UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

Subject: Response to Comments on the Docket ID: EPA-HQ-OPP-2010-0229
Pet Spot-on Analysis and Mitigation Plan

To: Docket ID: EPA-HQ-OPP-2010-0229

From: Lois Rossi
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Lois Rossi 9/30/11

The U.S. Environmental Protection Agency is actively pursuing a series of actions to increase the safety of spot-on pesticide products for flea and tick control for cats and dogs. Fulfilling its commitment to transparency, EPA requested public comments about how best to implement the actions that the Agency is pursuing. EPA opened a docket for a 60-day public comment period on 17 March 2010 (EPA-HQ-OPP-2010-0229). The Agency would like to thank everyone who submitted comments to the docket. This document is a response to the public comments EPA received.

The Agency received over 1,100 public comments, the majority of which reported incidents of adverse effects related to the use of pesticide products for flea and tick control. The Agency entered those incident reports into a database of pesticide-related incidents. Some members of the general public reported adverse effects associated with veterinary drugs, and EPA provided these comments to the U.S. Food and Drug Administration (FDA).

Of the remaining comments, many were from members of the general public, some were a result of a letter writing campaign, and others were from the following organizations: American Veterinary Medical Association (AMVA), Animal Health Institute (AHI), Humane Society of the United States (HSUS), Natural Resource Defense Council (NRDC), Beyond Pesticides, Hesperian Group, BioSpotVictims.org, TinyTimmy.org, and Companion Animal Parasite Council (CAPC). Many of the comments received from these organizations and members of the general public raised the same or similar issues. Therefore, EPA consolidated its response to the issues by topic below.

Issue 1: EPA Harmonization with FDA

The AVMA, AHI, BioSpotVictims.org, and members of the general public requested that EPA harmonize its pre- and post-marketing studies and adverse event reporting with the FDA as well as the Veterinary International Conference on Harmonization (VICH). The AVMA specifically commented that EPA should receive adverse events though FDA's new web portal, MedWatch, for ease of reporting adverse events by veterinarians.

EPA Response:

The Agency is considering measures to bring data requirements in line with FDA's requirements for similar products and with the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products.

EPA is also considering amendments to its Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) section 6(a)(2) implementing regulations at 40 CFR Part 159. These regulations govern how EPA collects adverse effects reports and uses that data to ensure the continued safety of the pesticide products it registers. Although regulatory changes may take several years to complete, EPA is considering standardized electronic reporting and required submission of incident details rather than the current aggregate summary incident reports that EPA currently receives.

EPA agrees that it would be convenient for veterinarians to report complaints or incidents about FDA-regulated veterinary drugs and EPA-regulated pesticides to a single source. However, current EPA regulations only require registrants to submit aggregate summaries of incidents directly to EPA.

Issue 2: Inert Ingredient Testing and Disclosure

HSUS, NRDC, Beyond Pesticides, and members of the general public suggested that EPA closely examine inert/other ingredients for their toxicity. Given the number of adverse incident reports, these organizations want the entire formulation of pesticide flea and tick control products, including inert/other ingredients, to be tested. They also requested that every ingredient be disclosed on the label.

EPA Response:

The current review of incident data has not resulted in evidence to suggest concern for any specific "inert" (non-active) ingredient in registered flea and tick control products. However, EPA is pursuing the following actions to further study inert ingredients and how they might contribute to toxicity or the potential for adverse effects:

- On a case-by-case basis, EPA is no longer allowing the interchangeable use of inert ingredients in pet spot-on formulations;
- EPA is working to determine whether additional information is needed and, if so, will request that information to evaluate certain inert ingredients; and,
- EPA will disallow inert ingredients that have suspected toxic effects when and if these are identified.

Information regarding EPA's review and risk assessment of inert ingredients for use in pesticide products can be found at http://www.epa.gov/opprd001/inerts/#science.

