

August 10, 2017

Jeannie Perron, JD, DVM  
Covington & Burling LLP  
One City Center, 850 Tenth Street, NW  
Washington, DC 20001-4956

Re: GRAS Notice No. AGRN 22

Dear Dr. Perron,

The Food and Drug Administration (FDA, we) completed our evaluation of AGRN 22. We received Royal Canin U.S., Inc.'s ("Royal Canin" or "the notifier") notice on July 7, 2016. This notice was filed on August 3, 2016 under CVM's GRAS Notification Pilot Program. Royal Canin submitted an amendment dated April 17, 2017 that clarified what information is considered confidential business information.

The notified substance is Marigold extract containing lutein that is derived from marigold flower petals of *Tagetes erecta* L. (also known as Aztec Marigold) by the process of extraction with hexane. This notice informs us of Royal Canin's view that the notified substance is generally recognized as safe (GRAS), through scientific procedures, for use as a nutritional source of the antioxidant lutein in the diets and treats of dogs and cats at levels not to exceed 5 milligrams lutein per 1000 kilocalories of metabolizable energy (ME).

As a part of the GRAS notice, Royal Canin provides a report of a panel of individuals (the GRAS panel) who evaluated the data and information that are the basis for the notifier's GRAS conclusion. The notifier considers the members of its GRAS panel to be qualified by scientific training and experience to evaluate the safety of the notified substance under its intended conditions of use. The conclusion of the GRAS panel, that the notified Marigold extract containing lutein is safe for its intended use, is based on the data and information provided by the notifier including data and information compiled from literature and results from unpublished studies.

FDA has evaluated the information that Royal Canin discusses in its GRAS notice and amendment as well as other data and information that are available to the Agency. As discussed more fully below, the notice does not provide a sufficient basis for a conclusion that Marigold extract containing lutein is GRAS under conditions of its intended use as a nutritional source of the antioxidant lutein in the diets and treats of dogs and cats at levels not to exceed 5 milligrams lutein per 1000 kilocalories of ME.

#### **Data and information that Royal Canin U.S., Inc. presents to support its GRAS conclusion**

Royal Canin describes the Latin binomial name and plant part for the source material, composition information on extract derived from marigold flower petals of *Tagetes erecta* L., method of manufacture, specifications, analytical methods, batch analysis for impurities and contaminants, stability of the marketed product and pet food containing the marketed product, and homogeneity of pet food containing Marigold extract.

To address utility, Royal Canin provides a description of the ubiquitous nature of carotenoids, including lutein, in plant-based foods; the function of lutein as an antioxidant generally; and the functionality of lutein as an antioxidant in dog and cat diets by supporting the immune response and reduction of exercise-induced oxidative damage.

To address target animal safety of the intended use of Marigold extract containing lutein, the notifier submitted a risk assessment on the constituents of Marigold extract containing lutein and an assessment of the components of the market formulation (Cuatroxan®) containing the Marigold extract containing lutein. The notifier addressed the safety of lutein/zeaxanthin together based on their similarities in chemical structure and toxicological profile. The risk assessment conducted by the notifier for lutein/zeaxanthin is based on reports and evaluations conducted by authoritative bodies such as the Joint Expert Committee for Food Additives (JECFA), the European Food Safety Authority (EFSA) and the National Research Council (NRC). From the JECFA evaluation, the notifier cites acute, short-term, long-term, reproductive, and ocular toxicity studies, and studies evaluating the immune system in cats and dogs. The notifier also cites the Acceptable Daily Intake (ADI) for lutein/zeaxanthin of 0-2 mg/kg bw/day, and 1 mg/kg bw/day, established by JECFA and EFSA, respectively.

#### **FDA's evaluation of the data and information in Royal Canin U.S., Inc.'s notice and other data and information available to FDA**

##### Manufacturing Chemistry:

Based on the information contained in the notice and amendment submitted by Royal Canin and other information available to the Agency, CVM has questions on the identity, method of manufacture, and specifications for the notified substance.

1. The notice does not provide Royal Canin's specifications that suppliers of Marigold extract containing lutein and suppliers of animal food components containing Marigold extract containing lutein must meet. The manufacturing information does not adequately describe the characterization of the notified substance, such as the extract ratio, the ratio of the amount of dried marigold flower raw material to the amount of final marigold extract oleoresin, which is useful to establish the identity of the Marigold extract containing lutein. The specification for Marigold extract containing lutein should include both upper and lower limits for the levels of xanthophylls and lutein to establish the identity and purity. It is not clear that only the levels of xanthophylls and/or lutein can adequately establish the identity of the Marigold extract containing lutein. Thus, the information contained in the notice does not adequately describe the relationship between the notified substance and the safety information that is used to conclude that Marigold extract containing lutein is GRAS under the intended conditions of use as a nutritional source of the antioxidant lutein in the diets and treats of dogs and cats.
2. The stability information contained in the notice is limited and inconsistent, and it does not adequately describe the stability of Marigold extract containing lutein in animal food components and pet food. For example, in both accelerated stability studies and real-time stability studies, limited information is provided to demonstrate stability. It is not clear that only a test for lutein content can adequately establish the stability of Marigold extract

containing lutein. In addition, information regarding lutein content in pet food that is beyond its shelf life may not be a substitute for a long term stability study.

