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July 12, 2011

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Copy by email to keller.kaitlin@epa.gov*

OPP Regulatory Public Docket (7502P)
Environmental Protection Agency
Rm. S-4400, One Potomac Yard, South Building
2777 S. Crystal Drive
Arlington, VA 22202

Re: Docket Number EPA-HQ-OPP-2009-0207
Comment on NRDC Second Petition Supplement Dated January 18, 2011

Dear Mr. Keigwin:

On behalf of Sergeant's Pet Care Products, Inc. ("Sergeant's") and with the approval and consent of Wellmark International ("Wellmark") (jointly the "Registrants"), please consider this letter, with Attachment 1 appended hereto, in response to the Agency's request for comment on the NRDC second petition supplement of January 18, 2011 ("NRDC Second Supplement") published by notice in the June 15, 2011, Federal Register¹. These comments provide information regarding Sergeant's pet collars registered under numbers 2517-61 and 2517-78 and Wellmark's pet collars registered under numbers 2724-454, 2724-275, 2724-491, and 2725-493 (jointly referred to as "Registrants' Collars").

In this Second Supplement, NRDC continues to urge the Agency to cancel the pet uses of propoxur, notably pet collars, claiming that EPA significantly underestimates exposure levels from pet collars based on inadequate assumptions concerning the hand-to-mouth toddler activities, fails to include the risk of dermal absorption resulting from petting and hugging pets, and fails to address the cancer risk associated with propoxur. The Registrants urge the Agency to disregard these assertions as groundless and needlessly provocative. As detailed below and in Attachment 1, the Registrants support the Agency's conclusions that the dermal route of exposure is not of interest and that evaluating cancer risk is not necessary. Furthermore, based on recently generated data, the Registrants urge the Agency to conclude that the resulting Margins of Exposure ("MOEs") for incidental hand-to-mouth exposure for children indicate no reasonable basis for concern for the safety of children from exposure to propoxur residues transferred from pet fur.

¹ 76 Fed Reg 34978 (June 15, 2011)

Dermal Absorption

NRDC's assertion that the Agency inappropriately ignored the risks associated with absorbing propoxur through the skin appears to be based on a misunderstanding of the available data on propoxur. EPA concluded in the April 7, 2010 Occupational and Residential Exposure and Risk Assessment² that the dermal route of exposure for propoxur is not considered of interest because cholinesterase inhibition was not observed after 6 hours of daily dermal exposure and because no dermal or systemic toxicity was observed following dermal dosing for 90 days at the limit dose (1,000 mg/kg/d) required by EPA. Therefore, it is not necessary or appropriate to evaluate potential dermal exposures and MOEs for those exposures. ***The extent of dermal absorption is irrelevant for propoxur because dermal toxicity data demonstrate no adverse effects via this route of exposure.***

Cancer Risk

NRDC asserts in the Second Supplement that the lifetime cancer risk from exposures to propoxur is around 5.01×10^{-4} , and that such risk exceeds the Agency's acceptable risk range³. The NRDC calculations supporting this risk calculation are fraught with faulty assumptions concerning the levels of exposure. But the accuracy of the calculations notwithstanding, the calculations are inappropriate based on available data. In the Final Work Plan for Registration Review of Propoxur⁴, the Agency has concluded that:

- Based on the current knowledge of the non-cancer mode of action for propoxur (i.e., rapid reactivation of the enzyme suppressed by exposure and then recovery), chronic dietary assessments are no longer appropriate for propoxur and are not intended to be conducted during registration review.
- A revised chronic cancer dietary assessment is also not intended to be conducted because the concentrations of exposure which elicited effects in the submitted studies are orders of magnitude greater than what would be expected based on registered use patterns of propoxur.

