Frequently Asked Questions by Pet Owners about

The EPA's Investigation of Spot-on Flea and Tick Treatments

In April 2009, the Environmental Protection Agency (EPA) issued an advisory concerning approximately 70 spot-on flea and tick control products because of an increase in the number of reports of adverse reactions to the products. Reactions reported included skin irritation, skin burns, seizures, and death. In May 2009, the EPA met with the manufacturers of the products to discuss the issue. In a July 2009 advisory, the EPA and the Food and Drug Administration (FDA) cautioned consumers to be cautious when using these products and to consult with their veterinarian. On March 17, 2010, the EPA announced it was taking steps to increase the safety of spot-on pesticide products for flea and tick control for cats and dogs. These steps include reviewing labels to determine which ones need stronger and clearer labeling statements, and developing more stringent testing and evaluation requirements for existing and new products.

The following questions and answers are based on the AVMA's interpretation of the EPA's evaluation and mitigation plan along with perspectives from various sources. If you need further clarification of the answers, or if you have additional questions, you may need to speak to an EPA representative. If you would like to suggest additional questions for this document, please contact Dr. Kimberly May or Dr. Lynne White-Shim.

Q: Why is the EPA involved in this? Doesn't the FDA regulate drugs?
A: Per the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), the EPA is responsible for, among other things, assuring that pesticides sold in the U.S. do not cause unreasonable risks to animal health when used properly. Although consumers might consider these spot-ons to be "drugs," they are largely under EPA regulation because the parasites they control (fleas, ticks and, to a lesser extent, mosquitoes, lice and mites) are considered pests, and these products are actually considered to be pesticides. Federal law requires EPA registration of pesticides before they can be sold to the public.

However, some spot-on products are actually considered animal drugs and are instead regulated by the FDA. Very few spot-ons are regulated by the Food and Drug Administration as prescription drugs. As a general rule of thumb, spot-ons that only treat external parasites (fleas, ticks, etc.) are regulated by the EPA. Spot-ons that treat external parasites AND internal parasites (intestinal worms, etc.) are considered animal drugs and are regulated by the FDA.

The best way to determine if the product you use is regulated by the EPA or the FDA, look on the label. If the product is regulated by the EPA, the label includes the words "EPA Registration Number" or "EPA Reg. No." followed by a number. Products regulated by the FDA have a New Animal Drug

Application number which can usually be found on the product's label and package insert, along with the statement "Approved by FDA." FDA-approved products can also be found at FDA's Green Book On-Line.

Q: Why did the EPA's investigation begin?
A: Per the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), the EPA is responsible for, among other things, assuring that pesticides sold in the U.S. do not cause unreasonable risks to animal health when used properly. When it is determined there is a concern, the FIFRA allows EPA to review data and take steps to reduce or eliminate risks.

When reviewing reports of adverse events, the EPA found that from 2007 to 2008, the numbers of adverse event incidents increased by 53%. There wasn't an obvious explanation for this increase, so the EPA intensified its evaluation of spot-on products to determine the cause. While the agency was performing its investigation, it advised consumers to use caution in using the products by following the label, watch for adverse reactions after product application, and seek guidance from their veterinarian about how to use these products safely and responsibly.

Q: What is an "acceptable" level of adverse events, and what level would be sufficient to trigger concern by the EPA?
A: There isn't a specific number or level that is acceptable – the EPA reviews the reports and considers each product (and its reported adverse events) on a case-by-case basis. In addition, any significant increase in the number of adverse events reported for a product will trigger a thorough review of the product and the reports.

Q: How long will the EPA's evaluation of these products take?
A: The initial EPA evaluation of spot-ons is complete. Now the EPA is determining ways forward in implementing steps to reduce adverse events associated with these products, including tighter regulation of spot-on products, product-specific labeling changes, and increased public outreach and education on proper pesticide use. The agency is also likely to standardize the adverse event reporting system to make it more uniform across manufacturers. The EPA is also working with the manufacturers about changes to specific products.

