Personal Care Products Council
Committed to Safety, Quality & Innovation

October 16, 2013

Dr. Ruth Lunn
Director, ORoC, DNTP
NIEHS, P.O. Box 1233, MD K2-14
Research Triangle Park, NC 27709

RE: Nominations to the Report on Carcinogens; Request for Information (78 Federal Register 57868)

Dear Dr. Lunn,

The Personal Care Products Council[1] appreciates the opportunity to provide comments on the above referenced topic. The list of substances nominated for possible review for future editions of the Report on Carcinogens (RoC) includes materials that are of interest to the personal care products industry. This document provides information and relevant comments on several of the listed substances.

Coconut Diethanolamide

Coconut Diethanolamide (International Nomenclature Cosmetic Ingredient name: Cocamide DEA) is used as a surfactant, foam booster, and/or viscosity increasing agent in a variety of personal care products. Use information for this ingredient was compiled in 2011 in response to its review by the Cosmetic Ingredient Review.[2] The published CIR report is enclosed with this submission in response to NTP's request for information.[3] Coconut Diethanolamide was also reviewed by CIR in 1996 and 1986, and these reports are enclosed as well.[4]

[1] Based in Washington, D.C. the Council is the leading national trade association representing the global cosmetic and personal care products industry. Founded in 1894, the Council's more than 600 member companies manufacture, distribute and supply the vast majority of finished personal care products marketed in the U.S. As the makers of a diverse range of products that millions of consumers rely on every day, from sunscreens, toothpaste and shampoo to moisturizer, lipstick and fragrance, personal care products companies are global leaders committed to product safety, quality and innovation.

[2] The Cosmetic Ingredient Review (CIR) Expert Panel is an independent, non-profit scientific body that assesses the safety of ingredients used in cosmetics in the U.S. in an open, unbiased, and expert manner and publishes the results of its work in peer-reviewed scientific literature. More information is available at www.cir-safety.org.

[3] Fiume, M.M. et al. (2013) Safety Assessment of Diethanolamides as Used in Cosmetics. 32(suppl): 36S-58S

[4] Cosmetic Ingredient Review. (1996) Amended Final Report on the Safety Assessment of Cocamide DEA. Journal of the American College of Toxicology. 15(6):527-542; Cosmetic Ingredient Review. 1986. Final Report on the Safety Assessment of Cocamide DEA, Lauramide DEA, Linoleamide DEA, and Oleamide DEA. Journal of the American College of Toxicology. 5(5):415-454.

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We question the value of reviewing coconut diethanolamide for consideration for listing in the RoC. The NTP evaluated coconut diethanolamide in F344/N rat and B6C3F1 mouse bioassays, with a result of 'clear evidence of carcinogenic activity" in the mouse, and 'no evidence' in the rat. The positive results seen in the mouse bioassay were concluded to be due to the presence of free diethanolamine in the test material, as is discussed below. Diethanolamine has already been evaluated for listing in the RoC and was found not to meet the criteria for listing. Because the activity in the coconut diethanolamide bioassay was due to a contaminant that did not meet the criteria for RoC listing, it would follow that coconut diethanolamide would likewise not meet the criteria for listing.

Briefly, NTP conducted carcinogenicity bioassays in F344/N rats and B6C3F1 mice with coconut diethanolamide.[5] It was concluded that there was "clear evidence of carcinogenic activity" in male mice based on liver tumors and renal tubule tumors and in female mice based on liver tumors; there was 'no evidence' of carcinogenic activity in the rat bioassay. The test material was reported in the NTP technical report to contain 18.2% free DEA as a contaminant. The tumors observed in the coconut diethanolamide study were of the same type and occurred in the same sites as the tumors in the NTP's diethanolamine study. The NTP concluded that the tumors observed in the male and female mice administered coconut diethanolamide were associated with the concentration of free diethanolamine in the coconut diethanolamide. The report states "(t)here was clear evidence of carcinogenic activity in male B6C3F1 mice based on increased incidences of hepatic and renal tubule neoplasms and in female B6C3F1 mice based on increased incidences of hepatic neoplasms. These increases were associated with the concentration of free diethanolamine present as a contaminant in the diethanolamine condensate."[6]

