# EPA UPDATE ON VERTEBRATE PESTICIDES

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## INTRODUCTION

The U.S. Environmental Protection Agency regulates pesticides under the authority of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Vertebrate pesticides are subsumed under the heading "rodenticides" and, under FIFRA, are regulated similarly to other pesticides.

Since its enactment in 1947, FIFRA has been amended many times (e.g., in 1959, 1964, 1972, 1978, and 1988.) These amendments generally have required progressively greater documentation of the effects of pesticides upon man, other nontarget species, and the environment prior to the issuance of full federal registration under Section 3 of FIFRA.

FIFRA's definition of "pesticide" (Section 2[u]) includes, as a first category, "any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest" and, as a second category, any substance used as a "plant regulator, defoliant, or dessicant." Vertebrate pesticides fall within the first category, which, incidentally, uses terminology borrowed from the definition of "insecticide" found in FIFRA's predecessor -- the "Insecticide Act of nineteen hundred and ten".

While most vertebrate pesticides consist of oral toxicants in bait formulations, the class "rodenticide" also includes pet and wild animal repellents which are claimed to exert effects mediated through the senses of smell, taste, or touch.

Ramifications of some provisions of recent amendments to FIFRA place registrations of many vertebrate pesticides in jeopardy, unless certain positive steps are taken to maintain these registrations. Changes to FIFRA require that data be submitted or cited to characterize hazards associated with particular use patterns in conjunction with Special Reviews or Reregistration. As most vertebrate pesticide compounds were registered many years before FIFRA required extensive documentation of hazards, a considerable amount of updating is required. While the most extensive requirements pertain to producers of technical products, some added expenses must be incurred to continue registrations for each formulated product. Registrants of rodenticides with limited markets will continue to be faced with decisions regarding whether to continue registrations of certain active ingredients, use patterns, and products.

This paper describes the current situation for rodenticides. It notes how FIFRA and its attendant regulations affect rodenticides in general and where certain compounds are in the regulatory process right now.

## REGISTRATION

For a pesticide to be fully federally registered, under Section 3(c)(5) of FIFRA, EPA must find that the product is constituted and labeled appropriately to ensure that it can be used reasonably effectively and reasonably safely. The essential findings necessary for a 3(c)(5) registration are quoted in Table 1.

The amount of actual research data required to support a determination that a pesticide may be registered has increased monumentally since the orginal passage of FIFRA in 1947. Many of the recent changes to FIFRA concern the collection of data to support existing registrations.

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Table 1. Basic determinations for federal pesticide registration under Section 3(c)(5) of the Federal Insecticide, Fungicide, and Rodenticide Act, as amended.

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"APPROVAL OF REGISTRATION. -- The Administrator shall register a pesticide if he determines that, when considered with any restrictions imposed under subsection (d)--

(A) its composition is such as to warrant the proposed claims for it;

(B) its labeling and other material required to be submitted comply with the requirements of this Act;

(C) it will perform its intended function without unreasonable adverse effects on the environment; and

(D) when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment. . . ."

(material quoted from Sec. 3[c][5] of FIFRA, as amended)

NOTE: Subsection 3(d) pertains to "CLASSIFICATION FOR GENERAL USE, RESTRICTED USE, OR BOTH". Determinations regarding usefulness, appropriate labeling, and likely effects on the environment take into account the types of uses permitted and the types of applicators who, legally, may use the product.

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CONDITIONAL REGISTRATION

Section 3(c)(7) of FIFRA permits registration of pesticide products, under certain conditions, when some of the data necessary for a full determination of registerability under Section 3(c)(5) are lacking. In all instances of such "conditional registration", EPA must find that conditional registration of the product would not cause or increase the risk of "any unreasonable adverse effect on the environment."

For most of the products that now are conditionally registered, the data necessary for making a full Section 3(c)(5) registration determination are being sought through the "Reregistration" process (discussed below) or through deadlines imposed upon the individual conditional registrations themselves.

