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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Special Review Project - Overview of Pet Pesticide Products

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The objective of this document is to provide an overview of pesticide products registered for direct use on animals (dogs and cats), the requirements for their registration and the incidents of adverse effects in animals. In addition, recommendations for evaluating these products, i.e. whether under special review or reregistration, will be presented.

SUMMARY

There are 1393 active Section 3 registered products for use on dogs and cats, according to REFS. Of these, 1262 are registered for flea and tick control. (This includes products registered for treating kennels, animal's bedding and premises.) Other pesticides

registered for use on domestic animals include products for ear mite treatment in dogs and cats, for insect (lice and grubs) control in cattle and as fly repellents on horses. The types of product preparations regulated by EPA include shampoos, sprays, dips, dusts, collars and spot-ons. Multiple products are often used simultaneously or sequentially. The most commonly used active ingredients in pesticide products for direct application to domestic animals are synergized pyrethrins, synthetic pyrethroids, organophosphates and carbamates. Many products contain combinations of active ingredients.

The safety requirements for regulation of pet pesticide products have been ill-defined and inconsistently applied in the past. Domestic animal safety studies are designed to determine the margin of safety of a final formulation in the labeled species. These studies have been included in Subdivision F of the Pesticide Assessment Guidelines, but detailed guidance on how to conduct the studies has not been prepared until recently. Prior to 1987, domestic animal safety studies were not consistently required for registration of pet products. The occurrence of a large number of adverse reactions, including deaths, in dogs and cats from a product containing DEET and fenvalerate (trade name Blockade) caused OPP to reexamine the safety requirements for these products. Most chemicals used in pet products have been previously registered for agricultural use. Long-term studies in dogs with the technical active ingredient are part of the required toxicity data base. Therefore, there is a good measure of the chemical's toxicity at exaggerated oral doses in this species. However, there are no such studies in cats, the domestic animal species which is most sensitive to xenobiotics. Cats are deficient in an enzyme responsible for the metabolism of drugs and chemicals. As stated previously, many pet products are combinations of active ingredients. The safety of such combinations cannot be assumed from studies on individual active ingredients.

Use experience, in the form of incident reports, is available from several sources, including the National Animal Poison Control Center (NAPCC), the American Association of Poison Control Centers and OPP's Incident Data System. Yearly reports from the NAPCC have consistently ranked pesticides as the number one group of chemicals involved in calls to the Center; insecticides have been responsible for the most calls reporting clinical signs of toxicosis. In 1984, of the 1260 insecticide cases in cats and dogs, one-third were judged to be definite or suspected toxicosis. In 1986, of the approximate 1767 insecticide calls in dogs, 36.2% were categorized as toxicosis or suspected toxicosis. Of the approximate 1304 insecticide calls in cats, 57.7% were classified as toxicosis or suspected toxicosis. Of the 440 calls in which pets were exposed via the topical route and had clinical signs compatible with the toxicant in question, 82% were due to insecticides. In 1992, the top 25 generic chemicals involved in the 12,611 cases in dogs and the 5351 cases in cats were listed. Of the top 15 generics, 14 in

dogs and 15 in cats were pesticides.

The Hennepin Regional Poison Control Center in the Twin Cities area of Minnesota reported that between 1990 and 1992, a total of 12,925 calls regarding domestic animals were received; 69% for dogs and 17.7% for cats. Pesticides were the number one toxicant category, comprising 20% of all calls.

There are more than 4,000 incidents for domestic animals in the Incident Data System (IDS), nearly as many as those for humans. Reports from registrants and other sources on individual products are referred to HED and EFED for review and a summary of the incident is entered into IDS. At present, due to resource constraints, there is a backlog for both entering reports into IDS and reviewing them in HED. Additionally, a few registrants of pet products have labeled their incidents as Confidential; these have not been entered into IDS. Some registrants also submit summary reports of all their products for a certain time period. These practices complicate both the inclusion of the incidents in IDS and their review by HED.

Chemicals used in pet products which have the most incidents in IDS are piperonyl butoxide (2410* total, in humans and animals), pyrethrins (1615* in animals), MGK-264 (1553* total, in humans and animals), permethrin (521 in animals), chlorpyrifos (277 in animals) and carbaryl (157 in animals). (The numbers marked with * are likely higher due to reports labeled confidential.) Of these, chlorpyrifos is presently undergoing reregistration and permethrin is scheduled for the fourth quarter of 1996. Carbaryl is on List A; the rest are on List B.

The only OPP data on the amount of pet pesticide products in use comes from the 1990 National Home and Garden Pesticide Use Survey. The top ten chemicals (accounting for approximately 68% of chemicals) used for the site cat, dog or kennel (in descending estimated thousands of products) were piperonyl butoxide, pyrethrins, MGK-264, carbaryl, aliphatic petroleum hydrocarbons, chlorpyrifos, propoxur, DEET, tetramethrin and ethyl alcohol.