Q: What is the evaluation process for these products to become approved in the first place?
A: Before a manufacturer can sell or distribute any pesticide in the U.S., the EPA must review the data from studies on the pesticide to determine that its use will not pose unreasonable risks to human health, to the environment, or to non-target species (the species the product isn't intended to control – in this case, the non-target species include dogs and cats, and the target species are the fleas and ticks). EPA's Guideline No. 870.7200, "Companion Animal Safety" lists pre-market testing requirements for pesticide products to be used in dogs and cats. The safety studies help assure safety and ensure an adequate margin of safety for products that are misused (overused). Safety of up to 5 times the labeled dosage must be demonstrated. Once it has been determined that the product does not pose unreasonable risks, it is licensed or registered for use only according to the label directions.

Currently, no pre-market clinical trials (ie, studies on owned pets before the product goes on the market) are required for EPA approval. This is one of the many things being evaluated by the EPA as they address this issue – it is possible that more safety testing will be required before a product is approved.

Q: Why weren't these problems caught when the products were first being evaluated for approval?

A: Although safety trials are performed prior to approval, these tests are performed on a limited number of animals in a controlled environment, not by pet owners in a "real world" situation. It is possible that this limited the agency's ability to detect safety concerns that became more apparent when the products were used in larger numbers of doses and in less controlled environments. In the summary of meetings between the EPA and spot-on manufacturers, the EPA stated that the investigative team also found that the data the EPA now requires (to illustrate the safety of these products for pets) do not accurately predict the toxicity when the product is approved and being widely used by consumers.

Q: What products are involved, and how many adverse events have been filed for each product?

A: All EPA-registered spot-on flea and tick preventive products, including those sold in retail stores and through veterinarians, are involved in the EPA's increased surveillance efforts and response plan. The active ingredients in these products include amitraz, cyphenothrin, dinotefuron, etofenprox, fipronil, imidicloprid, metaflumizone, permethrin, pyriproxyfen, and S-methoprene.

A total of approximately 43,000 reports were reported for 2008. Products containing the following active ingredients were involved in the analysis: cyphenothrin, pyriproxyfen, phenothrin, S-methoprene, permethrin, dinotefuran, imidacloprid, amitraz, methaflumizone, fipronil, and etofenprox. Specific products involved can be viewed on the EPA website at http://www.epa.gov/pesticides/health/petproductsders.html.

However, you shouldn't make assumptions based on the number of adverse reactions associated with each product because the number of adverse events reported may or may not be related to the total number sold. In addition, the location where the pet owner purchased the product (veterinary clinic, online, retail store, pet store, etc.) could have an effect on the pet owner's ability or interest in reporting adverse effects.

Q: Have any of these products been recalled?

A: None of these products have been recalled.

Q: What adverse events have been reported, and at what numbers?

A: A wide range of adverse events was reported, from minor incidents (such as skin irritation) to deaths. The EPA has 4 categories for adverse events:

- Domestic Animal Death: the animal died or was euthanized due to the adverse event
- Domestic Animal Major: the animal developed life-threatening clinical signs (symptoms) or a chronic disability as a result of the adverse event.
- Domestic Animal Moderate: the animal developed clinical signs (symptoms) that were more severe or prolonged than would be seen with a minor reaction, required treatment, and completely resolved.

Domestic Animal Minor: the animal developed clinical signs (symptoms) that were relatively minor and rapidly resolved. Animals that receive minimal treatment for a mild condition (for example, the veterinarian prescribes a medicated shampoo or an ointment for a mild skin rash) are often placed in this category.

The EPA estimates that in 2008, manufacturers received from pet owners approximately 43,000 reports of adverse events – of those 43,000, approximately 1,300 fit in the Domestic Animal Major or Domestic

Animal Death categories. The EPA states that approximately 1% of the adverse events associated with these products resulted in death in 2008.
Some manufacturers assign a "certainty index" to the reports, which is their assessment of how likely (or unlikely) the adverse reaction was related to the use of the product – however, not all manufacturers included the index in their reports to the EPA.