"SPECIAL LOCAL NEEDS" REGISTRATIONS

Section 24(c) of FIFRA authorizes states to register additional uses for registered pesticide formulations. These uses are to pertain to conditions that exist within the state which registers the additional use and that are relatively peculiar to that state.

Although "deemed registration under section 3 for all purposes" of FIFRA, Section 24(c) registrations are limited to the states where they have been issued. Section 24(c) registrations are effective immediately upon issuance, but are not effective for more than 90 days if "disapproved" by EPA within that time period.

Section 24(c) registrations may not be issued which permit applications to food or feed crops, unless there is a federal tolerance (or exemption from tolerance) in place for that use

pattern. By regulation (40 CFR, Section 162.152[a][3]), states are prohibited from issuing Section 24(c) registrations for uses that have previously been "denied, disapproved, suspended or cancelled" by EPA. New pesticide active ingredients may not be registered under Section 24(c).

## REGISTRATION MAINTENANCE FEES

FIFRA, as amended in 1988, requires registrants to pay fees for certain actions related to registration and reregistration. Although the registration maintenance fee, Section 4(i)(5), is the lowest of these fees, it applies to every registrant and must be paid annually. For 1989, the maintenance fee is $425 for each registered product up to 50. Once the total bill reaches $20,000, the registration maintenance fee drops to $100 for each additional registered product until the total bill reaches the maximum annual limit of $35,000.

Maintenance fees apply to Section 3 registrations and to Section 24(c) registrations.

Section 4(i)(5) further authorizes the Administrator of the EPA to adjust the maintenance fee to realize "to the extent practicable, an aggregate amount of $14,000,000 each fiscal year." If a maintenance fee is not paid, the Administrator of EPA is authorized to cancel the registration "by order and without hearing". These provisions mean that failure to pay fees can mean instant loss of registration and, as the number of remaining registrations declines, that the maintenance fees required for products still registered may increase. As fees have not been paid for many registrations in 1989, the first year of the maintenance fee program, the annual fee might increase sharply in 1990.

## DATA COMPENSATION

FIFRA's 1972 amendments, subsequent amendments, and regulations issued to implement these amendments have led to increasingly stringent requirements for characterizing risks associated with handling and use of pesticide active ingredients, formulated pesticide products, and certain "inert" ingredients in formulated products. To characterize such risks, registrants have been required to submit or to cite data submitted previously pertaining to product chemistry, toxicity, wildlife safety, and environmental fate. Data also have been required for exposure assessment including, for food or feed uses, data supporting petitions for tolerances or exemptions from tolerances.

Section 3(c)(1)(D) of FIFRA, which first appeared in the 1972 amendments, requires registrants citing data to offer to pay compensation to firms or other entities that "own" the data being cited.

The 1978 amendments added to FIFRA language, in Section 3(c)(2)(D), a "formulator's exemption" clause. This clause exempts applicants who intend to purchase registered pesticides in order to formulate them into the products for which registration is sought from requirements to submit or cite data pertaining to the pesticide products that they have purchased to use only for reformulation. Applicants entitled to a formulator's exemption are not required to offer to compensate those who "own" the data upon which the registrations of pesticides purchased for use in formulating other pesticides are based. However, if the basic suppliers of such "manufacturing-use pesticides" fail to develop data to support continued registrations, or certain uses, of pesticide active ingredients, formulators may elect to develop such data themselves.

## REREGISTRATION

The process of continuing previous registrations under the updated requirements of FIFRA has become known as "reregistration". In the mid-1970s, EPA considered several approaches to

reregistration which, ultimately, either were rejected by EPA as being unworkable or by courts as being illegal. The first approach to be implemented was the "Registration Standards" process.

Registration Standards were to be issued for individual active ingredients. When completed, the process was to result in the reregistration of all pesticide products containing the subject chemical as sole or principal active ingredient. EPA would identify use patterns on labels of registered products covered under each standard. EPA would then review all information on the subject chemical contained in EPA's registration data files or located through a "world-wide literature search", which typically was performed by a contractor. The Agency then prepared documents in which the results of its internal reviews were presented and the requirements for reregistration were outlined. Registrants were required to meet outstanding data and labeling requirements within specified time periods or to face possible suspensions of their registrations.