Thus, evaluation of the potential cancer risk for propoxur pet collars is not considered appropriate because **both** the known mode of action for propoxur is cholinesterase inhibition, which reaches a maximum within 15 minutes to 1 hour of exposure followed by rapid enzyme reactivation and recovery, **and** because the Group B carcinogen classification and cancer potency factor for propoxur are based on exposures that were orders of magnitude greater than would be expected from currently registered uses. ***At the low dose levels expected from the collars, the mechanisms that operate to cause cancer at the high doses used in the animal studies would not be expected to occur. Further, due to the rapid enzyme inhibition and recovery, a cancer risk assessment is not required.***

² Posted to Docket EPA-HQ-OPP-2009-0207 on July 23, 2010

³ NRDC Second Supplement, page 9

⁴ Posted to Docket EPA-HQ-OPP-2009-0806 on July 23, 2010

Transferable Residues on Pet Fur and Resulting MOE Calculations

Since the Agency's posting of the Final Work Plan for Registration Review of Propoxur⁵, the Agency posted to this Docket a supplement and correction to the April 7, 2010, Occupational and Residential Exposure and Risk Assessment for Propoxur Formulated Pet Collars dated July 12, 2010 ("July 2010 ORE")⁶. While the Registrants appreciate the Agency's correction of the active ingredient levels and recognition of the additional interim data provided by the Registrants, the Agency's July 2010 ORE perpetuates the fundamental problems previously addressed in our June 22, 2010, letter. The Agency's correction of active ingredient weight levels, while important, has little impact on the ultimate calculated Margins of Exposure because fundamental erroneous assumptions continue to be used. To restate from our June 22, 2010, letter (emphasis added):

The 2010 ORE is fundamentally flawed. It uses an unreasonable rate of release assumption and does not make use of the Agency's recently proposed transferable residue factors. As a consequence, the resulting estimated MOEs indicate a risk which is out of proportion to the estimated risk which should result if the assessment is properly conducted.... The data currently available and potential revisions to the SOPs suggest that much higher MOEs, as compared to those calculated in the 2010 ORE, are likely.

Nevertheless, to address the concerns raised by EPA regarding potential exposures associated with transferable residues from pet fur, the Registrants have sponsored a pet fur transferable residue study using a protocol approved, and modified, by the Agency (the "TR Study"). This TR Study was conducted using simulated petting with a multi-gloved mannequin hand on 17 dogs over a period of 28 days. Please see Attachment 1. Propoxur residues transferred to the mannequin hand for each of 15 treated dogs and two untreated controls were analyzed for each sampling occasion. The TR Study is complete and the data have been audited, but the final report is not yet available.⁷ As is evident from the Attachment, the transferable residues are significantly lower than the default assumptions used by the Agency in the July 2010 ORE. Indeed, the transferable residues range from 0.0715 % on Day 0 to 0.0033 % on Day 28, with a time-weighted average transferable residue of 0.0105 % over the 28 days of the study. These collars are intended to be worn for longer periods, up to 4 to 6 months. Therefore, the 28-day time-weighted average transferable residue constitutes a conservative estimate of potential transferable residues over the longer periods corresponding to actual use.

The TR Study indicates that the transferable residues decline quickly over the first 7 days following application, with the transferable residue on Day 1 being approximately 46 % lower than that on Day 0 and transferable residues on Day 2 being approximately 29 % lower than those on Day 1. Thereafter, the transferable residues continued to slowly decline

⁵ Docket EPA-HQ-OPP-2009-0806, June 17, 2010

⁶ Posted to Docket EPA-HQ-OPP-2009-0207 on July 23, 2010

⁷ The final TR Study is anticipated to be submitted to the Agency by the end of August 2011. Preliminary data have been provided to EPA.

throughout the course of the study.⁸ Clearly, there is no indication in the study of build-up on the pet of transferable residues.

The Agency's assumptions, especially concerning the rate of release, in the July 2010 ORE resulted in a release factor of 1.33% per day being used in the risk assessment. The TR Study demonstrates the conservatism in the Agency's assumptions concerning rate of release. ***The demonstrated time weighted rate of release, using a protocol approved and modified by EPA, is 0.0105 %, which is less than one percent of the release rate used by the Agency and NRDC.***

As recognized by the Agency in the July 2010 ORE, use of chemical- and formulation-specific information on pet fur residue transferability is an appropriate refinement to the default-based exposure calculations. Substituting the actual transferable residue data into the Agency's exposure equations from the July 2010 ORE results in Margins of Exposure ("MOE") in excess of 1,000 on Day 0 and up to 33,600 on Day 28 for the Registrants' Collars. Using the time-weighted average transferable residue estimate, MOEs are calculated to range from approximately 7,000 to 10,000. Clearly, these MOEs are greater than the 1,000 Level of Concern ("LOC") used by the Agency for propoxur in the absence of data from a Comparative Cholinesterase Assay ("CCA") study.

