosmetic Use, old report summary – The meaning of the following is not clear: “aromatic separates dimension stones”

Acute; Summary – Please correct: “smerllerite” (it should be “smellerite”)

Repeated Dose Toxicity; Table 6 – In the text, it would be helpful to state how the kidneys and urinary bladder were affected. Please note (text and table) that in the monkey inhalation study there was a quartz positive control group, and that fibrosis was observed in the quartz group, but not in the Zeolite exposed group.

Developmental and Reproductive Toxicity; Summary – In the descriptions of the developmental toxicity studies, please state the time during gestation when the animals were treated.

Carcinogenicity – In the description of the IARC review, please describe the data on which the conclusion was based.

Carcinogenicity, Inhalation – If correct, please change “lids” to “eyelids”
Dermal Irritation and Sensitization – Please revise this section – it is the guinea pigs that are induced and challenged, not the Zeolite subtypes.