Although changes were made over the years, this basic approach was used for all Registration Standards issued from the start of the program in 1980 through the end of 1988. Beginning in 1986, Registration Standards for certain compounds have been updated to incorporate findings from studies required under the original Standards. Updating of Standards includes reassessment of tolerances for food and feed uses.

The Registration Standards approach has been rather slow in bringing about complete resolution or reregistration for active ingredients. In many cases, very few of the studies required to support continued registration were in EPA's registration data files or were uncovered in literature searches. Studies pertaining to various data requirements often were found to be inadequate due to problems with the procedures used and/or with the extent of documentation provided.

Another weakness of the Registration Standards approach was that it required a great deal of review effort to prepare the Standard's documents. This effort was directed toward assessing what were almost invariably grossly inadequate data bases.

Registrants often were slow to provide the data required under the standards or did not reply at all. In efforts to speed compliance, EPA has invoked the data call-in powers of Section 3(c)(2)(B), which first appeared in the 1978 amendments to FIFRA. This section authorizes EPA to suspend registrations if data commitment and submission deadlines are not met.

Even when registrants committed quickly to perform the studies needed to fill the "data gaps" identified in standards, several years often elapsed before the studies were completed, submitted, and reviewed by EPA. If the results of the first round of studies indicated a need for more ("second tier") studies, still more time elapsed before the bulk of the data required under the standard was "in".

In some cases, registrants of technical materials decided not to develop the data needed to continue certain uses the compounds that were the subjects of Standards. In some instances, "basic" registrants declined to perform the studies needed to maintain registrations of the technical materials themselves. In these cases all registrants of formulated products made from this technical product were left without a source of the material unless one or more of such formulators assumed responsibility for generating the data to support the technical material.

In the 1988 amendments to FIFRA, a new approach to reregistration was detailed by the U.S. Congress. The amount of the Act directly devoted to

reregistration has been increased from a short paragraph (Section 3[g]) to a lengthy and totally new Section 4.

The essence of the new approach is to require registrants of manufacturing-use pesticides to decide whether to pursue reregistration and the required data development very early in the process and to make earnest commitments to reregistration if that option is selected. Those who seek reregistration of such products must commit to a schedule of data development and pay reregistration fees of up to $150,000.

FIFRA's 1988 amendments outline a five-phase approach to reregistration. These phases are summarized in Table 2.

In "Phase One", EPA must prepare four lists of active ingredients that are candidates for reregistration. These lists have been designated as "A", "B", "C", and "D".

List A was to include all active ingredients for which standards had been issued prior to December 24, 1988. List A was published in the Federal Register on February 22, 1989 (Campt, 1989a). List A covers a total of 356 chemicals which were included in the 194 Registration Standandards issued prior to December 24, 1988.

List B was to include "the first 150 active ingredients" determined to be of highest priority due to their involvements in "food or feed uses"; their potentials for producing significant residues in "potable ground water, edible fish, or shellfish; their having "significant outstanding data requirements"; and/or their uses in sites where "worker exposure is likely to occur" (FIFRA, Section 4[c][1][B]). List B was published on May 25, 1989 (Campt, 1989b).

List C was to include the 150 compounds determined to be of next highest priority using the criteria identified for List B. List C was published in the Federal Register on July 24, 1989 (Campt, 1989c).

List D is to include all pesticide active ingredients not included on Lists A, B, or C, except those that first were registered after November 1, 1984, and those which, between November 1, 1984, and December 24, 1988, were determined by EPA to have no outstanding data requirements and to have met all other requirements requirements under Section 3(c)(5) of FIFRA. The 1988 amendments require that List D be published by or before October 24, 1989.

Registrants of all products containing an active ingredient on Lists B, C, or D must indicate to EPA within 90 days of the publication of the respective lists whether they intend to seek reregistration of each product containing the ingredient in question. Registrants of manufacturing-use products must commit to fulfill data requirements and to meet their requirements under the remaining phases of the process (Table 2). Registrants eligible for formulators' exemptions must request them during Phase 2. Such registrants are then out of the process until Phase 4, when data Call-Ins and other requirements for reregistration of end-use products are issued.