Other diethanolamine condensates (lauric acid diethanolamine condensate, oleic acid diethanolamine condensate) were tested by NTP for carcinogenicity and the results were also consistent with the levels of free diethanolamine present in the test material (reported to be 0.83% and 0.19%, respectively)[7]. As with coconut diethanolamide, NTP attributed the weakly positive results seen with lauric acid diethanolamine to free diethanolamine in the test material ("some evidence of carcinogenic activity in female B6C3F1 mice based on increased incidences of hepatocellular neoplasms. These increases were associated with free diethanolamine, which was present as a contaminant of lauric acid diethanolamine condensate"). In the case of oleic acid diethanolamine , there was "no evidence of carcinogenicity" in B6C3F1 mice, and NTP noted the exposure to free diethanolamine was "the lowest concentration in any of the four studies."

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[5] TR-479 Toxicology and Carcinogenesis Studies of Coconut Oil Acid Diethanolamine Condensate (CAS No. 68603-42-9) in F344/N Rats And B6C3F 1 Mice (Dermal Studies)

[6] See footnote 5, page 55

[7] TR-480 Toxicology and Carcinogenesis Studies of Lauric Acid Diethanolamine Condensate (CASRN 120-40-1) in F344/N Rats and B6C3F1 Mice (Dermal Studies) http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr480.pdf; TR-481 Toxicology and Carcinogenesis Studies of Oleic Acid Diethanolamine Condensate (CASRN 93-83-4) in F344/N Rats and B6C3F1 Mice (Dermal Studies) http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr481.pdf

NTP went on to conduct a quantitative assessment of the association of incidence of hepatocellular neoplasms with diethanolamine exposure using the results of all of the above studies. The conclusion regarding statistical correlation between free diethanolamine exposure and liver tumors was summarized by NTP as follows: "The close agreement between observed and predicted rates strongly supports the conclusion that the liver neoplasm response in the diethanolamine study and the three diethanolamine condensate studies is determined primarily by the concentration of free diethanolamine."[8]

In 2002, diethanolamine was considered for possible listing in the RoC as "reasonably anticipated to be a human carcinogen". The recommendation from RG1, RG2, and the Board of Scientific Counselors RoC Subcommittee was not to list, as the listing criteria were not met. The vote against listing was 7-2 for RG1; 9-0 for RG2; and 8-1 for the RoC Board of Scientific Counselors.[9]

Since DEA did not meet the criteria for listing in the RoC, and free DEA was concluded by NTP to be responsible for the tumorigenic response of coconut diethanolamide in the NTP mouse bioassay, the evaluation of coconut diethanolamide would also not meet the criteria for listing. Therefore, it would not be of value for NTP to review coconut diethanolamide for possible listing in the RoC. We respectfully suggest that coconut diethanolamide not be reviewed for listing in a future edition of the Report on Carcinogens.

Botanical Ingredients

The National Toxicology Program ORoC is requesting information on several botanical ingredients, including Aloe vera whole leaf extract (*Aloe barbadensis* Miller), and *Ginkgo biloba* extract. Ingredients derived from these two botanicals are widely used within the cosmetic industry across a wide variety of product types.

Ingredients used in cosmetics which are derived from *Aloe vera* (a synonym of *Aloe barbadensis*) have been evaluated by the Cosmetic Ingredient Review (CIR) Expert Panel[10]. Information on use of the extracts in cosmetics was collected as part of the CIR review process. A report has been published in the *International Journal of Toxicology*[11], and is enclosed with this submission in response to NTP's request for information. The report provides detailed information regarding use of ingredients derived from *Aloe vera*, including product type and concentration of use.

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[8] See footnote 5, page 53

[9] http://ntp-server.niehs.nih.gov/ntp/htdocs/Liaison/111902.pdf

[10] The Cosmetic Ingredient Review (CIR) Expert Panel is an independent, non-profit scientific body that assesses the safety of ingredients used in cosmetics in the U.S. in an open, unbiased, and expert manner and publishes the results of its work in peer-reviewed scientific literature. More information is available at www.cir-safety.org.

