U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR VETERINARY MEDICINE

November 4, 2019

Margaret Whittaker, Ph.D.
Managing Director and Chief Toxicologist
ToxServices LLC
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Washington, DC, 20036

Re: GRAS Notice No. AGRN 30

Dear Dr. Whittaker:

The Food and Drug Administration (FDA, we) completed our evaluation of AGRN 30. We received Aker BioMarine Antarctic's ("Aker BioMarine") notice on December 21, 2018. The notice was filed on February 19, 2019. Aker BioMarine Antarctic submitted an amendment to the notice on April 4, 2019 to address issues regarding Aker BioMarine's contact information, analytical methods and test results, references, and stability information.

The notified substance is *Euphausia superba* (krill) meal. The notice informs the FDA of Aker BioMarine Antarctic's view that *Euphausia superba* (krill) meal is GRAS, through scientific procedures, for use as a source of protein and lipid in dry adult dog food at an intended use rate of 3%.

Aker BioMarine provides information about the identity, method of manufacture, and specifications of the notified *Euphausia superba* (krill) meal. The notified substance is manufactured in a continuous process from fresh Antarctic krill aboard a fishing vessel. The krill are heated in cookers, followed by separation of solids and liquids. The solids are dried, cooled, screened to remove shell fractions which have high fluoride concentration. Aker BioMarine also provides information on contaminants, stability, and packaging.

Aker BioMarine provides a finished ingredient specification along with test method and acceptance criteria: Color (brownish pink to orange), Total dry matter (≥ 92 g/100g), Moisture (6 ± 2 %), Crude Protein (62 ± 7 %), Fat (26 ± 6 %), Ash (≤ 13 %), Salt (NaCl) (≤ 4 %), Total omega-3 fatty acids (≥ 17 g/100g fat), Astaxanthin esters (80 – 160 mg/kg), Total volatile nitrogen (≤ 0.3 %), Peroxide value (< 10 meq peroxide/kg), Cadaverine (< 10 mg/kg), Histamine (< 10 mg/kg), Meat bone meal (not present), Phosphorous (< 2 %), Calcium (< 3 %), Iodine (< 50 mg/kg), Copper (67 mg/kg), Fluoride (≤ 800 mg/kg), Cadmium (< 1 mg/kg), Mercury (< 0.1 mg/kg), Lead (< 0.05 mg/kg), Total Arsenic (< 8 mg/kg), Inorganic Arsenic (0.5 mg/kg), Total Plate Count (≤ 20,000 cfu/g), Enterobacteriaceae (≤ 300 cfu/g), *Salmonella* spp. (1 sample of 25 g Negative), Yeast (≤ 100 cfu/g), Mold (≤ 100 cfu/g).

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To address the intended use of the notified substance, Aker BioMarine indicates that "at the proposed upper use level of 3%, Qrill™ Pet would provide 9.6% of the protein requirement and 15.8% of the fat requirement for adult dogs." The relatively large amounts of fluoride in krill meal limits its use as a source of protein and lipid for animal food. The notice includes publicly available information in mink, pigs, and rats, but not adult dogs, to demonstrate that the protein and lipids in krill meal are digestible and information to support that these monogastric species digest protein and fat in a similar manner. Published information shows the digestibility of nutrients, specifically protein and fat, is comparable between dogs and mink. A study found that protein digestibility of krill meal in mink is comparable to other sources of protein, including fish meal, and that krill meal supports the growth and reproduction of mink. The notice also includes the results of a study that compares the digestibility of krill meal and fish meal in male castrated pigs. The digestibility of a krill protein concentrate (KPC) in rats is also provided. Although KPC has a different composition than krill meal (KPC has 33% less lipids and 75% less ash than whole krill meal), the results of this study support the conclusion that krill protein is digestible by rats.

Two unpublished studies in the notice are corroborative and show that dogs fed a diet containing 8% krill meal have an increase in red blood cell omega-3 fatty acid index, suggesting that the fat in krill meal is digestible. Furthermore, dogs fed krill meal consume food and maintain body weight similarly to dogs fed a control diet.

To address the target animal safety, Aker BioMarine provides publicly and non-publicly available information to support the safety of the intended use of *Euphausia superba* (krill) meal as a nutritional source of protein and fats in the food of adult dogs. The information submitted addresses: 1) the toxicity of krill meal; 2) the toxicity of krill meal-derived fluoride; 3) the toxicity of krill meal-derived astaxanthin (ATX), and 4) the suitability of mink as a model for toxicity studies in dogs. Aker BioMarine identifies the studies by Krogdahl *et al*. 2015 in growing and adult mink as pivotal studies in the target animal safety assessment of the intended use of krill meal in food for adult dogs and identifies unpublished studies as supportive information.