If no registrant of a particular active ingredient indicates an intention to seek reregistration of that ingredient, EPA must publish in the Federal Register a notice of intent to remove the active ingredient from the reregistration list and a notice of intent to cancel all pesticides that contain the active ingredient. A period of 60 days is provided for comment on such notices. Cancellation can be blocked if, during the comment period, someone acquires the rights to a registration subject to the notice, commits to reregister the active ingredient, identifies "missing or inadequate data", and pays an appropriate portion of the reregistration fee.

Total fees for reregistration may be up to $150,000 for active ingredients registered for major food or feed uses. Total fees for pesticides not

Table 2. Phases of the new pesticide reregistration process.

| PHASE | "ACTOR(S)" | ACTIVITIES |
|---|---|---|
| 1 | EPA | Publish lists A, B, C and D scheduling pesticide active ingredients for reregistration |
| 2 | All registrants of subject chemical | Indicate whether reregistration is sought |
| | Registrants subject to "generic" data requirements | Identify data gaps |
| | | Commit to filling data gaps |
| | | Pay first part of reregistration fee |
| | Registrants of "formulated" products | Request formulator's exemption |
| 3 | Registrants subject to "generic" data requirements | Summarize and reformat previously submitted studies |
| | | Certify access to raw data |
| | | "Flag" data |
| | | Pay remainder of reregistration fee |
| 4 | EPA | Review Phase 2 and Phase 3 submissions |
| | | Identify data gaps |
| | | Publish identified data gaps |
| | | Issue Data Call-In (if necessary) |
| | Registrants subject to Data Call-In | Respond to Data Call-In |
| 5 | EPA | Review all data |
| | | Reregister products or take other action as appropriate |

registered for major food or feed uses are to be no less than one half of the fees for major food use pesticides. The reregistration fee for each List A pesticide is to be between $50,000 and $100,000. Reregistration fees may be reduced for active ingredients used solely in "minor uses", for certain "antimicrobial active ingredients", and for certain registrants who qualify under a "small business" determination. If more than one party seeks to pursue reregistration of the same active ingredient, these parties are to pay total fee collectively.

The new approach is intended to achieve complete reregistration of active ingredients for which Registration Standards were not issued prior to the end of 1988. This process is expected to take nine years. As it took nearly nine years for the List A standards to be issued, the new approach is expected to accelerate the completion of reregistration.

Much time saving is expected through Phases 2 and 3, which require registrants to make commitments and assess data gaps before EPA invests extensive amounts of its own resources in the review of individual active ingredients. By the time that EPA does get heavily involved with individual compounds, in Phases 4 and 5, the pool of materials under consideration will have been reduced to the compounds that have registrants who are committed to reregistration.

The new requirements for reregistration are directed toward data generation and submission. Actual registration (or reregistration) is determined by the findings that the data received permit the Agency to make under the provisions of Section 3(c)(5) of FIFRA.

## SPECIAL REVIEW

EPA has developed a Special Review process to weigh risks and benefits of pesticide active ingredients which the Agency has reason to believe may be especially hazardous to man, nontarget animals, or the environment in general, even when used according to current label precautions.

Special Review is a complicated process in which available data on risks are "balanced" against available data on benefits, including the relative benefits of the chemical under study and alternative pest control measures that might be used in specific sites where hazards associated with use of the subject pesticide chemical have been presumed. In Special Reviews, EPA assesses whether certain (or any) uses of an active ingredient may be permitted to continue. In most cases, use of the compound is not interrupted while the Special Review process is ongoing.

Once a Special Review is completed, EPA issues its findings, identifies any outstanding label or data requirements, and issues timetables for compliance with the Agency's regulatory position.

