



NATURAL RESOURCES DEFENSE COUNCIL

SENT BY EMAIL AND MAIL

October 18, 2013

Dr. Antonia Mattia
Office of Food Additive Safety
U.S. Food and Drug Administration
Mail Stop HFS-255
College Park, MD 20740
Email: antonia.mattia@fda.hhs.gov

Re: Comments on GRN#466: GRAS exception notification polyglycerol polyricinoleic acid (PGPR) for use in condiments and spreads, flavors, and snacks (cheese powders)

Dear Dr. Mattia:

NRDC respectfully submits these observations on FDA's GRAS exception notification for polyglycerol polyricinoleic acid (PGPR). We appreciate FDA's practice of posting the additive manufacturer's notice on its website and hope it will consider these comments before taking final agency action.

In GRN#466, McCormick & Company, Inc. notified the Office of Food Additive Safety that it had determine that the use of polyglycerol polyricinoleic acid (PGPR) as an emulsifier for use in condiments and spreads, flavors, and in the cheese powders in snacks was "generally recognized as safe" (GRAS). The company expects these products to be consumed by the general population.¹

We have concerns with the scientific procedures McCormick's has used to justify its claim that PGPR is GRAS for its intended use. Chief among our concerns is the company's flawed calculation of the cumulative estimated daily intake (EDI) based on known uses; if calculated following FDA's guidance, this value would be well above the established acceptable daily intake (ADI). Furthermore, there appears to be additional uses never disclosed to the agency which will bring the EDI to values even greater than the ADI.

¹ GRN #466. GRAS Exemption Notification Polyglycerol polyricinoleic acid (PGPR) for Use in Condiments and Spreads, Flavors, and Snacks (Cheese Powders). Received March 1, 2013. U.S. Food and Drug Administration Office of Food Additives Safety. Page 3. See http://www.accessdata.fda.gov/scripts/fcn/gras_notices/GRN000466.pdf

FDA clearly indicates that when the EDI is greater than the ADI the substance is not shown to be safe.² In this situation, the substance should not be GRAS and FDA, not the notifier, should make the safety decision through a food additive petition. NRDC also has concerns that outdated scientific information was used as a basis for evaluating the toxicity of PGPR and that the developmental toxicity of this compound, which is a crucial concern, is untested.

Therefore, FDA should issue a letter to McCormick saying that the notice does not provide a sufficient basis for a GRAS determination.

More details about our concerns are below.

Additive manufacturer's expanded use in notice

McCormick has determined that PGPR is GRAS under the conditions of intended use in three food categories: condiments and spreads at levels of 0.28% by weight, flavors at levels up to 0.1% by weight, and in cheese powders in snacks at levels up to 0.15% by weight of the snack.³

McCormick reports that there are an additional four GRAS exemption notifications for PGPR used as emulsifier in chocolate, margarine, low fat margarine, spreads, creamers, dairy analogs and vegetable fat coatings, and in the formulation of color additives intended for use in processed foods. However, NRDC has identified 1,340 food products currently available in the U.S. market listing PGPR as an ingredient in additional food categories including cereal, candy, nutrition bars, cookies and crackers among others.⁴ It is unclear whether these additional uses are covered by already reviewed GRNs or the one submitted by McCormick.

Concerns with this notice that are common to others

NRDC has serious reservations about the GRAS program administered by FDA. First, we believe that Congress intended that the food additive petition, and not the GRAS exemption, should be the primary mechanism to determine the safety of new chemicals added to food under the Food Additives Amendment of 1958. The agency has wrongly allowed industry to expand the loophole so it has essentially swallowed the law.

Second, although we recognize the perceived benefits of agency review through the voluntary GRAS notification program, we think it is inappropriate for FDA to be running this program based on nothing more than a proposed rule. While the agency may describe its "no question" letters as informal opinions that are not agency actions, in practice, these letters are used as a stamp of FDA approval. The letters thus meet the definition of an agency action.

