Department of Pesticide Regulation

Julie Henderson
Director

Gavin Newsom
Governor

Yana Garcia
Secretary for Environmental Protection

MEMORANDUM

TO: Jennifer Teerlink, PhD
Deputy Director and Science Advisor
Registration and Evaluation Division

From: Shelley DuTeaux, PhD, MPH
Chief, Human Health Assessment Brar
On behalf of the Exposure Assessment Section:
Eric Kwok, PhD MPhil DABT

DATE: December 31, 2024

SUBJECT: Response to Comments by the Elanco on DPR's March 2024 Draft Human Exposure Assessment for Non-Agricultural Uses of Imidacloprid

Background

Elanco US Inc. submitted comments and data to the Department of Pesticide Regulation (DPR) on April 25, 2024 following review of the draft Human Exposure Assessment Document (EAD) for the Non-Agricultural Uses of Imidacloprid. The submission includes specific comments that Elanco believes should be reconsidered during the finalization of the EAD.

This memorandum outlines DPR's responses to Elanco's comments made in the draft imidacloprid exposure assessment including: (1) the assumption that imidacloprid in pet collar formulations exists as half liquid and half solid, (2) the use of spot-on application as a surrogate, (3) the fraction of the application rate available as transferable residue (F_{AR}), and (4) the dermal absorption factor (DAF).

It should be noted that the references cited in this memorandum pertain specifically to Elanco's requests and may not overlap with those in the draft or final EAD. While efforts have been made to directly quote Elanco's comments, some have been condensed for clarity and brevity.

Supportive Information: Liquid-to-Solid Ratio of Pet Collar Formulation

Elanco Comment 1 – Assumption that the imidacloprid impregnated in the pet collar formulation exists as half liquid and half solid: In its February 2019 Updated Residential Exposure Assessment (EPA-HQ-OPP-2008-0844-1616), EPA utilized a 99.71% liquid to 0.29% dust ratio based on data provided by Bayer as related to the physical form of residues released from the Seresto collar.

DPR Response: The original assumption that pet collar formulations exists as half liquid and half solid (i.e., 0.5/0.5 liquid-to-solid ratio) was based on the lack of formulation-

specific data. However, according to new information provided to DPR by the US Environmental Protection Agency (US EPA, 2024), the pesticide registrant submitted two studies that allowed US EPA to derive a liquid-to-solid ratio of 0.9971/0.0029 for assessing residential hander exposure from pet collar usage (Jiritschka, 2011; Hammer, 2016; US EPA, 2019a). Accordingly, all exposure calculations used in this assessment have been updated from the assumption of a 0.5/0.5 liquid-to-solid ratio to the experimentally determined liquid-to-solid ratio. All exposure estimates involving pet collar use scenarios have been revised in the EAD. The accompanying risk estimates for pet collar scenarios have also been revised and can be found in the final Risk Characterization Document (RCD) for the Non-Agricultural Uses of Imidacloprid.

Comment 2 – Use of spot-on application as a surrogate for application rate (i.e., 100% exposure to the actives): The Seresto collar is designed for an eight-month period of use versus monthly application as is typical for most spot-on products. As presented in the Registrant's 2010 occupational and residential exposure risk assessment (ID 33861, included with this submission), approximately 40% of the collar's imidacloprid content is released over that eight-month period. Conversely, approximately 60% of the imidacloprid remains in the collar after eight months of use.

DPR Response: Based on the new data provided by the registrant (Lunchick, 2010), the application rates of small and large pet collars have been scaled by 0.4.

Comment 3 – Discrepancy in FAR (fraction of the application rate available as transferable residue): EPA corrected the FAR to 0.02 in its February 2019 updated residential exposure assessment (EPA-HQ-OPP-2008-0844-1616). Bayer subsequently provided data for refinement of the FAR via fur stroke studies in which test animals wearing the Seresto collars were stroked per a set protocol (area of the body, pattern and number of strokes, etc.) by technicians wearing cotton glove dosimeters over latex gloves. Residues captured by the glove dosimeters in fur stroke studies are considered the transferable (available) residues. The FAR is then calculated by dividing the glove residue by the application to obtain the fraction of application rate available as transferable residues. Based on these studies, Seresto FARs were determined as 0.001 for the small collar and 0.0037 for the large collar. These FARs were accepted by EPA as implemented in EPA's November 2019 draft human health risk assessment for imidacloprid (EPA-HQ-OPP-2008-0844-1613).