The California Department of Pesticide Regulation has recently put into place several outreach initiatives to educate pet owners and groomers about pesticides used on animals. These initiatives resulted after a state senator inquired about the safe use of these products. In addition, a study was conducted which linked illnesses in groomers to dermal exposure to pet products.

RECOMMENDATIONS

OREB recommends the following actions be taken regarding pet pesticide products.

1) Pet products should be evaluated under the reregistration of

individual active ingredients rather than considering them as a group under special review. The classes of chemicals and individual active ingredients in pet products vary enough in toxicity and use patterns that regulating them as a group would not be efficient.

2) Registrants should be required to conduct domestic animal safety studies for products containing active ingredients undergoing reregistration, if such studies were not done at the time of the initial registration. Studies should be conducted in all of the species on the label.

3) The review and analysis of incident data and reports, both in the Incident Data System (IDS) and the veterinary literature, were major contributions to the recent chlorpyrifos and propoxur reregistration evaluations. The chemicals in pet products scheduled for reregistration in the near future, specifically permethrin and pyrethrins, have large numbers of incidents in IDS, most of which have not been reviewed by HED. Given the value of the incident reports and the lack of resources for their review, OREB recommends that OPP purchase data from the National Animal Poison Control Center (NAPCC). An additional consideration is the quality of the incident reports from NAPCC. Detailed information on each case is collected, causality of an incident is evaluated by a veterinary toxicologist on a product-by-product basis and follow-up calls are made to establish the final outcome of a case. The NAPCC can also design a summary report based on the information most relevant to OPP's needs.

4) In their response to the PR Notice on pet product labeling, the Chemical Specialties Manufacturers Association argued that labeling language should be chemical or product specific. OREB agrees with this argument in principle and recommends that pet product labels be extensively reviewed when individual active ingredients undergo reregistration. The results of the domestic animal safety studies and the analysis of the incident reports (for both animals and humans) should be factors considered in any labeling revisions.

BACKGROUND

The Occupational and Residential Exposure Branch (OREB) has been asked to provide the Special Review Branch (SRB) with an overview of pesticides registered for direct use on domestic animals. It is our understanding that the issue of pet pesticide products has been on the SRB's unfunded list for several years. The Branch has requested a recommendation from OREB about whether the products should be placed under Special Review or considered separately during reregistration of the active ingredients.

TYPES OF PET PESTICIDE PRODUCTS

The vast majority of pesticides registered for use on domestic animals are products for control of fleas and ticks on dogs and cats. According to REFS, there are 1393 active Section 3 registered products for use on dogs and cats.[a] Of these, 1262 are registered for flea and tick control on dogs and cats. (This includes products registered for treating kennels, the animal's bedding and premises.)[b] Other pesticides registered for use on domestic animals include products for ear mite treatments in dogs and cats, for insect (lice and grubs) control on cattle and as fly repellents on horses.

The types of product formulations for flea and tick control include shampoos, sprays, dips, dusts, collars, spot-ons and systemic preparations. Multiple products are often used simultaneously or sequentially on an animal. An insecticidal shampoo may be followed by a dip, spray, collar or all three. At the same time, the treated animal may be exposed to a premise treatment. Many of the products contain multiple active ingredients. The potential for synergistic action of the chemicals and enhanced toxicity of multiple product use are discussed later.

Insecticidal shampoos are usually formulated with synergized pyrethrins or pyrethroids.[1] These are effective in killing fleas and ticks immediately but have no residual efficacy. A few shampoos contain an additional residual insecticide such as an organophosphate or carbamate.

Sprays are the most widely sold products for ectoparasite control. Most contain synergized pyrethrins or pyrethroids. Some also are combinations of different classes of chemicals. Products which contain microencapsulated or stabilized synergized pyrethrins have

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[a] This number was derived with Site Codes 54001, 54002, 54003, 54004, 54005, 54007, 54008, 56002, 56011 and 56028.

[b] Products for direct application to dogs and cats cannot be identified in REFS due to the system design. See further discussion under Estimate of the Number of Incidents for Pet Products in IDS.

claims for both immediate and residual efficacy without the use of organophosphates or carbamates for residual control.

Dips are concentrated formulations, usually containing organophosphates or carbamates, which must be diluted prior to application. Because of their residual activity, they are often used after a shampoo which had immediate flea kill but no residual activity.

Dusts are one of the safest methods of flea control and have few contraindications. However, they have been replaced by sprays which are easier to apply, kill fleas quicker and do not leave a deposit on the coat.

Flea collars are usually made of a polyvinyl chloride material impregnated with an insecticide which is released slowly. Collars are most often impregnated with organophosphates or carbamates, although other classes of chemicals, such as formamidines (amitraz) are also used.

Spot-on preparations are relatively new methods of application for flea and tick control. The formulations usually contain a higher concentration of active ingredient than other preparations. After application to one spot on the animal, usually between the shoulder blades, the insecticide is distributed over the body by grooming or movement of the animal.