The EPA determined that most of the incidents were minor, but deaths were reportedly associated with all of the products. Approximately 1.9% of the incidents in 2007 were deaths and 2.9% were major incidents, while in 2008 1.4% of incidents were deaths and 1.6% were major incidents. The most common systems affected in both dogs and cats were the dermal (skin), gastrointestinal, and nervous systems.

Q: Have all of these complaints been verified? If not, how many have been verified?
A: No, not all of these complaints have been verified. The EPA can't really investigate or verify the reports – the agency can only review the information that is presented by the manufacturers or through its adverse event reporting system on the National Pesticide Information Center website. In addition, although all manufacturers are required to file reports to the EPA, there are differences in how each manufacturer reports the information: most manufacturers only provide aggregate reports, which give the total count of deaths, major, moderate, and minor incidents, while others provide much more detailed reports.

For its incident report analysis, the EPA requested that the manufacturers provide detailed reports for further review. Some of the manufacturers included the certainty index (the manufacturer's assessment of how likely – or unlikely – the adverse reaction was related to the use of the product) in their detailed reports, but not all of them did so. Despite the inconsistency in the reports, the EPA did gain a lot of valuable information from the manufacturers.

Q: Were certain animals more likely to have adverse events from spot-on flea and tick products? If so, why are they more likely to have a problem?
A: The EPA found that young dogs (less than 3 years old) and small-breed dogs (weighing 10-20 pounds) tended to be the most commonly reported for all products. Small breeds were over-represented especially with cyphenothrin- and permethrin-containing products. Chihuahuas, Shih Tzus, Miniature Poodles, Pomeranians, and Bichon Frises appeared to be generally over-represented across the spot-on products (as compared with their respective American Kennel Club popularity rankings).

There are three possible explanations for these findings:

1) the weight ranges listed on the products might be too wide, resulting in too-high doses for dogs toward the bottom of the weight range;
2) misuse of the products, such as buying a product labeled for a higher weight range and dividing the product between two or more smaller dogs, could result in too-high doses for smaller dogs;
3) small dogs might be more likely to have adverse reactions, even when treated with the appropriate product in the appropriate amount.

In cats, the weight seemed to be less of a factor because most cats fall into a range of 5-15 pounds. There was a high number of severe incidents associated with misuse of permethrin-containing dog products in cats, despite labels that warned against their use in cats.

Q: Is a product with more adverse event reports considered less safe than one with a higher number of reported adverse events?

A: There is no way to determine relative safety of spot-on products by counting incident reports, because of several factors: 1) the total number of doses of each product sold in a given year is not publicly known; 2) some of the incident reports were discarded because they didn't contain enough information, and were considered invalid; 3) there were possible confounding factors, such as differences in pet owners' interest in reporting adverse events (which may be influenced by where they purchased the product); and 4) it could not be confirmed in all cases that the adverse event was caused by the spot-on product and not something else.

Q: Are the increased number of reported adverse events actually due to more adverse events occurring, more products being sold, more products being sold over-the-counter (ie, without veterinary involvement), or a change in the reporting system?

A: It is difficult to know why there were increased reports filed from 2007 to 2008 because there is a substantial amount of unknown information. We know that a total of approximately 270,000,000 doses of these products were sold in the U.S. in 2008, but we don't know the details of those sales. The manufacturers' sales information is confidential information and the companies don't report their sales in the same way, so it isn't clear whether or not the increase in reports of adverse reactions is due to increased sales or an actual increase in the relative number of adverse reactions..

For example, if 5 adverse reactions were reported associated with the use of Product A last year, but 10 reactions were reported this year, we don't have enough information to know if those extra 5 reactions reported occurred because more doses of Product A were sold this year, or if Product A is causing more reactions this year.

Q: It seems to me this spike in adverse event reports coincides with the time many of these products became available online and in pet stores. Could this be the cause?

A: How the pet owners got the product – whether it was from a veterinary practice, online source, or retail or wholesale store – wasn't reported for most of the cases, so we don't really know if that affected the number of reports. However, based on the probability that products sold by veterinarians could have caused fewer problems because the pet owners were more likely to receive proper guidance and instructions for safe use of the product on their pets, it is possible that products purchased from veterinary clinics accounted for a lesser number of adverse events. For example, one of the major causes of adverse events is the use of dog-only products on cats. If a cat owner purchases a product from a store, it is possible for them to pick up the wrong box, or maybe they don't notice a warning not to use it on cats. However, a veterinarian won't give a cat owner a spot-on flea/tick product labeled only for use on dogs, and this decreases the risk of incorrectly using the product.