DPR Response: Based on the new data provided by the registrant on pet collars as found in US EPA's updated Residential Exposure Assessment (2019b), the F_{AR} values for small and large collars have been updated to 0.001 and 0.0037, respectively.

Comment 4 – Dermal absorption factor (DAF): In EPA's 2019 "Imidacloprid: Updated Residential Exposure Assessment in Response to Draft Risk Assessment (CRA) Comments" (EPA-HQ-OPP-2008-0844-1616), EPA updated the DAF from 7.2% to 4.8% based on data

provided by Bayer (in vivo dermal absorption study with GAUCHO FS 350). Elanco recognizes CDPR's use of a DAR of 17% based on the same study, but notes that the stratum corneum is a skin layer of the epidermis not considered to be transmissible. The amount of imidacloprid in the stratum corneum of the low dose animals remained constant at 9, 24, 72, and 168 hours which supports the assumption that active ingredient in the stratum corneum is not being absorbed over time and is assumed to be sloughed off.

DPR Response: The section on dermal absorption factor derivation has been revised based on recommendation from US EPA. Specifically, among all the monitoring periods at the lowest test dose, there was no significant decrease in the percentage of bound skin residue in the stratum corneum (based on ANOVA followed by Tukey's Honestly Significant Difference (HSD) post-hoc test). This suggests that the bound skin residue may not be available for absorption. Hence, the derivation of the potentially absorbable dose (PAD) was revised to now consist of the percentage of directly absorbed and total at the dose site, equaling 4.823% as appeared in Odin-Feurtet (2009). The rounded-up value of 5% was used for updating all dermal exposure values in the exposure assessment. The resulting risk estimates based on dermal routes of exposure have been similarly updated in the final RCD.

References:

Hammer, M. 2016. Flumethrin Release from Seresto Collars by Torsional Stressing. Project Number: S00UI/006938, 44739. Bayer HealthCare, LLC. : Bayer HealthCare, LLC. Animal Health Division P.O. Box 390, Shawnee Mission, KS 66201-0390. MRID 50140804. (DPR Vol. No. 51950-1007, Record No. 309034) 12.

Jiritschka, W. 2011. Imidacloprid/ Flumethrin 10%/ 4.5% Collar (All Sizes) - Investigation of Composition of Surface Abrasion After Mechanical Stress. Project Number: 37090, 1427, TGOLL111028. Bayer HealthCare, LLC.: MRID 50140803. (DPR Vol. 11.

Lunchick, C. 2010. Occupational and Residential Exposure and Risk Assessment for PNR 1427 Dog and Cat Collars Formulated with Imidacloprid and Flumethrin (ID 33861). Bayer HealthCare LLC, Animal Health Division, P.O. Box 390, Shawnee Mission, KS 66201-0390: Bayer HealthCare LLC, Animal Health Division, P.O. Box 390, Shawnee Mission, KS 66201-0390. (DPR Vol. No. 51950-1009, Record No. 354387) 17.

US EPA 2019a. Imidacloprid. Updated Residential Exposure Assessment in Response to Draft Risk Assessment (DRA) Comments. In *EPA-HQ-OPP-2008-0844*. https://www.regulations.gov/document?D=EPA-HQ-OPP-2008-0844-1616.

US EPA 2019b. Imidacloprid: Draft Human Health Risk Assessment (DRA) for Registration Review – Response to Comments. In *EPA-HQ-OPP-2008-0844*. https://www.regulations.gov/document?D=EPA-HQ-OPP-2008-0844-1613.

US EPA 2024. US EPA Review of California's Department of Pesticide Regulation March 2024 Draft Human Health Assessment on Non-agricultural Uses.