Systemic preparations act on the ectoparasite only when it feeds on the animal's blood or tissue fluid. They may be administered orally, by injection or by dermal application. Under a Memo of Understanding with the Food and Drug Administration (FDA), flea products which have this mechanism of action are regulated by FDA.[2] Fenthion, sold under the trade name Pro-Spot Solution for Dogs, is available in 5.6% and 13.8% concentrations. It is regulated by FDA. However, a 20% fenthion solution (Spotton) for use on cattle is registered by EPA.

ACTIVE INGREDIENTS IN PET PRODUCTS

The most commonly used chemicals in pesticide products for direct application to domestic animals are synergized pyrethrins, synthetic pyrethroids, organophosphates and carbamates. Organochlorines were widely used in the past but have been phased out due to regulatory control and introduction of less toxic chemicals.

Pyrethrins and Pyrethroids

Pyrethrins are the most common insecticide in animal sprays, shampoos and dusts.[1] They are used in the range of 0.05 to 0.2% in ready-to-use products and 0.2 to 7.5% in concentrated products such

as dips. They are never used without a synergist which functions to extend their activity and efficacy. Piperonyl butoxide is the most frequently used synergist. It is used alone at concentrations of 0.1 to 2% or combined with n-octyl bicycloheptene dicarboxamide (MGK 264); this chemical is rarely used as the only synergist.

Synthetic pyrethroids were developed to obtain increased chemical stability.[3] The pesticides included in this class are permethrin, allethrin, tetramethrin, resmethrin, fenvalerate and cypermethrin.

Pyrethroids with a cyano substituent at the alpha-carbon of the phenoxy-benzl moiety are classified as Type II pyrethroids while those which lack this alpha-cyano moiety are Type I. The introduction of this moiety has resulted in increased toxicity to both insects and mammals in the form of a paresthetic reaction. When liquid or volatilized Type II pyrethroids (fenvalerate and cypermethrin) come in contact with human or animal skin they produce a stinging, burning, itching or tingling sensation which can progress to numbness.[4] The effect is presumed to result from pyrethroid contact with sensory nerve endings in the skin. The reaction is not allergic in nature and sensitization does not occur. Toxicity is also influenced by the isomer form of a compound; trans-isomers are more rapidly eliminated and less toxic than cis-isomeric forms.[3] The addition of a synergist also influences the toxicity of a formulation. Pyrethrins and pyrethroids are metabolized by ester hydrolysis and oxidation by liver microsomal enzymes. Synergists act by inhibiting these enzymes. This delay in metabolism increases the toxicity of the product to the treated animal.

Pyrethrins and pyrethroids have been considered among the safest insecticides. However, poisonings have become more commonplace with increasing use of these products in dogs and cats.[3]

Carbamates

The two major carbamates used for flea control are carbaryl and propoxur. Carbaryl's use has decreased, possibly due to acquired resistance of fleas and ticks to the chemical in certain geographic regions.[1] Propoxur is used alone or in combination with other chemicals mainly in flea collars.

Carbamates, like organophosphates, are cholinesterase inhibitors. Both classes of chemicals bind to acetylcholinesterase and inhibit its activity on acetylcholine.[5] The accumulation of acetylcholine results in nervous system stimulation. The resulting clinical signs in dogs and cats vary, depending on the chemical, dosage and individual susceptibility, from salivation to seizures and death. Carbamates are reversible inhibitors of acetylcholinesterase, whereas organophosphates are irreversible inhibitors.[6] If the carbamate is removed from the reaction with acetylcholinesterase,

the enzyme recovers rapidly. Organophosphates are more tightly bound and recovery takes longer. This difference affects diagnosis and treatment. Pralidoxime chloride (2-PAM) is administered in organophosphate toxicosis in an effort to regenerate acetylcholinesterase, whereas it is generally considered to be ineffective and contraindicated in carbamate poisoning.[5,7,8,9]

Organophosphates

Organophosphates (OPs) used for insect control on pets include chlorpyrifos, diazinon, dichlorvos, phosmet and tetrachlorvinfos. Chlorpyrifos is included in sprays, dips and collars used on dogs, sometimes in combination with other chemicals. The only registered use in cats is in flea collars. All OPs, except malathion at dilute concentrations, are toxic to cats.[7] The only registered use for diazinon in dogs is in flea collars. Dichlorvos is not as widely used for flea control as in the past. A large percentage of the active products containing this chemical are collars. Phosmet is registered for use on dogs as dips, collars and dusts. Tetrachlorvinphos (Rabon) is used in a variety of formulations for use in small and large animals.

As stated previously, fenthion, an OP, is registered for use on cattle by EPA, while canine use is regulated by FDA.