Q: Why are some of these products available over-the-counter (OTC), while others can only be purchased from a veterinarian?

A: EPA-registered spot-on products are in fact available as "non-restricted use" products that are commercially available through a wide variety of sellers – the EPA does not determine who can sell these non-restricted use products, and there is no "over the counter" vs. prescription classification of pesticide products. Basically, it's up to the manufacturer to determine how they want to distribute their product.

Q: Are the over-the-counter (OTC) products associated with higher numbers of reported adverse events?

A: First of all, we need to clarify that although many people refer to spot-on flea and tick products as "over-the-counter" if they can be sold at discount or retail stores, there really isn't an official designation. The product is simply registered with the EPA. There are "restricted use" and "non-restricted use" categories, but all of the spot-ons used on pets fall into the "non-restricted use" category. In addition, the EPA doesn't determine who will sell the product (whether it's through veterinarians, through stores, or other outlets) – that decision is made by the manufacturer.

Since the EPA doesn't distinguish "over-the-counter" products from those available only through veterinarians, there's not enough information to say that a product sold through one outlet is more of a problem than one sold through a different outlet.

Regardless of where the product is purchased, it is important that the label directions are closely followed because deviation from labeled directions is not necessarily safe and is illegal.

Q: As a veterinarian, what do I tell my clients when they ask me if these products are safe?

A: EPA-registered products are generally very safe products to use, especially when they are used according to the manufacturer's label recommendations and when used by owners in consultation with their veterinarian. It is very important that pet owners consult with their veterinarian to determine which product may be the best choice based on the pet's health, age, and lifestyle.

Veterinarians should reiterate to their clients that , when using spot-on products, it is vital to read the product label and follow all instructions. Veterinarians should ensure that their clients are using the correct spot-on for your specific pet and particular pest problem and species of animal. Spot-on products labeled for dogs must only be used on dogs (and not cats), for example. In addition, clients must observe all age and/or size restrictions and any reapplication intervals identified. And finally, veterinarians should assess each animal individually because spot-on products may not be appropriate for use on weak, aged, medicated, sick, pregnant, or nursing animals and because pets have varying sensitivities to pesticides.

Veterinarians should also recommend that clients closely observe their pets during and after treatment and monitor thme for any signs of an adverse reaction, particularly when using these products for the first time.

For more information see the EPA factsheet, "Taking care of fleas and ticks on your pet."

Q: How can I file an adverse event report regarding a spot-on product?

A: To report adverse events associated with spot-on (topical) flea or tick products, contact the National Pesticide Information Center (NPIC) online or by calling 1.800.858.7378. To report problems with FDA- approved drugs go to How to Report An Adverse Drug Experience.

Pet owners who think their pets are experiencing an adverse event related to the use of a spot-on product should immediately contact a veterinarian. Pet owners can also report adverse events to the NPIC directly by calling 1.800.858.7378.

The ASPCA Animal Poison Control Center (888.426.4435) can also provide emergency guidance for pet owners and veterinarians. The center usually charges a fee for consultation.

Q: What are the possible outcomes of the EPA's evaluation of these products?
A: The EPA is considering various approaches to address the safety concerns it has determined are associated with spot-on products. First, product-specific and labeling changes might be needed, such as narrower dosage weight ranges in some cases, more easily understood labeling, and more obvious warning statements and labels for some products (for example, more obvious labeling that certain products should not be used on cats). The EPA is also discussing inert ingredients (the other ingredients in the product that are important but don't specifically account for the labeled effect of the product – for example, the inert ingredients in a spot-on are the ones that don't actively kill or repel the fleas or ticks, but are still ingredients in the product) in individual meetings with registrants. The EPA may tighten the restrictions on the inert ingredients.