Please see the following web page for efforts that EPA has underway with regards to public disclosure of inert ingredients in pesticide products: http://www.epa.gov/opprd001/inerts/inertdisclosure.html

Issue 3: Risk to Children

The NPDC, the Hesparian Group, and members of the general public requested that EPA change its assessment of pesticide risks to children as a result of the common, well-known use of these flea and tick control products. Biospotvictims.org expressed concerns with EPA's risk assessment process. Members of the general public requested that EPA investigate the health risks associated with the amount of chemicals in the products and fully characterize the possible exposure risks to children.

EPA Response:

EPA agrees with this comment and views the protection of children from pesticide exposure, particularly those pesticides used in residential environments, to be a priority. EPA assesses pet pesticide treatments, including spot-on products, using a screening level approach with conservative assumptions (e.g., assessment of human exposure on the day of application using the maximum application rate allowable by product labeling and incorporating a high end assumption of transfer from the treated pet to the exposed individual) and refines those assumptions as appropriate given data availability and applicable changes in methodologies. This screening level approach is referred to as a "tiered risk assessment method." The use of such an approach is consistent with overall Agency guidance for pesticide exposure and risk assessment.[1] EPA's review of pesticide products routinely includes evaluating possible dermal and oral exposures from the application of pet products and subsequent contact with treated pets.[2] The methods EPA uses to evaluate these types of pesticide exposures are outlined in standard procedures for considering residential exposures in assessments, such as evaluations of extensive dermal contact from young children and adults hugging treated animals and also toddlers mouthing their hands after contact with their treated animals (e.g., vigorous petting). EPA conducts these risk assessments to ensure that children are protected from exposure to pesticide treated pets. The FIFRA Scientific Advisory Panel has discussed and reviewed EPA's risk assessment methods on several occasions including in 1997, 1999, and 2010.[3]

The Agency refines its risk assessment methodologies as new information becomes available to ensure that its assessments reflect the current state of the science and are fully protective. As discussed at the 2010 FIFRA SAP meeting, EPA is currently in the process of updating the residential standard operating procedures (SOPs) for conducting exposure assessments to pet products using the most recently available data in a manner that is consistent with the use of data involving human research. In all cases screening

[1] U.S. EPA Guidelines for Exposure Assessment (U.S. EPA; Federal Register Volume 57, Number 104; May 29, 1992)
[2] U.S. EPA Standard Operating Procedures (SOPs) for Residential Exposure Assessments (1997)
[3] http://www.epa.gov/scipoly/sap/meetings/index.htm

level estimates are used as a starting point for evaluating the risks associated with the use of chemicals (e.g., values for total time spent with animals and not just that involved with direct contact and vigorous residue sampling methods result in conservative estimates of exposure). The application rates of products for all animal sizes are assessed. When appropriate information is available and it is warranted, probabilistic methods have been employed in order to develop a more thorough understanding of the possible risks associated with pesticides and what factors are responsible for those risks. The use of probabilistic methods, like use of a tiered approach, is consistent with Agency policy and widely recognized in the scientific literature.

Issue 4: Ban Products That Can Kill Cats

Some ingredients in spot-on products formulated for dogs can have adverse effects on cats. Members of the general public requested that EPA ban pesticide products that can kill cats. The comments also suggested that if EPA did not ban those products, it should require very explicit labeling on the spot-on products for dogs that describes the danger the products pose to cats.