Hand-to-Mouth Events as a Factor in the Child Exposure Risk Assessment

NRDC states that "EPA assumed that a child would have only one hand-to-mouth event per day after exposure"⁹ and compares that assumption to hand-to-mouth assumptions used by the Agency in the Organophosphate Cumulative Risk Assessment (9 events per hour) and in the DDVP assessment (2 hours exposure per day)¹⁰. NRDC then proceeds to use the combination of these two prior assessments to generate an 18 event per day factor¹¹. This increased event factor is apparently used with the Agency's faulty July 2010 ORE assumptions to generate MOEs ranging from 3 to 5. This is a suspect exercise in manipulating data on several levels to accomplish a pre-established goal of demonstrating high risk from pet collars. The resulting MOEs from this manipulation bear no relationship to the reality of the low risks posed to children by exposure to pets wearing collars containing propoxur. Specifically, the statement that the Agency assumes one hand-to-mouth event per day, while accurate within the narrow confines of the sentence, misconstrues the risk assessment process. As has been explained by EPA staff in meetings with the Registrants, ***the "one event" assumption currently used by the Agency reflects steady-state transfer of residues to hands over a day and does not truly represent a single hand-to-mouth event.*** In addition, the use of factors considered in the Organophosphate and DDVP assessments is inappropriate since the formulas and protocols used to assess residential exposure and risk have evolved over the years and because those assessments were conducted for purposes other than a single product assessment.

⁸ Attachment 1, Figure 1

⁹ NRDC Second Supplement, page 5.

¹⁰ NRDC Second Supplement, pages 5-6.

¹¹ NRDC Second Supplement, page 6, Table 3

Inclusion of "Poison on Pets II" Residue Data

NRDC specifically incorporates the "Poison on Pets II" report in this Second Supplement and uses the data to bolster their erroneous calculations, as described above.¹² However, use of the "data" in the "Poison on Pets II" report in any fashion is inappropriate. In order for data generated in intentional human exposure studies to be relied upon by EPA in taking regulatory actions under FIFRA, the sponsor of such a study must demonstrate compliance with the ethical requirements of the regulations regarding the Protection of Human Subjects, 40 CFR Part 26. NRDC has failed to provide such requested documentation.¹³ As a consequence, the Agency cannot rely on these data, and NRDC misrepresents the status and quality of those data by implying that the data are part of the evidence which should be considered by EPA in evaluating their Petition.

However, the transferable residue data which the "Poison on Pets II" study apparently attempted to generate has now been ethically generated by the Registrants. The TR Study described above measured the transferable residues from pet fur over a 28-day period and demonstrates exceedingly low levels of transferable residue, and does so in a manner which fully complies with all EPA requirements.

Conclusion

In summary, the Registrants urge the Agency to disregard the NRDC's assertions concerning the risk posed to children, dermal absorption, and cancer risk by exposure to pets wearing collars containing propoxur. Transferable residue data recently developed by the Registrants indicate MOEs in excess of the Agency's 1,000 LOC, which indicates that there is no reasonable basis for concern about harm to children contacting pets wearing propoxur collars. In addition, the Registrants support EPA's conclusion that dermal absorption is not relevant to characterizing exposures and risks because no dermal or systemic toxicity was observed at the maximum dose required by EPA for dermal toxicity studies. And, finally, the Registrants also support EPA's conclusion that the cancer risk for propoxur is not of concern because the known mode of action is cholinesterase inhibition with demonstrated rapid recovery and the doses which elicit carcinogenic effects in animals are orders of magnitude greater than what would be expected from currently registered uses.

¹² NRDC Second Supplement, page 11: "Taken together, the evidence provided here and in previous NRDC submissions demonstrates...."

¹³ To the best of our knowledge and as of publication of the Final Work Plan, June 2010.

Thank you for this opportunity to provide comments to the NRDC's Second Petition Supplement dated January 18, 2011. Please contact me if there are any questions.

Regards,



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Attorney for Sergeant's Pet Care Products, Inc.