Second, the EPA plans to implement tighter regulations associated with spot-on products in general, including standardized adverse event reporting data and sales report data, and equivalent standards to those used by FDA Center for Veterinary Medicine in approving and reviewing animal drugs. The EPA is also evaluating its requirements for safety testing prior to the approval and consumer sales of these products, and will take steps to bring data requirements more in line with the FDA's testing requirements to allow the EPA to more thoroughly assess the safety of the products.

At this time, once a product is registered with the EPA, it is registered forever, with a registration review every 15 years, unless the EPA cancels the registration. Because it can be more difficult to revoke a registration once a product is approved an on the market, the EPA is also considering conditional registration. A conditional registration would have time limitations (like an expiration date for the registration) and more strict conditions placed on the registration, which would allow the EPA more freedom to evaluate the products' safety on a regular basis. If a product was only conditionally registered, when that approval is due to expire, the EPA could re-evaluate the product's safety to determine whether or not they would renew the registration.

Finally, the EPA plans to work more closely with the manufacturers and with veterinarians to educate pet owners about he safe use of spot-on products.

Q: Is there a chance that flea & tick products will once again become prescription-only products?
A: No. EPA does not have legal authority to regulate where spot-on products are sold or who sells them.

Q: What is being done by the EPA to prevent problems like this in the future?
A: Specific steps being considered by the EPA include the following:

- Changes in product labels to deter misuse and to ensure appropriate weight ranges for products
- Increased pre-approval safety testing and post-sales surveillance
- Conditional product registrations with time limitations (see question above for an explanation), and
- Standardized sales and adverse events reporting

Q: What can veterinarians do to prevent problems like this in the future?
A: Veterinarians can do their part by educating their clients on the choice and safe use of these products.

Veterinarians should not use (or recommend the use of) these products in any way that differs from the label. Most animal **drugs** used by veterinarians to treat their patients are regulated by the FDA, and there are provisions in the Animal Medicinal Drug Use Clarification Act (AMDUCA) that allow what is called "extralabel use" of the drug under certain circumstances. These provisions do not exist for EPA-labeled products. So, for example, a veterinarian cannot legally recommend or use an EPA-registered spot-on product more frequently than the label directions state.

Similarly, there are specific rules that must be met when veterinarians are repackaging these products for sale. This includes selling individual doses from a multi-dose pack or removing a dose (or doses) from the original package. Any repackaged product must be packaged in child-proof containers and must be labeled with all of the applicable directions, including:

a. The common or trade name(s) and percentage(s) of the active ingredient(s)
b. The EPA product registration number
c. Directions for the use
d. The name and address of the veterinarian
e. An antidote statement (what should be given if the product is ingested or a person or animal is improperly exposed to the product)
f. Directions for appropriate disposal of the pesticide and the packaging
g. Human safety precautionary statements, including but not limited to "for application to animals only," "keep out of reach of children," and "in case of accident, contact local physician immediately

More information on repackaging can be found in "Pesticide repackaging: what veterinarians need to know to avoid steep fines," a 2005 JAVMA News article.

Q: What can pet owners do to prevent problems like this in the future?
A: First and foremost, they should always follow label directions! The AVMA recommends that pet owners discuss the use of spot-on products with their veterinarian to determine the safest and best choice for each pet. Products labeled for use on dogs should only be used on dogs, and **never** on cats. Owners need to apply the product as instructed by the label, and at the time intervals as directed by the label. They should always talk to their veterinarian before applying any spot-on products on the dog or cat if it is weak, aged, ill, on medications, pregnant or nursing.

One pet may react differently to a product than another pet. When using these products, owners should monitor their pet for any signs of an adverse reaction, including anxiousness, excessive itching or scratching, skin redness or swelling, vomiting, or any abnormal behavior. And most importantly, owners should report these incidents to their veterinarians so adverse event reports can be filed.

Q: How do I reach the EPA if I have additional questions about this issue?
A: There are additional questions and answers on the EPA's "Frequent Questions" page. If your question has still not been answered, additional contact information can be found on the EPA's "Contacts and Organization" page or by emailing pets@epa.gov.