EPA Response:

Although EPA does not intend to cancel dog spot-on products containing ingredients that may be toxic to cats at this time, EPA is working with the registrants of spot-on dog products to change product labels to clearly address the risks these products may pose to cats. EPA is requesting that registrants update their registrations to address public concerns with spot-on products for dogs. A letter will be sent to registrants asking that revised labels be submitted within 6 months to make the following changes:

- Split pet spot-on registrations which bear use for both cats and dogs into two separate product registrations;
- Include on product labels either the word "cat" or "dog" in the product name and increase the size of this word to at least 75% the height of the largest letter in the primary brand name;
- In product directions for use on the label repeat either the word "cat" or "dog," throughout the directions for use;
- On product labels of spot-on products for dogs include a (1.5 cm x 1.5 cm) "cat prohibition icon" (i.e., an image of a cat with a line through it) in a box located at the lower right hand corner of the front and back panel in yellow with black images. A cat prohibition icon should also be placed on the immediate container for the applicator vial and/or the vial itself;
- Include on the back panel of dog spot-on product packaging the following language:
    - Products containing permethrin, cyphenothrin, or phenothrin - "DO NOT USE ON CATS – MAY BE FATAL. Keep cats away from treated dogs for 24 hours. If applied to a cat or ingested by a cat, contact your veterinarian immediately." or
    - All other dog spot-on products - "DO NOT USE ON CATS. Keep cats away from treated dogs for 24 hours. If applied to a cat or ingested by a cat, contact your veterinarian."

Issue 5: Professional Guidance

The CAPC, AVMA, HSUS, and members of the general public commented that there is a lack of direct professional involvement between veterinarians and pet-owners that increases the possibility of adverse events associated with pet products. CAPC stated that veterinary professionals should be the source of information for the pet-owning consumer and that only products specifically dispensed or recommended by trained professionals be used by pet-owners. HSUS and the AVMA also stated that veterinarians should play a bigger role in the use of pet spot-on products, including obtaining an accurate current pet weight in a veterinary visit prior to product use.

EPA Response:

Although direct veterinary involvement in the dispensing or administering of spot-on products may have the potential to reduce the number of adverse incidents associated with these products, EPA lacks the authority to require that all pet pesticide products be dispensed only by veterinarians instead of over the counter. Further, EPA recognizes the importance of the availability of products to control fleas and ticks.

However, EPA does recommend that pet owners consult their veterinarians about the best way to protect their pets from fleas and ticks,[4] and also provides a link to the AVMA web page[5] for additional information.

Issue 6: Registrants Reporting Adverse Events and Conducting Studies

Members of the general public commented that pesticide registrants have a conflict of interest when registrants are responsible for both reporting adverse events to EPA and conducting toxicology studies on their products. Many comments suggested that either EPA or independent researchers collect the adverse event reports and conduct the toxicology studies.

EPA Response:

FIFRA makes clear that EPA must establish guidelines on the conduct of the types of studies and information necessary to support pesticide registration applications. In addition, FIFRA provides EPA with the authority to require the applicant or registrant to conduct these studies.

The Agency's registration practices and enforcement policies help ensure that registrant-developed data represent sound science. EPA's Good Laboratory Practices Standards (GLPS) compliance monitoring program helps ensure the quality and integrity of test data submitted to the Agency in support of a pesticide product registration under FIFRA[6].

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[4] "Safety Tips for Pet Owners" http://www.epa.gov/pesticides/factsheets/flea-tick.htm
[5] "Resources, American Veterinary Medical Association" http://www.epa.gov/opp00001/health/pets.htm
[6] http://www.epa.gov/compliance/monitoring/programs/fifra/glp.html

Applicants and registrants must use an extensive set of guidelines[7] and protocols for the development of required product registration data. Further, to assure the quality and integrity of data submitted to the Agency, all labs conducting studies that support or are intended to support applications for registration of pesticide products must follow proscribed GLPs. EPA also conducts inspections of these laboratories and data audits to monitor compliance.

EPA scientists conduct extensive analysis of the data submitted by applicants or registrants to ensure that the studies are appropriate and that the data are collected and analyzed accurately. In addition to registrant-submitted studies, EPA scientists also review pesticide studies from peer-reviewed scientific journals and data from a wide variety of sources when they are available. In so doing, the Agency scientists identify hazards and characterize risks using the best data available for review.