Aker BioMarine selected the no observable adverse effect level (NOAEL) from the mink studies and used allometric scaling for deriving a NOAEL for krill meal in dogs. Aker BioMarine calculates the EDI and ADI for krill meal of 1.13 g/kg bw/day, and 1.25 g/kg bw/day, respectively. Aker BioMarine also addresses the safety of fluoride because krill has naturally high levels of fluoride and it is the limiting factor for using krill meal in food. Aker BioMarine considers the safety of fluoride as the prevalent factor in the target animal safety assessment of krill meal. Aker BioMarine calculated an EDI of fluoride resulting from the inclusion of 3% krill meal (containing up to 800 ppm fluoride) of 0.9 mg/kg bw/day, and the ADI of fluoride of 1.56 mg/kg bw/day. Aker BioMarine also addresses the safety of ATX resulting from the inclusion of 3% krill meal of 2.06 mg/kg bw/day, and the ADI of 31.6 mg/kg bw/day. Aker BioMarine's calculations were based on the body weight of terriers because small dogs consume the highest amount of food on a body weight basis, and they are expected to be exposed to the highest levels of krill meal.

Aker BioMarine lists relevant studies to justify the species extrapolation from the mink studies to dogs. Aker BioMarine cites that mink is typical of other mammals and toxicological results can

be extrapolated from mink to other animal species and humans. Aker BioMarine considers that for the target animal safety assessment of krill meal-derived fluoride, mink is a suitable and complementary model to dogs since chronic studies in mink show effects of fluoride were related to bone changes. In addition, Aker BioMarine conducts allometric scaling for converting the NOAELs and lowest observed adverse effect level (LOAELs) from the mink studies to dog equivalent exposures and shows they are slightly below or very similar to the NOAEL of 5.2 mg F/kg/day selected from the chronic dog study by Greenwood *et al*. 1946.

Aker BioMarine also provides information on other minerals, heavy metals, and environmental contaminants in krill meal. The environmental contaminants included are dioxins/PCBs, PAHs, and organochlorine pesticides.

The Association of American Feed Control Officials (AAFCO) publishes a list of names and definitions for accepted feed ingredients. FDA recognizes these names as being the "common or usual" names for feed ingredients. FDA recognizes the name "krill meal" as the common or usual name for the notified krill meal.

Section 301(ll) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

Section 301(ll) of the FD&C Act prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FD&C Act, a biological product licensed under section 351 of the Public Health Service Act, or a drug or a biological product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions in section 301(ll)(1)-(4) applies. In our evaluation of Aker BioMarine's notice concluding that *Euphausia superba* (krill) meal is GRAS, under its intended conditions of use we did not consider whether section 301(ll) or any of its exemptions apply to foods containing *Euphausia superba* (krill) meal. Accordingly, our response should not be construed to be a statement that foods containing *Euphausia superba* (krill) meal if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusion

Based on the information contained in the notice and amendment submitted by Aker BioMarine Antarctic, as well as other information available to FDA, we have no questions at this time regarding Aker BioMarine's conclusion that *Euphausia superba* (krill) meal is GRAS when used as a source of protein and lipid in dry adult dog food at a use rate of 3%. The agency has not, however, made its own determination regarding the GRAS status of the intended use of the notified *Euphausia superba* (krill) meal in animal food under 21 CFR 570.35. Unless noted above, our evaluation did not address other provisions of the FD&C Act. As always, it is the continuing responsibility of Aker BioMarine to ensure that animal food ingredients that it markets are safe and are otherwise in compliance with all applicable legal and regulatory requirements.

In accordance with 21 CFR 570.275(b)(2), the text of this letter responding to AGRN 30 is accessible to the public on our website for the Current Animal Food GRAS Notices Inventory at

https://www.fda.gov/animal-veterinary/generally-recognized-safe-gras-notification-program/current-animal-food-gras-notices-inventory.

If you have any questions about this letter, please contact Dr. Manisha Das at 240-402-5920 or by email at Manisha.Das@fda.hhs.gov. Please reference AGRN 30 in any future correspondence regarding this GRAS notice.

Sincerely,

/s/
Timothy Schell, Ph.D.
Director
Office of Surveillance and Compliance
Center for Veterinary Medicine

References

Krogdahl, A., Ø. Ahlstrom, L. Burri, S. Nordrum, L.C. Dolan, A.M. Bakke, and M.H. Penn. 2015. Antarctic krill meal as an alternative protein source in pet foods evaluated in adult mink (Neovison vison). I. Digestibility of main nutrients and effect on reproduction. *Open Access Animal Physiology* 7:29-42.

Greenwood, D. A., J.R. Blayney, O.K. Skinsnes, and P.C. Hodges. 1946. Comparative studies of the feeding of fluorides as they occur in purified bone meal powder, defluorinated phosphate and sodium fluoride, in dogs. *Journal of Dental Research* 5:311-326.