Toxicoses from OP insecticides can occur in dogs and cats when yard or agricultural formulations are ingested or misused, when dips are incorrectly diluted, when cholinesterase-inhibiting compounds are used in conjunction with other topical or systemic OPs, when products labeled for dogs only are used on cats, when animals are retreated with OPs or when unusually sensitive pets are exposed.[8,10] All of the OP-containing pesticide products for use on animals are registered under general use and access to them is not limited. They are available in grocery stores, pharmacies, feed stores, veterinary clinics and pet stores. They are often poorly labeled and lacking adequate instructions for their safe use.[11]

Organochlorines

The organochlorine which has been used most frequently for flea and tick control is lindane. However, in 1983 many of the uses of lindane were canceled or restricted as a result of a Rebuttable Presumption Against Registration which was issued in 1977. Presently, there are only a few dips containing lindane on the market for use on dogs. The American Veterinary Medical Association has petitioned EPA to place these products in the restricted use category.[12]

New Chemicals in Pet Products

There have been two recent registrations of new chemicals for use

in flea and tick control. Imidacloprid, a nitroquanidine insecticide, was registered in March 1996 as a spot-on preparation under the tradename Advantage. Its mechanism of action is the inhibition of the nicotinic receptor of acetylcholinesterase.[13] This receptor is more common in insects than other animals, thus the chemical should not be as toxic in mammals as other cholinesterase inhibitors. Fipronil, a phenyl pyrazole, acts by inhibiting the neurotransmitter gamma-aminobutyric acid. Spray and spot-on products were registered under the trade name Frontline in May 1996.

SAFETY REQUIREMENTS FOR REGISTRATION OF PET PRODUCTS

Domestic animal safety studies are included in Subdivision F of the Pesticide Assessment Guidelines. However, detailed guidance on how to conduct the studies was not provided until recently. A workgroup of veterinarians in HED has prepared draft guidelines which will be presented to the Scientific Advisory Panel this year. The guidelines require testing the final formulation on each of the labeled species at 1, 3 and 5 times the recommended dosage. Animals are then monitored for clinical and laboratory evidence of acute toxicity. The regulated industry has acknowledged that EPA's safety requirements for pet insecticides are less rigorous than those of the Food and Drug Administration for veterinary drugs (including topical preparations).[14]

Prior to approximately 1987, domestic animal safety studies were not consistently required for registration of pet products. The occurrence of a large number of adverse reactions, including deaths, in dogs and cats from a product containing DEET and fenvalerate (trade name Blockade) caused OPP to examine its requirements. (See National Animal Poison Control Center for more details.)

Pet products usually contain chemicals which are also registered for agricultural use. Therefore, OPP has a complete toxicology data base on the chemical. The oral subchronic and chronic studies at high dosages in dogs with the technical chemical provide a good measure of toxicity for this species. However, there are no such studies in cats, the domestic animal species which is the most sensitive to xenobiotics. Cats, as compared to other domestic animals, are relatively deficient in their ability to conjugate xenobiotics with glucuronic acid which is the most important step in the metabolism of such substances.[15] Pet owners often treat cats with human or canine dosages and dosage regimens of common over-the-counter drugs that result in acute toxicity. For example, due to the decreased metabolism, the dosage regimen for aspirin is every 48 hours in cats as opposed to the generally accepted every 4-6 hours in humans and twice daily in dogs. [16]

Additionally, as indicated previously, many pet products are combinations of active ingredients. It cannot be assumed that the

combination will not be more toxic than the individual active ingredients. The effects of two chemicals given simultaneously will produce a response that may be simply additive of their individual responses or may be greater or less than that expected by the addition of their individual responses.[17] An additive situation results when the combined effect of two chemicals is equal to sum of the effect of each agent alone. When two organophosphate insecticides are given together, the cholinesterase inhibition is usually additive. A synergistic situation results when the combined effect of two chemicals is much greater than the sum of each agent alone. Potentiation is the situation when one substance does not have a toxic effect on a certain organ or system but when added to another chemical it makes the latter more toxic. Antagonism is the situation in which two chemicals, administered together, interfere with each other's actions or one interferes with the action of the other chemical.

As stated previously, flea and tick control products are often used sequentially. There are no requirements for testing such products in combination, even if there are recommendations on the labeling for such use. For example, Hartz Mountain has a group of products marketed as Hartz Control Pet Care System. The labels for individual products in this "system" and promotional literature on the products advise that they should be used together in a step wise sequence.[18] For dogs, Step A is Flea and Tick Conditioning Shampoo (registration # 2596-133) which contains 0.1% d-trans allethrin. Step B recommends the use of Flea and Tick Repellent (registration # 2596-122) which contains 1% rabon and for added protection Hartz 2 in 1 Flea and Tick Control Collar (registration # 2596-62) which contains 14.5% rabon. Step C advises that the home be treated with either Home Flea & Tick Killer (registration # 2724-401-2596) containing 0.007% methoprene and 0.25% permethrin or Home Fogger (registration # 2724-454-2596) containing 0.09% methoprene and 0.58% permethrin. No testing was ever done to assure that exposure to these chemicals simultaneously or in sequence is safe at the recommended doses. The margin of safety may be so small that, especially for these active ingredients, minimal overdosing by the pet owner could cause toxicity.