Issue 7: Hazardous Chemicals in Products

Beyond Pesticides and members of the general public requested that EPA reconsider, and ban if needed, the use of hazardous chemicals (pyrethroids, neonicotinoids, dinotefuran, amitraz) in pet products. These comments pointed out that such hazardous chemicals can increase pets' risk of cancer and human exposure to these toxic pesticides can have adverse effects. These comments also suggested that EPA encourage registrants to seek out new, less toxic ingredients that can be safely used on pets and advocate for alternatives to pesticide products such as frequent grooming and bathing, regular vacuuming, steam cleaning, and laundering to control fleas and ticks.

EPA Response:

EPA evaluates the human exposure and safety of all registered pesticides (see Issue #3), including evidence of carcinogenic potential.

EPA provides information about integrated pest management techniques (http://www.epa.gov/pesticides/factsheets/ipm.htm) on its website. EPA neither recommends nor discourages the use of spot-on products on pets, but recognizes that use of these products is important to many pet owners for control of fleas, ticks, and other parasites (see Issue # 11). Further, flea and tick products can be appropriate treatments for protecting your pets and your family's health because fleas and ticks can transmit disease. If EPA were to become aware of an increase in pet cancer incidence from the use of these products, EPA would carefully investigate the problem and consider appropriate regulatory action.

Issue 8. EPA Analysis Methods for Pet Products:

The AHI, HSUS, CAPC, and SpotVictims.org comments addressed various aspects of EPA's analysis of the adverse effects incident reports associated with spot-on products and safety testing of spot-on products. Similar comments are grouped together below.

[7] http://www.epa.gov/ocspp/pubs/frs/home/guidelin.htm

The AHI commented that registrants did not have the opportunity to provide input into the analysis of spot-on incidents.

> **EPA Response:** EPA must conduct analysis of adverse effect incident reports in an independent and unbiased manner. Once EPA completed its analysis, EPA met with registrants to communicate the findings, released the finding to the public on the Agency's web page and in the docket in the *Review of Enhanced Reporting of 2008 Pet Spot-on Incidents*, and presented our findings to the public via webinar.

AHI commented that there was little public transparency in EPA's criteria used for the "cleaning" of the data, which can lead to erroneous conclusions if performed inconsistently. CAPC commented that EPA did not perform a statistical analysis, evaluate causality, or consider product purchase source. Others commented that EPA did not consider spontaneous background rates.

> **EPA Response:** EPA data "cleanup" was required because the registrant submissions varied widely in format and information reported. As reported in the *Review of Enhanced Reporting of 2008 Pet Spot-on Incidents*: "Because the data were prepared by the registrants on short notice, the data varied in quality and there were often inconsistencies in terminology, spelling, and formats both between companies and within the same spreadsheet. Two companies sent caveats concerning these problems with their submissions. Sometimes there were multiple information values in the same cell (breed + species + age, for example). Not evaluated were incidents with multiple animals, repeat records for the same incident, non-USA incidents, incidents with no registration numbers, species not named, and ambiguous data." EPA assigned one person to the task of data "cleanup" and sorting in order to ensure consistency between registrant reports.
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> EPA determined that statistical analysis was not appropriate because of the variance in data quality among registrant reports. EPA requested that registrants assign a causality or certainty index to each report; however, not all registrants assigned a certainty index due to the large number of incidents associated with their products. Therefore, EPA did not have all the necessary information needed to evaluate causality for each incident.
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> EPA did not include spontaneous background rates in the *Review of Enhanced Reporting of 2008 Pet Spot-on Incidents* because EPA's qualitative assessment identified sensitive populations or patterns of use, not a count of the total number of adverse effects incidents associated with pet spot-on products.
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> EPA did not include information on product purchase source in the *Review of Enhanced Reporting of 2008 Pet Spot-on Incidents* because this information was generally not available in incident reports.
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> To ensure sound science and scientific integrity of the *Review of Enhanced Reporting of 2008 Pet Spot-on Incidents*, EPA held an external scientific peer review panel workshop that included technical expert reviewers from the FDA's Center for Veterinary Medicine (CVM) and Health Canada's Pest Management Regulatory Agency (PMRA) incident

team, and received input from Australia's Director of Advanced Veterinary Therapeutics, Dr. Stephen Page.