Finally, we urge FDA to proactively and formally invite comment to its proposed exemption notifications and to respond to concerns raised. The public, including competitors, academic researchers, non-governmental organizations, and other governments, can add value to this decision-making process and identify issues the agency might have missed. This is especially important given the conflicts of interest inherent in allowing additive manufacturers themselves to

² Alger, HM et al. Perspectives on How FDA Assesses Exposure to Food Additives When Evaluating Their Safety: Workshop Proceedings. 2013. Comprehensive Reviews in Food Science and Food Safety 12:90-119. Page 93

³ GRN #466, page 2

⁴ Based on proprietary database by the Gladson, Inc. using the March 15, 2013 version. See <http://www.gladson.com>.

make safety decisions, and it will ameliorate to at least a small extent the reality that the agency is under-resourced and without adequate expertise in its staff on the wide range of scientific issues often involved.

This particular notice also has problems that are common to many in the program. These problems include:

1. The McCormick analysis ignores FDA's guidance on the conduct of a proper safety assessment. Specifically, it does not assign a Concern Level that is essential to determining what minimum testing should be conducted according to FDA's recommendations. In fact, based on the information provided in the notice, the proper Concern Level for PGPR would be 3 – the highest level.
2. NRDC questions whether the scientist who made the safety assessment is qualified to make the decision because of financial conflicts of interest.⁵ This scientist is a consultant representing the additive manufacturer that will financially benefit for the decision. These conflicts of interest are severe enough that, based on FDA's guidance,⁶ he appears to have a disqualifying financial conflict that would render him ineligible to advise the agency if it sought guidance on the issue from outside experts. Therefore, he should not be making the final safety decision. Regardless of his professional expertise and best of intentions, the science on conflicts of interest and the 2009 Institute of Medicine report make clear that conflicted experts may not fully and objectively capture possible contradictory data, describe gaps or flaws in the available data, and fairly characterize the scientific community's assessment on the use of this additive in food.⁷

Concerns with specific issues in this notice

McCormick's calculation of the EDI for uses described in this notification and the calculation of the cumulative EDI including previous GRAS notifications is flawed and confusing.

- A) Calculation of EDI did not follow FDA's guidance. The notice neither provides information on average and 90th percentile exposure nor identifies the high consumer group. It simply calculates the EDI by adding the daily intake of PGPR for the proposed three uses (spreads and condiments, flavors and snacks) and divides it by body weight. The result is 4.17 mg/kg bw/day.⁸ There is no evidence that McCormick performed a dietary exposure assessment to calculate the 90th percentile exposure as recommended by the FDA.⁹
- B) Calculation of EDI did not consider subpopulations: The notice fails to consider subpopulations, which is particularly important for this additive because one of the foods where PGPR will be used is in snacks (cheese powder), which are foods particularly

⁵ Neltner, TG et al. Conflicts of Interest in Approvals of Additives to Food Determined to Be Generally Recognized as Safe. Out of Balance. Journal of the American Medical Association. Internal Medicine. 2013. Published online August 07, 2013. doi:10.1001/jamainternmed.2013.10559

⁶ U.S. Food and Drug Administration. Guidance for the public, FDA advisory committee members, and FDA staff on procedures for determining conflicts of interest and eligibility for participation in FDA advisory committees. 2008. See

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125646.pdf>

⁷ Conflicts of interest in medical research, education and practice. Institute of Medicine. 2009. National Academies Press

⁸ GRN #466, page 11

⁹ U.S. Food and Drug Administration. Guidance for Industry: Estimating Dietary Intake of Substances in Food. Section IV. Modeling Intake Analysis, Subsection E. Upper Percentile Estimates. August 2006. See <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm074725.htm#chro>

popular among children and adolescents. In fact, the previous GRNs for use in chocolate and chocolate-type confectionary showed that these subpopulations consume the most PGPR-containing foods. Therefore, the calculated EDI is flawed for using the body weight of an adult and ignoring the groups that are most like high consumers.

- C) Calculation of cumulative EDI was flawed: It appears that McCormick may have “cherry-picked” (i.e. used a bias selection of evidence for) the EDI’s from previous GRNs to keep the cumulative EDI below the established ADI.
- 1) McCormick did not use the 90th percentile EDI for the use of PGPR in chocolate of 4.7 mg/kg bw/day reported in GRN #9.¹⁰ Instead, it chose the less protective average EDI of 2.4 mg/kg bw/day for the same group. The selection of the lower EDI allowed the calculated cumulative EDI to stay below the ADI of 7.5 mg/kg bw/day.¹¹ The company does not provide any explanation its decision to vary from FDA’s recommendation.
 - 2) Even if McCormick’s calculations had used an average EDI, the company also erred in omitting the EDI from chocolate and chocolate-type confectionery calculated in GRN# 266¹²: average of 1.8mg/kg bw/day for a child and 0.8mg/kg bw/day for an adult. GRN# 266 also included a 2x average calculation (3.7mg and 1.5mg/kg bw/day for child and adult, respectively). Once again, this shows that children are likely to consume more PGPR per body weight.¹³