[11] Cosmetic Ingredient Review. (2007) Final Report on the Safety Assessment of Aloe. International Journal of Toxicology 26(Suppl. 2):1-50.

Ginkgo biloba is also widely used within the cosmetic industry, and is on the CIR Priority List for review in 2014[12]. Detailed use information for cosmetics will be collected as a part of that process, and can be provided to NTP.

We are aware of testing done by NTP on specific extracts of the botanicals that are nominated for possible review for the RoC. If the botanical extracts are nominated for formal review by the RoC, we urge NTP to clearly define and limit the material to be reviewed to the substance that was tested in the NTP bioassays. The evaluation of botanical mixtures is inherently challenging due to the complex composition of the materials. Botanical composition is known to vary greatly due to factors such as sourcing location, time of harvest, and growth conditions, among others.[13] [14] Once harvested, different parts of the plant, such as leaves, flowers, stems, etc. may be extracted in the manufacture of the ingredient, and each would result in a product with a unique chemical composition. Extraction methods and conditions – i.e., choice of solvent, time and temperature – will also affect the composition of the final product. The results of testing conducted with a single extract cannot be extrapolated to other extracts from the same plant as the materials are likely to be significantly different in composition.

Aloe vera serves as a good example. The substance that is proposed for NTP review is "Aloe vera whole leaf extract (*Aloe barbadensis* Miller)", which is the material tested by NTP in 2-year drinking water studies in rats and mice[15]. The outcome of the NTP bioassay in rats was the finding of "clear evidence of carcinogenic activity of a nondecolorized whole leaf extract of Aloe vera in male and female F344/N rats based upon increased incidences of adenomas and carcinomas of the large intestine." (There was 'no evidence' of carcinogenicity in the NTP mouse bioassay). The NTP technical report describes the test material as being produced by grinding whole leaves of Aloe vera plants; all parts of the leaf are retained in the test material. Anthraquinones, which are known to be present in the latex portion of the leaf (present at the margins of the Aloe vera plant) and which have well recognized toxic properties, were not removed.

The NTP-tested material is not the same as the material used within the cosmetic industry. Removal of the anthraquinones is a significant difference between the NTP-tested material and cosmetic ingredients derived from aloe vera. The conclusion of the CIR safety assessment on aloe-derived ingredients (referenced above and enclosed) is that the ingredients derived from *Aloe barbadensis* [aloe vera] "are safe as cosmetic ingredients in the practices of use and concentrations as described in this safety assessment, if anthraquinone levels in the ingredient do not exceed 50 ppm". The Panel "considered the available data on the several Aloe Barbadensis extracts and found that anthraquinone levels are well understood and can conform to the industry-established level of 50 ppm."

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[12] http://www.cir-safety.org/supplementaldoc/2014-draft-priorities-memo

[13] Batista, R., Oliveira, M. (2010) Plant natural variability may affect safety assessment data. Regul. Toxicol. Pharmacol. 58(3 Suppl):S8-12.

[14] Harrigan, G.G., Glenn, K.C., Ridley, W.P. (2010) Assessing the natural variability in crop composition. Regul. Toxicol. Pharmacol. 58(3 Suppl):S13-20

[15] TR 577 Toxicology and Carcinogenesis Studies of a Noncolorized Whole Leaf Extract of Aloe Barbadensis Miller (Aloe Vera) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies) http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/TR577_508.pdf

Therefore, any conclusions drawn on the carcinogenicity of the Aloe vera whole leaf extract tested by NTP are not relevant to the aloe vera-derived ingredients used within the cosmetics industry. Aloe used by the cosmetics industry is processed to limit the level of anthraquinones to no more than 50 ppm. The finding of tumors in the large intestine in the F344/N rat bioassay has been postulated to be due to the presence of the anthroquinones aloin A and aloin B ("...anthrone C-glycosides aloin A and aloin B, found in the latex, are converted to aloe emodin-9-anthrone by bacteria present in the gastrointestinal tract of rats and humans, and sequentially oxidized to aloe-emodin, which is genotoxic and could be responsible for the reported tumours.")[16]