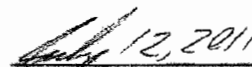
cc: Kaitlin Keller, Chemical Review Manager, by email only
Kelly Hoskins, Sergeant's Pet Care Products, Inc.
James McFadden, Wellmark International

By signature below, Wellmark International, concurs with the statements and conclusions provided above, concludes that the statements and conclusions are applicable to the Wellmark registrations 2724-454, 2724-275, 2724-491, and 2725-493, and requests that the Agency disregard the NRDC assertions in the Second Supplement as set forth above.



Name: James McFadden

Title: Sr. Regulatory Project Mgr.



Date

ATTACHMENT 1

Summary of Revised Exposure and Risk Calculations for Pet Collars Containing Propoxur Conducted with Data from a Transferable Residue Study

July 12, 2011

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Summary of Revised Exposure and Risk Calculations for Pet Collars Containing Propoxur Conducted with Data from a Transferable Residue Study

Sergeant's Pet Care Products (Sergeant's) and Wellmark International (Wellmark) manufacture and market pet collar products containing 9% and 10% propoxur, respectively, for the purposes of flea and tick protection. The U.S. Environmental Protection Agency (EPA) has recently conducted an exposure and risk assessment for residential uses of Sergeant's and Wellmark pet collar products containing propoxur (EPA, 2010a,b). This summary compares EPA's 2010 risk assessment with revised calculations based on data generated in a pet fur transferable residue study conducted by the registrants.

Propoxur – Routes of Exposure and Toxicity Endpoints

For non-cancer effects, EPA (2010b) has concluded that only post-application oral hand-to-mouth exposures for children are of interest for propoxur pet collars. Hand-to-mouth exposure for adults is anticipated to be negligible. Dermal exposure is not of interest for propoxur because cholinesterase inhibition was not observed after 6 hours of daily dermal exposure and because no dermal or other systemic toxicity was observed following dermal dosing for 90 days at the limit dose (1,000 mg/kg/d) required by EPA for a subchronic dermal toxicity study (EPA, 2010b). Finally, inhalation exposures are not anticipated to be a viable route of exposure for pet collars. Risks associated with oral hand-to-mouth exposures to propoxur are characterized using the benchmark dose (BMDL₁₀) of 0.28 mg/kg/d, which is based on red blood cell cholinesterase inhibition observed in adult male rats (EPA, 2010b). The level of concern (LOC) for propoxur is 1,000, reflecting the standard 10X inter- and intra-species uncertainty factors and the 10X Food Quality Protection Act (FQPA) factor that has been retained by EPA (2010b) because a comparative cholinesterase assay (CCA) study was not available for propoxur.

In a recent risk assessment (EPA, 2010b) and the Work Plan for Registration Review (EPA, 2010c), EPA concluded that the calculation of cancer risks for propoxur pet collars is not appropriate. EPA has noted that the Group B carcinogen classification and cancer potency factor for propoxur are based on exposures that were orders of magnitude greater than would be expected from currently registered uses (EPA, 2010b). In addition, the known mode of action for propoxur is cholinesterase inhibition, which reaches a maximum within 15 minutes to 1 hour of exposure followed by rapid enzyme reactivation and recovery (EPA, 2010c). Therefore EPA (2010c) has stated that only non-cancer endpoints will be assessed during the registration review process for propoxur. Accordingly, only non-cancer effects of propoxur are addressed for pet collar products.

EPA 2010 Risk Assessment – Margin of Exposure Calculations

In the default-based exposure and risk assessment, EPA (2010a,b) assumed that all of the propoxur in pet collars is released over a period of 15 days and that 20% of the resulting residue on a pet would be transferable, which corresponds to 1.33% transferable residue per day. Using this assumption, EPA (2010a) estimated oral hand-to-mouth incidental ingestion exposures for

children with corresponding margins of exposure (MOEs) of 55 to 82. Because these default-based MOEs are below the LOC of 1,000, EPA concluded that hand-to-mouth exposures for children who come into contact with pets wearing collars are of concern. However, based on interim data previously provided by the registrants (i.e., rate of release data from pet collars), EPA (2010a) also indicated a belief that additional anticipated chemical- and formulation-specific data on the transferability of propoxur residues on pet fur would demonstrate lower risks.