NRDC is also concerned about the use of the Annual Volume Intake Method for the PGPR exposure calculation. This calculation is well established for estimating exposure to flavors, but this is not a flavor. FDA does not recommend this method for non-flavor direct additives such as PGPR. FDA guidance clearly established that “*OFAS estimates upper percentile intakes of substances in the diet to account for individuals who are considered “high level” consumers of specific foods that contain these substances.*” “*OFAS typically uses the 90th percentile intake estimates (based on 2- or 3-day survey data) to represent long-term or “lifetime averaged” daily intake estimates, in large part, because of the conservatism built into the intake estimates.*”¹⁴ FDA reiterated this approach in 2011.¹⁵

Beyond the concerns with the EDI, NRDC questions some of the toxicology data presented in this notice. It appears, McCormick did not perform any new toxicology testing, rather it relied upon safety data included in previous GRNs and published articles. The safety data reported in the previous GRNs are in fact quite outdated and limited with regards to developmental studies; they

¹⁰ GRN #9. GRAS Notification for Polyglycerol Polyricinoleic Acid (“PGRP”) Exemption Claim. Received October 22, 1998. U.S. Food and Drug Administration Office of Food Additives Safety. Page 29. See http://www.accessdata.fda.gov/scripts/fcn/gras_notices/grn000009.pdf

¹¹ JECFA. Toxicological evaluation of certain food additives with a review of general principles and of specifications (Seventeenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series. No. 53, 1974. WHO Technical Report Series, No.539, 1974 and corrigendum.

¹² GRN #266. GRAS Notification for Polyglycerol Polyricinoleate (PGPR) in Vegetable Fat Coatings. Received November 13, 2008. U.S. Food and Drug Administration Office of Food Additives Safety. Page 55. See http://www.accessdata.fda.gov/scripts/fcn/gras_notices/grn000266.pdf

¹³ The scientist’s omission may be explained by the note: “vegetable coatings using the same concentration limits as noted for chocolate in GRN 000009”. However, the EDI calculated in GRN# 9 was for chocolate candy, while the one in GRN#266 was for chocolate and chocolate-type confectionery.

¹⁴ U.S. Food and Drug Administration. Guidance for Industry: Estimating Dietary Intake of Substances in Food. Section IV. Modeling Intake Analysis, Subsection E. Upper Percentile Estimates. August 2006. See <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm074725.htm#chro>

¹⁵ Alger et al

are derived from studies conducted by a single company (Unilever) in the 1950s and 1960s and only published the year (1998) of the first GRAS notification, GRN# 9, was submitted to FDA. Only three of the five papers provide detailed information about the studies; the other two, the human study and the three-generation reproduction study in Wistar rats, are provided only as summaries of the data and do not provide the details necessary for scientific review of the safety assessment.^{16, 17}

It is clear that none of the studies followed FDA's "Redbook" recommendations. For instance, GRN# 9 states "*The No Observed Adverse Effect Level from the most sensitive study, the multigeneration reproductive study, was 1.5% (equivalent to 750mg/kg bw/day), the only level tested,*"¹⁸ unlike the FDA recommended 3-5 doses¹⁹. The agency reiterated these preferred approaches in 2011.²⁰ Similarly, the human study cited was also conducted between 1964 and 1965; although some of the individuals had altered blood chemistry (increased bilirubin, decreased albumin), the study concluded that the effects were not associated with the ingestion of PGPR without further explanation.²¹

Importantly, we also note that developmental studies are altogether missing; this data gap is particularly important because, as we mentioned above, children and adolescents are consuming the highest levels of PGPR.

Lastly, we want to bring to FDA's attention that the European Food Safety Authority is currently reviewing the safety of PGPR.

Appendix A is a summary of the studies described in McCormick's GRAS notification.