INCIDENTS OF ADVERSE REACTIONS TO PET PESTICIDE PRODUCTS

National Animal Poison Control Center

The National Animal Poison Control Center (NAPCC) is a 24 hour service located at the University of Illinois which receives calls concerning animal poisonings from veterinarians, human poison control centers, government agencies, and animal owners.[19] Calls are answered by veterinary toxicologists who give advice on treatment and management of poisonings. In addition, the information on each case is evaluated and entered into a data base. The certainty of an association between the suspected agent (pesticide, drug, plant, etc.) and the poisoning is assigned to

each case. Previously, the certainty categories applicable to companion animals were toxicosis, suspected toxicosis, doubtful toxicosis, exposure, and information only.[c,20] Presently, the categories are high, medium, low or doubtful reaction, exposure only, information only or other.[21]

The National Pesticide Telecommunications Network (NPTN) refers some animal calls to NAPCC.[22] The cases typically referred deal with requests for treatment advice or incidents of animal deaths. Prior to 1987, yearly summary reports of all of NAPCC's pesticide cases were available to OPP. However, due to budget cutbacks, a detailed case report is now provided only for the referred cases.

NAPCC has periodically published yearly reports in the veterinary literature. The following is a summary of the incidence of pesticide-related calls. In 1984, the Center received almost 8000 calls regarding dogs and cats; there were more calls regarding insecticides than any other class of toxicant.[20] Of the 1260 insecticide cases in cats and dogs, one-third were judged to be definite or suspected toxicosis. Rodenticides were the second most prevalent category of agents. NAPCC postulated that the reasons for the prevalence of this class of pesticides were: 1) rodenticides are often placed in areas in which both rodents and pet animals are present; and 2) the NAPCC has an agreement with the manufacturers of the anticoagulant brodifacoum so that their telephone number is on products containing this chemical. Regardless of the chemical involved, the vast majority of anticoagulant rodenticide calls were for exposure only (no clinical signs of toxicity).

The number of calls to NAPCC increased to roughly 20,000 in 1986 and 25,000 in 1987.[23] In the yearly report for 1986, details on the number of calls by toxicant class and individual toxicant were provided. The top three classes of toxicants involved in the 14,721 calls concerning dogs were rodenticides (22.7% of all calls), human medicines (17.0%) and insecticides (12.0%). Of the rodenticide calls, 77.6% were categorized as exposure only. Of the insecticide calls, 36.2% were categorized as toxicosis or suspected toxicosis. Brodifacoum was the number one generic agent involved in canine calls; 83.9% of the 2058 calls concerning this chemical were exposure only. The other pesticides in the generic ranking for dogs were cholecalciferol (#8), propoxur (#10), hydramethylon (#11), 2,4-D (#12), boric acid (#13), diazinon (#14), diphacinone (#17), chlorpyrifos (#18), pyrethrins (#19) and bromodiolone (#20).

There were 5075 calls of poisonings in cats in 1986. The top three

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[c] Toxicosis: all criteria are met (high degree of assurance of adequate toxicant exposure); suspected toxicosis: criteria are met, but a limited amount of confirming information is unobtainable; Exposure: no clinical signs at time of the call; Doubtful: findings not appropriate for the toxicant, timeframe or degree of exposure in question.

toxicant categories were insecticides (25.7% of all calls), plants (21.4%) and human medicines (9.9%). Of the insecticide calls, 57.7% were categorized as toxicosis and suspected toxicosis. Pyrethrins were the number one generic agent involved in feline calls; 60.9% were classified as toxicosis or suspected toxicosis. Six deaths in cats were associated with pyrethrins exposure. The other pesticides in the generic ranking for cats were brodifacoum (#2), chlorpyrifos (#3), boric acid (#6), d-limonene (#7), diazinon (#9), carbaryl (#12), propoxur (#14) and phosmet (#15).

It was noted in the 1986 report that poisoning is relatively uncommon in animals undergoing topical exposure but this was not true of insecticides. Of 440 calls in which pets were exposed via the topical route and had clinical signs compatible with the toxicant in question, 82% were due to insecticides.

Detailed information was not provided for 1987. However, it was noted that there were 1135 calls in this year for Blockade (a DEET-fenvalerate combination). Forty percent (40%) of the calls were classified as toxicosis or suspected toxicosis. Cats were more often affected but deaths were reported in cats and dogs. This product was first registered in May 1986. In a December 14, 1987 letter to EPA, the Hartz Mountain Company, the registrant, acknowledged being blamed for 366 pet deaths, 2700 pet injuries and 56 alleged unsubstantiated human injuries. [24] The product was taken off the market but was reintroduced in 1989 with the same formula but relabeled. The revised label advised pet owners to apply the product lightly and to not use on kittens, puppies, pregnant cats or sick pets. The company was fined $45,000 for failure to report the complaints to EPA. Subsequently, the registrant developed other products for cats and dogs containing 3.99% DEET (50% the Blockade concentration) and 0.025% esfenvalerate to replace Blockade; these are marketed under the names Hartz Flea and Tick Repellent for Cats III (Reg. # 2596-120) and Hartz Flea and Tick Repellent for Dogs III (Registration number 2596-121). The Blockade registration will be canceled when all of the product is off the shelf which could be as long as two more years.[25]

A very short article on the top 25 generic agents involving dogs and cats for which the NAPCC received calls in 1992 was recently published.[26] During this year, 12,611 cases involving one or more dogs and 5351 cases involving one or more cats were evaluated. Of the top 15 generics for dogs, 14 were pesticides; all of the top 15 for cats were pesticides. Table 1 lists the chemicals by ranking.