Pet Fur Transferable Residue Study

To address the concerns raised by EPA regarding potential exposures associated with pet collars containing propoxur, Sergeant's and Wellmark have sponsored a transferable residue study (Welch, 2011) using an EPA-approved protocol to generate formulation- and chemical-specific transferable residue data. The study has been completed, and the data have been audited, but the study report itself is not yet available. The final report is anticipated to be submitted to EPA by the end of August 2011. In the meantime, the preliminary data have been provided to EPA by Sergeant's and Wellmark.

A summary of the transferable residue study follows:

- The study included 17 Beagle dogs (15 treated and 2 untreated controls).
- Treated dogs were fitted with collars containing 10% propoxur. Collars were weighed prior to fitting and applied according to label directions. The excess portion of each collar was removed and weighed in order to determine the amount of propoxur in the collar placed on each animal. Applied collars averaged 22.75 grams in weight, so 2.275 grams of propoxur were applied on average.
- On the day that collars were applied (Day 0) and at specified intervals afterward (i.e., 1, 2, 4, 7, 14, 21 and 28 days after application), the dogs were stroked by a research technician to collect transferable residues on a mannequin hand. Stroking consisted of a series of complete strokes along the back line and on each side of the animal a total of 20 times, taking no notice of the position of the collar (i.e., the collar was not avoided during stroking), for a total of 60 strokes.
- The dosimeter on the mannequin hand consisted of five layers of cotton gloves. A nitrile glove was placed on the mannequin hand under the dosimeter gloves to protect it from potential contamination. Residues on the cotton gloves were analyzed individually, starting with the outermost glove. Initial analyses demonstrated that no detectable propoxur residues on the 4th and 5th glove, so only the outer three gloves were analyzed for propoxur residues.

The data from this study indicate very low transferable residues, with higher values on the first few days following application and lower levels on later days. Average transferable residues, expressed as percent of the propoxur in the applied collar, were 0.0715% on Day 0 and 0.0033% on Day 28. The transferable residue data demonstrate a two-phase decline in which a period of

fast decline is followed by an extended period of slower decline. Transferable residues declined quickly over the first few days following application (e.g., the transferable residue on Day 1 is 46% lower than that on Day 0, and the transferable residue on Day 2 is 29% lower than that on Day 1), and the rate of decline continued to diminish over the course of the study (see Figure 1). The time-weighted average transferable residue measured in this chemical- and formulation-specific transferable residue study was 0.0105% over the 28-day study period. This measured value is substantially lower than the 1.33% estimate resulting from EPA's default assumptions (EPA, 2010a,b).

Impact of Transferable Residue Data on Exposure and Risk Calculations

As stated previously, EPA (2010a) used default assumptions and estimated MOEs for post-application oral hand-to-mouth ingestion exposures for children of 55 to 82 for pet collars registered by Sergeant's and Wellmark. However, using chemical- and formulation-specific transferable residue data, the revised assessment indicates MOEs greater than 1,000 on Day 0 and MOEs up to 33,600 on Day 28. Using the 28-day time-weighted average transferable residue, MOEs are estimated to range from approximately 7,000 to 10,000. These MOEs are greater than the LOC of 1,000, which indicates that the exposures for children contacting pets wearing propoxur dog collars are not of concern. Finally, these MOE estimates are conservative because they are based on the entire collar weight, whereas in the study 38% of the original collar weight, on average, was removed and discarded upon application.