Biospotvictims.org commented that EPA did not evaluate incidents prior to 2008 and only included incidents reported by the registrants in the evaluation. In addition, comments noted that a disproportionately large amount of data was presented for dogs versus that for cats.

EPA Response: EPA did not evaluate incidents prior to 2008 because it focused on the most relevant and recent reports associated with current products. EPA's focus on incident reports from 2008 provided an adequate number of reports in order to conduct the analysis. The *Review of Enhanced Reporting of 2008 Pet Spot-on Incidents* evaluated adverse effects incidents submitted by spot-on pet product registrants because the great majority of incidents are reported to registrants, and then to EPA. EPA was able to more fully assess the incident information associated with dogs because registrants submitted more data for dogs than for cats, particularly regarding dog breeds and weights.

Biospotvictims.org recommended that EPA require registrants to conduct companion animal safety studies that include diverse breeds. HSUS specifically recommended that EPA follow the precautionary principle approach. These and other similar comments also stated that EPA should encourage consumers to exercise significant caution when using these products on their pets.

EPA Response: EPA is considering a requirement for registrants to perform field trials as required by FDA and the international community that will include diverse breeds. Further, on a case-by-case basis, EPA is requiring that registrants continue to provide enhanced adverse effects incident reports so EPA can better track incidents associated with any individual pet spot-on product and determine if unreasonable adverse effects are occurring.

With regard to the comment that consumers should be encouraged to exercise caution, the Agency fully agrees. On EPA's website, the Agency encourages consumers to use caution with spot-on pet products. In addition, EPA is requesting enhanced label warnings on registered products (see Issue # 4) as well as informational videos to better disseminate warnings to consumers.

Biospotvictims.org commented that the efficacy report for the Sergeant's cyphenothrin product, EPA Reg. No. 2517-85, reported neurological signs that were not observed in the safety study. The comment also noted that labeled dosages are approximately 2X larger than the 1X dosages that Sergeant's assessed in the safety study and a 5X margin of safety was not demonstrated.

EPA Response: EPA reported these issues in the review of spot-on incidents, *Review of Enhanced Reporting of 2008 Pet Spot-on Incidents* and EPA discussed these at length in the registration for the two cyphenothrin products. The efficacy study reported clinical signs at a 1X dose. Three other studies tested at equal or higher doses (1X to 5X) and did not report similar clinical observations. EPA considers it likely that the clinical observations reported in the efficacy study may have been typical behavior of laboratory dogs which other observers may not have reported. As a precaution, EPA required that

the registrant change the application site to a stripe halfway along the dogs' back rather than along the entire length of the back to prevent ingestion of product.

Issue 9: Label Changes

HSUS recommended that EPA include the following on spot-on pet product labels:

- an expanded toxicity warning listing potential side effects and descriptions of possible adverse reactions for the animals alongside the chemical(s) that may produce these effects;
- directions for a pet owner if a pet seems to be experiencing any of the side effects; and,
- clear acknowledgment on all packaging that spot-on products are pesticides.

In addition, Beyond Pesticides and BioSpotVictims.org, stated that the Humane Society recommended label changes did not go far enough, and BioSpotVictims.org requested that EPA adopt FDA label regulations for pet products.