Table 1: Top 15 Generics for Which NAPCC Received Calls in 1992

Ranking	Dogs	Cats
1	Brodifacoum	Allethrin
2	Diphacinone	Permethrin
3	Cholecalciferol	Pyrethrins
4	Chlorpyrifos	Resmethrin
5	Diazinon	Tetramethrin
6	Phosmet	Tralomethrin
7	Carbaryl	Chlorpyrifos
8	Methomyl	Diazinon
9	Propoxur	Phosmet
10	Amitraz*	Propetamphos
11	Ivermectin	Tetrachlorvinfos
12	Allethrin	Carbaryl
13	Pyrethrins	Propoxur
14	Permethrin	DEET
15	Tralomethrin	d-Limonene

* Amitraz is also contained in a dip approved by the Food and Drug Administration for the treatment of demodectic mange in dogs.

It is unknown what percentage of the calls involving the above chemicals resulted because of direct application of a pet product or exposure to an agricultural product. It is also unknown how many calls involved clinical signs of illness and how many illnesses were caused by the pesticide exposure.

Other Poison Control Centers

The American Association of Poison Control Centers (AAPCC) reported 41,854 animal exposure cases in 1990; 7,368 cases involved exposure to insecticides.[27] Of these, 94 resulted in death; 41 were classified as a major effect and 237 as a moderate effect. The AAPCC has no mechanism for collecting species-specific information. However, based on a sample of cases, it is assumed that 99% of the animal cases represent poisonings in companion animals with about 75% in dogs, 20% in cats and 4% in other pets. The leading types of products responsible for the deaths in 1990 were ethylene glycol and related compounds (9.6% of deaths), anticoagulant rodenticides (9.2%) and organophosphates (7.3%).

The Hennepin Regional Poison Control Center in the Twin Cities area

of Minnesota is one of the 37 regional Poison Control Centers. Since 1989, this center has had a Pet Poison Information Service to encourage the veterinary community to utilize the service. A summary report of the calls between 1990 through 1992 has been published.[28] A total of 12,925 calls were received for those years; 69% were for dogs and 17.7% for cats. Pesticides were the number one toxicant category, comprising 20% of all calls. Of the 8,919 calls involving dogs, 21.4% concerned pesticides; of the 2,292 feline calls, 19.5% concerned pesticides.

Incident Data System

The OPP Incident Data System (IDS), a data base for reports of adverse events due to pesticide exposure, was created in 1992. The reporting of such events is required under 6(a)(2) of FIFRA. Reports from registrants, private citizens, regional offices, health care facilities and other government agencies are received in the Information Services Branch of PMSD. There, they are logged into IDS and then forwarded to either HED or EFED for review, depending on whether the report involved health or environmental effects. In HED, a short summary of the report is entered into a HED Screen of IDS and a determination is made as to whether there was a causality relationship between the pesticide and the effects. The certainty categories presently in use are definite, probable, possible, unlikely, unrelated and unknown. A substantial proportion (over 40%) of incidents in IDS to date involve domestic animals.

Incidents may be received as single reports, as packages containing multiple reports, either for the same product or several products produced by the same registrant, or as summaries of incidents for a certain time period. Each submission is given a package number, regardless of whether it is an individual incident, a package or a summary. If the reports are received as a package, Information Services Branch enters a summary of the total package in the Package Screen field of IDS. Each individual incident in the package is then entered and evaluated by HED. For example, package number 20 has 97 incidents. The package description is, "Compilation of domestic animal incidents, 9 SmithKline products; cats, dogs, rabbits, boa constrictors; also lack of efficacy." The HED screen for incident number one describes two cats which developed adverse effects after exposure to Adams Flea & Tick Shampoo. Other incidents in this package involve other products. Therefore, in order to analyze the number and type of adverse effects with a particular product or chemical, it is essential to review the HED screens. Due to resource constraints, the majority of the incidents for domestic animals have not been evaluated and entered into the HED Screens.

In addition, the Information Services Branch is having difficulty processing all of the incoming reports. As of April 26, 1996, a total of 11,876 incidents had been entered into IDS, while 1685 were awaiting processing.[29]

CONFIDENTIAL

Review of the IDS animal reports is also complicated by summary reporting and confidentiality issues. Some registrants have submitted summaries of incidents on multiple products for a certain time period. For example, package number 1358 contains 471 incidents for the month of August, 1994, for the Solaris Subsidiary of the Monsanto Company. The incidents involve a wide variety of products, including some for direct application to dogs and cats. These summary reports are not entered as individual incidents but only as a package. Therefore, if this package would appear on a print-out of pet product incidents using IDS, there would be no mechanism to determine how many involved animals without going back to the original submission from the registrant.