Conclusion

In conclusion, it is clear that children and teenagers are the high consumers of PGPR, a fact stated in the other GRNs. The use of the average EDI instead of the 90th percentile is inconsistent with FDA guidance. All known uses of PGPR do not appear to have been added for the EDI, and if they had, the EDI would have exceeded the established ADI. Therefore, the claim that PGPR is GRAS for the intended uses is incorrect."

¹⁶ Wilson R, Smith M. A three-generation reproduction study on polyglycerol polyricinoleate (PGPR) in Wistar rats. [Food Chem Toxicol](#). 1998 Sep-Oct; 36(9-10):739-41.

¹⁷ Wilson R, Smith M. Human studies on polyglycerol polyricinoleate (PGPR). [Food Chem Toxicol](#). 1998 Sep-Oct; 36(9-10):743-5.

¹⁸ GRN# 9, page 31

¹⁹ U.S. Food and Drug Administration. Guidance for Industry and Other Stakeholders. Toxicology Principles for the Safety Assessment of Food Ingredients. *Redbook 2000*. Chapter IV.B.1. General Guidelines for Designing and Conducting Toxicity Studies. Section IV. Experimental Design, Subsection C. Dose Groups. November 2003. See <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm078315.htm>

²⁰ Maffini, MV et al. Enhancing FDA's Evaluation of Science to Ensure Chemicals Added to Human Food Are Safe: Workshop Proceedings. 2011. *Comprehensive Reviews in Food Science and Food Safety* 11:321-341. Page 328.

²¹ GRN# 9, page 117

Please do not hesitate to call or email with questions. I can be reached at 202-513-6244 and mmaffini@nrdc.org.

Thank you for your prompt attention to this request.

Sincerely,

A handwritten signature in black ink that reads "Maricel Maffini". The signature is written in a cursive, flowing style.

Maricel Maffini, Senior Scientist
Natural Resources Defense Council, Inc.
1152 15th Street NW, Suite 300
Washington, DC 20005
202-513-6244
(202) 289-1060 FAX
mmaffini@nrdc.org

Appendix A: Comparison of studies recommended by FDA for Concern Level 3 additives to those described in the GRAS notification

Appendix A

Comparison of studies recommended by FDA for Concern Level 3 additives to those described in the GRAS notification

FDA recommend type of study	Type of publication ²	Year of publication	Year study conducted	Study details available	Redbook compliant ³	GLP compliant ⁴
Genetic toxicity tests	None	None	None	No	N/A	N/A
Short-term toxicity tests with rodents ^{5,6}	A, C	1998 (review)	1950s, 1960s	Some details in GRN#9	No	No
Subchronic toxicity studies with rodents ^{5,6}	A, C	1998 (review)	1950s, 1960s	Some details in GRN#9	No	No
Subchronic toxicity studies with non-rodents ^{5,6}	A	None	1950s, 1960s	In GRN# 9	No	No
One-year toxicity studies with non-rodents ⁶	None	None	None	No	N/A	N/A
Chronic toxicity or combined chronic toxicity/carcinogenicity studies with rodents ⁶	A, C	1998	1950s, 1960s	Only a summary published. Some details in GRN#9	No	No
Carcinogenicity studies with rodents	A, C	1998	1950s, 1960s	Yes	No	No
Reproduction studies ⁶	A, C	1998	1950s, 1960s	Only a summary published. Some details in GRN#9	No	No
Developmental toxicity studies ^{6,7}	None	None	None	No	N/A	N/A
Metabolism and pharmacokinetic studies ⁷	A, C	1998	1950s, 1960s	Yes	No	No
Humans studies ⁷	A, C	1998	1950s, 1960s	Only a summary published. Some details in GRN#9	No	Not applicable

¹ FDA. 2006. Guidance for Industry. Summary table of recommended toxicological testing for additives used in food. See

<http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm054658.htm>

² (A) unpublished, (B) published but not peer reviewed, (C) peer-reviewed and published, or (D) conducted by a government agency

³ FDA. 2000. Toxicological principles for the safety assessment of food ingredients. See www.fda.gov/downloads/Food/GuidanceRegulation/UCM222779.pdf.

⁴ 21 C.F.R. Part 58.

⁵ If needed as preliminary to further study.

⁶ If indicated by available data or information.

⁷ Including screens for neurotoxicity and immunotoxicity (available in 1993 Draft Redbook II).