The example of *Aloe vera* also illustrates the importance of exposure route. Since bacteria in the GI tract is a necessary component of the postulated mechanism, the exposure route (oral *vs.* dermal) would be of great significance in the event anthraquinones were present. NTP has acknowledged the lack of relevance of the results of the drinking water bioassay to dermal use, noting that "(a)pplying Aloe vera gel on the skin is not likely to cause harm."[17]

In summary, *Aloe vera* and *Gingko biloba* are important botanicals in the personal care product industry. If the botanical nominations to the RoC proceed to the formal review stage, it is critically important that the substance(s) being evaluated is clearly defined, and that the result of the review is not extrapolated to different extracts from the same plant. Differences in material composition are critically important to assessing the relevance of the data.

Polyacrylates

Another nomination of interest is polyacrylates. The scope of the polyacrylates nomination should be narrowed, and specific polyacrylates of interest should be identified, to provide for a meaningful review if a formal nomination goes forward.

A large number of polyacrylate ingredients are used in personal care products. The ingredients represent a wide variety of different structures and functions. Examples include carbomers (synthetic, high molecular weight, nonlinear polymers of acrylic acid, cross-linked with a polyalkenyl polyether; carbomers function as emulsifying agents); acrylate co-polymers (copolymers of two or more monomers consisting of acrylic acid, methacrylic acid or one of their simple esters; commonly function as a binder, film former, and/or viscosity-increasing agent); and crosslinked alkyl acrylates (crosslinked polymers in which the co-monomers consist of at least one of the following: acrylic acid, sodium acrylate, methacrylic acid, or alkyl acrylate; functions in cosmetics include absorbents, film formers, emulsion stabilizers, viscosity increasing agents, and suspending agents). Polyacrylates include cross-linked as well as linear compounds, and each of the listed categories includes a large number of distinct ingredients. The Cosmetic Ingredient Review has reviewed and published reports on Acrylates

[16] Grosse Y. et al. (2013) Carcinogenicity of some drugs and herbal products. Lancet Oncology 14:807-808.
[17] http://www.niehs.nih.gov/health/materials/aloe_vera_508.pdf

Copolymer and 33 Related Cosmetic Ingredients[18]; Carbomers-934, -910, -934P, -940, -941, and -962[19]; and Crosslinked Alkyl Acrylates [23 ingredients].[20] The reports are enclosed with this submission.

Polyacrylates have a vast array of uses in a variety of industries outside of cosmetics. Examples include neutralized cross-linked polyacrylic acids used in diapers, elastic sealants, cable wrap, and horticultural applications; polyacrylate resins and a variety of acrylic dispersions used as adhesives; polyelectrolyte polyacrylates used in soap, detergent and cleaning products; and sodium polyacrylate used for its super-absorbancy, functioning as a sequestering agent, thickening agent, or coating; also used as an approved secondary direct food additive in food for human consumption (21CFR173.73).

We believe that the nomination of 'polyacrylates' as a substance for review for the RoC is entirely too broad and undefined. The range of substances falling under this heading is great even within the personal care product industry. The range of structures and functions becomes much broader as other industries are considered.

It is clear from the above that the term 'polyacrylates' needs to be better defined and its scope narrowed if a formal nomination is made for RoC review.

Thank you for your attention to these issues.

Sincerely,

[Redacted]

Linda Loretz, Ph.D., DABT
Director, Safety and Regulatory Toxicology

[18] Cosmetic Ingredient Review. (2002) Final Report on the Safety Assessment of Acrylates Copolymer and 33 Related Cosmetic Ingredients. Intl. J. Toxicol. 21(Suppl. 3):1-50.
[19] Cosmetic Ingredient Review. (1982) Final Report on the Safety Assessment of Carbomers-934, -910, -934P, -940, -941, and -962. J. Amer. Coll. Toxicol. 1(2):109-141.
[20] Cosmetic Ingredient Review. (2011) Crosslinked Alkyl Acrylates as Used in Cosmetics. Final report. http://www.cir-safety.org/sites/default/files/crossl092011final_for%20posting.pdf