A few registrants of pet products have labeled their incident submissions confidential and are considered Confidential Business Information by OPP. As of April 26, 1996, there were 67 packages labeled as confidential; data for 1590 incidents in these packages were not entered into IDS. A significant number of the packages are from the Hartz Mountain Company. Most of their reports involve Blockade for Cats, Blockade for Dogs, and various products containing tetrachlorvinphos (Rabon) and synergized pyrethrins. The total number of incidents for April 1, 1992 through December 31, 1995 appears in the table below. It should be emphasized that the numbers are estimates based on a cursory review of the incident reports. The reason for presenting this table is to illustrate the number of incidents which may not be entered into IDS.

Table 2: Estimates of the Number of Incidents Reported by Hartz Mountain Company 4/1/92- 12/31/95

	Number of Incidents	Number of Deaths
Collars with Rabon	265	ND
Powders with Rabon	45	ND
Sprays with Rabon	173	ND
Blockade for Cats	219	22
Blockade for Dogs	258	12
Synergized Pyrethrins	647	ND

ND = not determined

ESTIMATE OF NUMBER OF INCIDENTS FOR PET PRODUCTS IN IDS

The number of incidents reported to IDS for the chemicals listed in the NAPCC's top 25 generics for 1992 was estimated. The number of products containing each of these chemicals was also obtained from REFS. See Table 3 below. The limitations on these data should be emphasized. First, if a product contains multiple active

ingredients, a single incident will appear in IDS for both chemicals. Second, the data provide only the number of incidents and no indication of the seriousness of the health effects. Additionally, they are presented with no certainty indices of the causal relationship between the chemical and the adverse effect. Third, based on past experience, it can be assumed that there is an under-reporting of incidents to IDS by registrants. Fourth, as indicated above, some incidents have not been entered into IDS because of confidentiality issues and some packages contain multiple incidents. Fifth, there are no codes in REFS which will give products used directly on dogs and cats. For example, there are six separate codes for dogs - 54003 dogs (all or unspecified), 54004 dogs (puppies) (pet), 54005 canines (pet), 54007 dogs (adult), 56002 dogs (special-e.g. military, show) and 56011 dogs (lab). A search using all the codes for a particular chemical for the pest species fleas will give products for direct application to dogs and also for premise treatments. PMSD advised that use of codes 54004, 54007, 56002 and 56011 would search for products applied directly to dogs. However, this search missed some products. For example, if the four codes are used for amitraz, the one registered product, a flea collar, is missed. It was found using all six codes.

Table 3: Pet Products and Incidents by Chemical

Chemical (PC Code)	Number of Active Products for Dogs[a]	Number of Active Products for Cats[b]	Number of Incidents in IDS for Animals[c]
Brodifacoum (112701)	0	0	18
Allethrin[d]	85	54	96
Diphacinone (67701)	0	0	0
Permethrin (109701)	270	120	521
Cholecalciferol (202901)	0	0	7
Pyrethrins (69001)	589	420	1615
Chlorpyrifos (59001)	106	4	277
Resmethrin[e]	157	64	2
Diazinon (57801)	8	5	28
Tetramethrin (69003)	26	17	32
Phosmet (59201)	6	1	14
Tralomethrin (121501)	1	0	4
Carbaryl (56801)	117	100	157
Methomyl (90301)	0	0	2
Propoxur (47802)	11	5	49
Amitraz (106201)	1	0	59
Propetamphos (113601)	0	0	3
Tetrachlorvinphos (83701)	21	18	12
DEET (80301)	3	3	23
d-Limonene (79701)	7	6	24

a Use Codes 54003, 54004, 54005, 54007, 56002 and 56011
b Use Codes 54001, 54002, 54008 and 56028
c IDS cannot be searched by animal species
d Includes PC Codes 4001, 4003 and 4005
e Includes PC Codes 97801, 97802 and 97804

The synergists PBO and MGK-264 were not on NAPCC's list of the top 25 generics. There are more incidents in the IDS for these

chemicals than any of the ones in the above table. The total number for PBO and MGK-264 are 2410 and 1553, respectively. The number of animal incidents has not been determined, but it is likely that the vast majority involve animals.

USE INFORMATION

The National Home and Garden Pesticide Use Survey gathered information on the non-agricultural use of pesticides in and around 2,078 households in 29 states during August and September 1990.[30] The survey includes data on the estimated thousands of products by specific sites and also the estimated percentage of a product used for that site. It is assumed that the majority of products used for the site cat, dog or kennel are for flea and tick control. The top ten chemicals, which account for approximately 68% of all products, are listed in Table 4.