3. It is not clear that all ingredients used in the marketed products are appropriate for use in animal food. We note that all ingredients used in marketed products must be either approved animal food additives published in Title 21 of the Code of Federal Regulations (21 CFR) part 573 (21 CFR 573), substances that are GRAS for the intended use, or are otherwise acceptable ingredients for use in animal foods, such as those defined in the most recent Official Publication of the Association of American Feed Control Officials.

#### Target Animal Safety:

Based on information available to the agency, including the information contained within this notice, we have questions regarding the target animal safety of the notified use of Marigold extract containing lutein as a nutritional source of lutein in the diets and treats of dogs and cats at levels not to exceed 5 milligrams lutein per 1000 kilocalories of metabolizable energy for the following reasons:

1. Information on the specifications/composition of Marigold extract containing lutein is marked as Confidential Business Information (CBI) in the amendment of the GRAS notice. Information on the levels of potential contaminants/impurities present in the notified substance is necessary in the target animal safety evaluation for estimating the maximum exposure of these components resulting from the intended use of Marigold extract containing lutein that could be of toxicological concern in the target animals. Therefore, this information as it pertains to the safety evaluation of the notified substance should not be classified as CBI.
2. Information on the potential contaminants of Marigold extract containing lutein is not adequate for concluding the safety of Marigold extract containing lutein for its intended use in the target species for the following reasons:
  - a. The notice did not contain data on the level of heavy metals or mycotoxins in the notified substance.
  - b. The substance analyzed in the Royal Canin CoAs is not clearly identified by the notifier in order to estimate exposure (it is unclear if the presence of the pesticides is from Marigold extract containing lutein or Cuatroxan®), and the presence of any pesticide in the notified substance is not addressed by the notifier.
  - c. The notifier did not clearly state the substance analyzed in the Royal Canin CoAs titled “Tagete,” “Marigold Extract,” and “Tagete 45%”. It is unclear if the substance analyzed is Marigold extract containing lutein or Cuatroxan®. In addition, it is not clear how the dioxins and PCBs analyses listed in the Royal Canin CoAs are consistent with the average level of dioxins and dioxin-like PCBs given by the marigold extract oleoresin supplier for six batches of extract (see Table in section II.B.1 of the dossier). The notifier did not clarify why the latter values differ from the values listed in the CoAs.
3. Although the notice estimates the maximum dietary exposure to lutein, the notice does not adequately describe the inclusion rate of Marigold extract containing lutein (which excludes

other ingredients used for technical effect) in diets and treats for dogs and cats for the purpose of estimating the maximum dietary exposure to n-alkanes, fatty acids, gums and resinous matter resulting from the inclusion of Marigold extract containing lutein at the maximum proposed use level in the diets and treats of dogs and cats. Marigold extract containing lutein exposure in the notice is estimated based on the composition of two marketed products.

**Section 403(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)**

Under section 403(a) of the FD&C Act, a food is misbranded if its labeling is false or misleading in any way. We question whether the information provided in the notice substantiates that Marigold extract containing lutein is a nutritive antioxidant when used at a level sufficient to provide no more than 5 mg lutein per 1000 kcal metabolizable energy in the food and treats for dogs and cats. If products containing Marigold extract containing lutein bear any claims on the label or in labeling regarding the function of the notified substance, these claims must be supported by appropriate data and information. FDA may take enforcement action if any claims on labels or labeling are found to be false or misleading.

**Conclusion**

Based on the information that you provided, as well as other information available to FDA, the notice does not provide a sufficient basis for a conclusion of GRAS status for the intended use of Marigold extract containing lutein as a nutritional source of lutein in the diets and treats of dogs and cats at levels not to exceed 5 milligrams lutein per 1000 kilocalories of metabolizable energy.

In accordance with 21 CFR 570.275(b)(1), the information in this notice described in 21 CFR 570.225(c)(2) through (c)(5) will be accessible to the public at <http://www.fda.gov/AnimalVeterinary/Products/AnimalFoodFeeds/GenerallyRecognizedasSafeGRASNotifications/ucm243845.htm>.

If you have any questions concerning this letter, please contact Dr. Louis Carlacci at 240-402-2921 or by email at [Louis.Carlacci@fda.hhs.gov](mailto:Louis.Carlacci@fda.hhs.gov). Please refer to AGRN 22 in any future correspondences.

Sincerely,

/s/

David Edwards, Ph.D.  
Director, Division of Animal Feeds  
Center for Veterinary Medicine