EPA Response

EPA is requesting, via letter, that registrants make appropriate label changes for individual cat and dog spot-on products within 6 months of receipt. See also the response to Issue #4. Similar to FDA-approved drug labels, EPA is working to ensure product labels include information on side effects and possible adverse reactions, and instructions in case of an adverse reaction. For example, EPA proposes the following language under the heading, Side Effects: "*Monitor your cat/dog after application. Side effects may include signs of skin irritation such as redness, scratching, or other signs of discomfort. Gastrointestinal signs such as vomiting or diarrhea have also been reported. If these or other side effects occur, consult your veterinarian or [Registrant at 1-800-number].*"

AHI commented that EPA should make spot-on pet product label changes on a product specific basis without brand or trade names restrictions because such restrictions would not deter the occurrence of adverse events.

EPA Response:

EPA reviewed and considered label changes for particular brand and/or trade names. After meeting with spot-on product registrants, EPA determined that changes to product names would be a difficult task for most registrants. At this time, EPA is recommending that the word, "cat" or "dog," appear in or in close proximity to the product name. EPA proposed this change due to the results of its evaluation of pet incidents which identified that consumers may confuse cat and dog products resulting in adverse effects incident reports, and unintentional cat exposure to dog products.

Issue 10: Counterfeit Products

A member of the general public commented that EPA should take a tougher stance on counterfeit products, stating the rise in adverse effects could, in part, be due to ingredients used in counterfeit products.

EPA Response:

EPA is aware of counterfeit pet pesticides designed to look like legitimately registered pesticide products. EPA makes information about counterfeit pet products available online to help consumers avoid unregistered pet products.[8] In addition, EPA may take civil or criminal enforcement action against those who sell, distribute, or import unregistered or counterfeit pet products, and has done so in the past. For example, EPA cooperated in the recent prosecution of a Rhode Island man for the internet sale of counterfeit pet pesticides that resulted in a prison sentence[9]. In addition, in 2004 EPA issued stop sale, use, and removal orders to retailers and other distributors of counterfeit products for use on pets.[10]

Issue 11: Pet Pesticide Products are Beneficial

Organizations, including AHI, AVMA, and CAPC, as well as members of the general public wanted EPA to keep in mind that flea and tick control products are important to pets' quality of life. CAPC specifically noted that the relative safety and value of a product should be evaluated with consideration of the benefits derived from their use.

EPA Response:

EPA agrees that flea and tick control products can be important to pets' quality of life and has acknowledged that in public statements and communications. As reported in EPA's *Review of Enhanced Reporting of 2008 Pet Spot-on Incidents*: "Control of these external parasites is desirable because they can cause discomfort to the pet, skin disease, and anemia. In addition, fleas can transmit tapeworms to pets, and ticks can cause tick paralysis and can transmit diseases such as Lyme disease and Rocky Mountain Spotted Fever, to both pets and people. Severe flea infestations can result in flea bites to people." Further, under FIFRA, EPA considers the risks and benefits of pesticide products in making regulatory decisions.

Issue 12: Stricter Regulations

Member of the general public expressed their support of EPA's mitigation plans[11] and encouraged EPA to impose tougher regulations regarding spot-on products. AVMA noted their appreciation for EPA's initiative. The AHI recommended that EPA work with individual

[8] http://www.epa.gov/opp00001/factsheets/petproduct.htm
[9] http://www.epa.gov/compliance/resources/cases/criminal/highlights/2011/buerman-john-03-01-11.pdf
[10] http://www.epa.gov/opp00001/factsheets/retailerfactsh.pdf
[11] http://www.epa.gov/opp00001/health/petproductseval.html#mitigation

registrants to address issues and take precise (as opposed to categorical) action with respect to individual products and address any label changes on a product- and active ingredient-specific basis.

EPA Response:

EPA appreciates the public's support of EPA's efforts to impose stricter regulations on pet spot-on products.

EPA continues to work with individual registrants to implement necessary label changes and improve safety testing. EPA is making some categorical action because pet spot-on products as a category result in significant pet adverse event reporting. However, EPA is also taking precise, product-specific action and tailoring label changes by product and active ingredient. Further, EPA is willing to discuss mitigation actions and/or product-specific concerns with registrants upon request.