Table 4: Top 10 Chemicals Used for the Treatment of Cats, Dog or Kennels[a]

Chemical/Product	Estimated Thousands of Products	Estimated Percentage of Products
Piperonyl butoxide	9,376	18.23
Pyrethrins	8,822	17.15
MGK-264	6,800	13.22
Carbaryl	3,053	5.94
Aliphatic petroleum hydrocarbons	1,695	3.30
Chlorpyrifos	1,467	2.85
Propoxur	1,043	2.03
DEET	1,031	2.00
Tetramethrin	927	1.80
Ethyl Alcohol	796	1.55

a Extracted from Table E.1, National Home and Garden Pesticide Use Survey, Final Report, Volume I

Any attempt to compare the number of incidents to the amount of product used is fraught with problems and would be misleading. The number of incidents is an underestimate due to underreporting by the registrants and the IDS problems previously described. An estimate of the thousands of products used cannot be equated to the number of applications of a product, which is the best measure for comparison to the number of incidents.

PR NOTICE FOR PET PESTICIDE PRODUCTS

On September 15, 1994, the Registration Division published the availability of a draft PR notice which would require registrants of pet pesticide products to revise their labeling. The basis for this requirement were reports of adverse effects to IDS, mostly in dogs and cats, but also in humans following exposure to such products. The labeling revisions would include additional use directions and precautions to ensure that the products are used safely. On August 31, 1995, the Chemical Specialties Manufacturers Association (CSMA) responded with suggestions for compromise on the label revisions. One of CSMA arguments was that pet products should not be considered as a group but that label information should be product specific. A workgroup within OPP is in the process of developing a consensus response to the CSMA proposal.

Products for direct application to domestic animals will not be addressed with the Consumer Labeling Initiative.[31]

HUMAN EXPOSURE VIA PET PRODUCTS

The California Department of Pesticide Regulation (DPR) recently notified EPA that it is considering placing all pesticide products formulated as dips and shampoos for use on dogs and cats into its reevaluation process.[32] The reason for the concern is the number of illnesses by applicators as a result of being dermally exposed to these products. At issue is the lack of precautionary statements on the label requiring the use of gloves or goggles. From 1982 through 1990, 71 illnesses associated with pet products were reported. The majority involved sprays (30 cases) and dips (25 cases). A large proportion of the sprays were antimicrobials and are not applied to animals. Four active ingredients accounted for 60% of the total cases - phosmet, pyrethrins/PBO, sodium hypochlorite and D-limonene. The Department of Pesticide Regulation indicated that it suspects the number of illnesses is greatly under-reported in this particular group of users.

The California DPR also has prepared informational sheets for pet owners which pet groomers can provide to their customers.[33] The sheet describes the insecticide used, how the pet owner can reduce his/her exposure and signs in the pet of possible toxicity due to the insecticide. A similar sheet was prepared for pet groomers which provides labeling requirements, safety procedures when handling pesticides, proper disposal and employer responsibilities.[34] The preparation and distribution of these sheets were in response to an inquiry by a state senator whose constituent alleged that both she and her dog became ill after the dog was treated for fleas by a groomer using chlorpyrifos.[35]

Reports from California have also implicated the use of pet products in water quality problems. Treated effluent being discharged by the Central Contra Costa Sanitary District (Contra

San) has been toxic to an aquatic organism commonly used as an indicator species to assess water quality.[36] The concentrations of diazinon and chlorpyrifos have exceeded the LC_{50} levels for *Ceriodaphnia dubia*. Central San has identified the following sources of the chemicals: residential, pet groomers and kennels and commercial pest control operators. A sampling program of these sources showed that the mean concentrations of chlorpyrifos in wastewater from groomers and kennels greatly exceeded the other two sources. A survey of stores selling flea products containing chlorpyrifos showed all sales of these products per year in this area accounted for nine pounds of active ingredient. Based on the survey and sampling, it was predicted that only a few daily uses of chlorpyrifos-containing flea dips could contribute to Central San's effluent toxicity. A public information campaign was initiated to promote the proper use and disposal of pesticides.

The National Research Council in its *Pesticides in the Diets of Infants and Children* included pet products in its chapter on estimating exposures of children to pesticides.[37] Flea control products, especially sprays and dips, may persist on the animal's fur and be transferred to children during contact with the pet, Flea collars are designed so that the chemical is released gradually. Most pet product labels contain the KEEP OUT OF REACH OF CHILDREN statement but do not warn against contact with the treated animal. The labels for many collars do warn that children should not be allowed to handle or play with them.

FUTURE OF FLEA CONTROL

A recent article in the *Journal of the American Veterinary Medical Association* discussed the future of flea control with several veterinarians expert in the field.[38] Their opinion was that the focus of flea control is changing from treatment to prevention and from using chemicals to "natural" means of control. New products recently marketed include an insect development inhibitor (IDI) for oral administration and a collar impregnated with a insect growth regulator (IGR). Other novel approaches include parasitic nematodes for outdoor flea control, borate carpet treatments and diatomaceous earth household treatments.

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