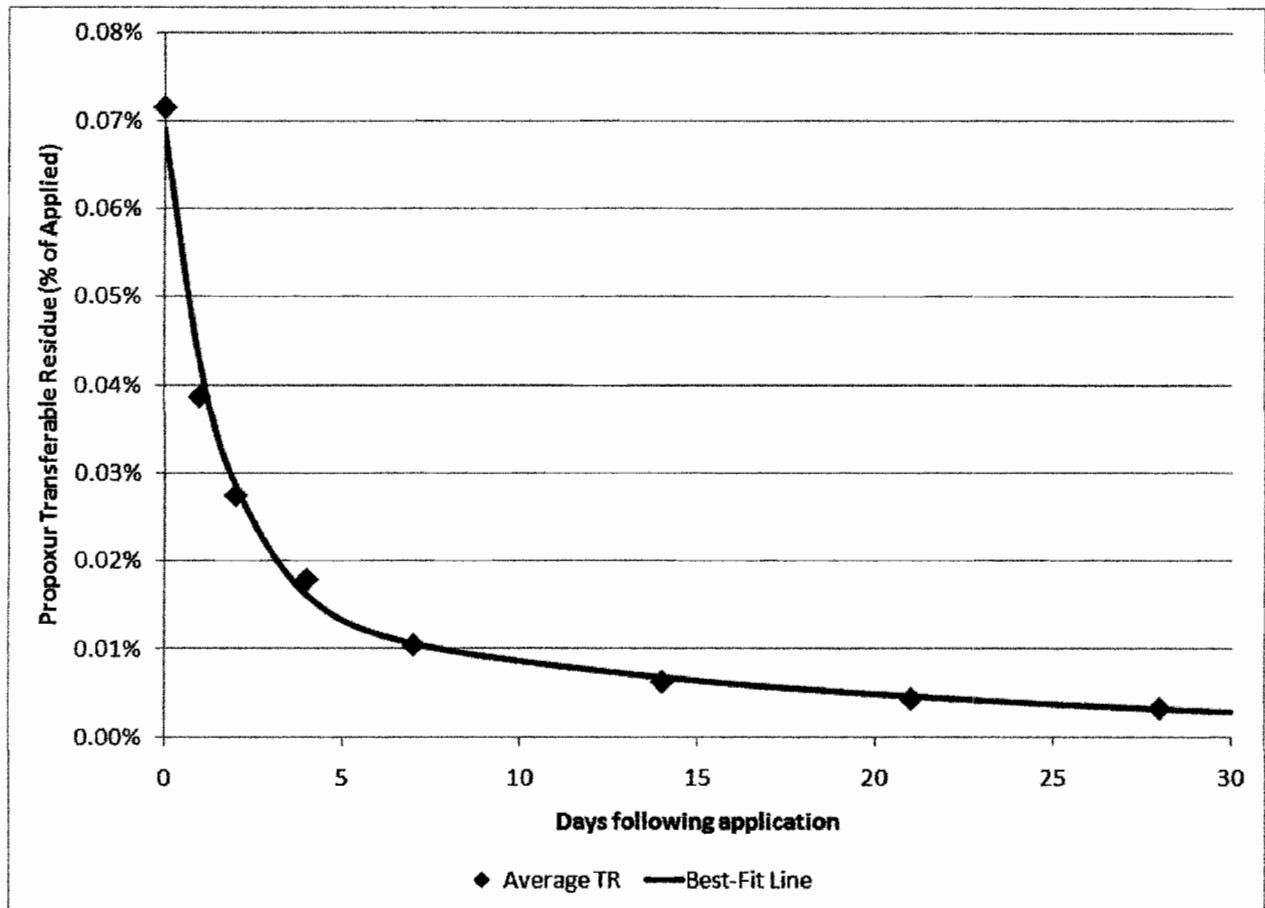
Conclusion

The dermal route of exposure for propoxur is not considered of interest for propoxur because cholinesterase inhibition was not observed after 6 hours of daily dermal exposure and because no dermal or other systemic toxicity was observed following dermal dosing for 90 days at the limit dose (1,000 mg/kg/d) required by EPA.

Cancer risk for propoxur pet collars is likewise not considered significant because the known mode of action for propoxur is cholinesterase inhibition, which reaches a maximum within 15 minutes to 1 hour of exposure followed by rapid enzyme reactivation and recovery, and because the Group B carcinogen classification and cancer potency factor for propoxur are based on exposures that were orders of magnitude greater than would be expected from currently registered uses.

Chemical- and formulation-specific transferable residue data for dog collars containing propoxur indicate very low transferable residues. The average transferable residues, expressed as a percentage of the propoxur in the collar, declined from 0.0715% on the day of application to 0.0033% on Day 28, with a time-weighted average of 0.0105% over the 28-day study period. When the measured transferable residue data are incorporated into standard EPA equations to estimate incidental hand-to-mouth exposure for children, the resulting MOEs range from greater than 1,000 on the day of collar application to 33,600 at 28 days after application. These MOEs, which are greater than the LOC for propoxur, indicate that exposures for children contacting pets wearing propoxur dog collars are not of concern.

Figure 1. Decline Trend of Average Transferable Residues (TR) Measured on Dogs Wearing Propoxur Collars



References

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