## GOOD LABORATORY PRACTICES

A regulation expanding requirements for following Good Laboratory Practice (GLP) standards in pesticide testing was published in the Federal Register on August 17, 1989. GLP standards will be required for pesticide studies begun after October 16, 1989, that are submitted to support applications for registrations, Experimental Use Permits (Section 5 of FIFRA), Emergency Exemptions (Section 18), and petitions for tolerances. Expanded GLP requirements apply to studies designed to predict a pesticide's effects, metabolism, efficacy (where required), chemical fate, environmental fate, "persistence and residue, or other characteristics in humans, other living organisms, or media" (Reilly, 1989). Prior to the adoption of this rule, GLP requirements applied only to studies pertaining to toxicity, metablolism, and related areas. GLP requirements now apply to laboratory and field trials.

The purpose of GLP requirements is in insure good quality and integrity of data submitted pursuant to pesticides. GLP standards include requirements for facilities, collection and maintenance of test data and other records, establishing standard operating procedures (SOPs) for various procedures, preparation of specific protocols, retention of test samples, reporting of results, and many other aspects of research. GLP standards also require that an independent quality assurance unit be established to monitor each study. Quality assurance units are expected to inspect facilities, records, equipment, and other aspects of the research periodically during and after the time that the study is conducted.

Due to requirements for extra personnel and expanded facilities, the expanded requirements for GLP standards are expected to increase the costs of pesticide testing.

## VERTEBRATE PESTICIDE UPDATE

Table 3 indicates current statuses of active ingredients used in vertebrate pesticides. Compounds not specifically listed are expected to be included in Reregistration List D. Note that virtually all compounds still registered will be on one of the reregistration lists. This includes compounds, such as Strychnine and Sodium Fluoroacetate (1080) which also are subject to data call-ins resulting from Special Reviews.

Table 3 also lists two compounds for which all vertebrate pesticide registrations have been lost in recent years. Other compounds might be lost in the near future due to increasing costs associated with maintaining pesticide registrations and fulfilling data requirements.

For compounds for which data call-ins have been issued (e.g., Strychnine, Warfarin, Zinc Phosphide), many registrations have been suspended for a time. Some of these registrations still are suspended.

## FUTURE OF VERTEBRATE PESTICIDE PESTICIDE REGISTRATIONS

Although FIFRA's provisions do not differentiate vertebrate pesticides from other types of pesticides, certain other circumstances do. When compared to agricultural insecticides and herbicides, most vertebrate pesticide compounds are used in very small amounts. However, most vertebrate pesticide toxicants are toxic to a wide variety of nontarget vertebrate animals including man, his pets, and livestock. Vertebrate pesticides are implicated in many nontarget exposure incidents annually, some of which result in fatalities. Despite the small volumes of use of vertebrate toxicants, the potentials for risk for many of these compounds are very high and must be characterized.

Unlike many classes of pesticides, submission of efficacy data often is required for vertebrate pesticides as such products often are used to control organisms that can vector diseases of significance to public health. As the palatability of a rodenticide bait is very important to its effectiveness, efficacy data for such products often are considered to be formulation specific. This means that each formulation must be tested.

To keep any vertebrate pesticide toxicant registered will require a commitment on the part of a registrant or other concerned party to pay the reregistration fee and to develop the data needed to fill the "data gaps" first identified by the registrant and, perhaps, adjusted by EPA. Due to the small markets for many vertebrate pesticides, it is unlikely that all compounds on lists B, C, and D will (or can) be supported. For many of these compounds to be supported may require extensive cooperation among users, manufacturers, and government agencies. Such cooperation may help to reduce costs to any one party while addressing the mutual goal of maintaining registration. Indeed, data consortia may be the wave of the future. A consortium

Table 3. Current statuses of compounds that have or recently have had vertebrate pesticidal claims.

| CATEGORY | COMPOUND | MAJOR VERTEBRATE USE(S) |
|---|---|---|
| Voluntarily cancelled | DDT | Bats (rabies abatement only) |
| Registration Standard issued (1980-1988) compound not supported, all registrations cancelled | Fumarin (and its $Na^+$ Salt) | Rodent toxicants |
| Registration Standard issued (1980-1988) all registrations with vertebrate claims cancelled | Coal tar | Bird repellent |
| Registration Standard issued (1980-1988) and some or all vertebrate uses retained | 4-Aminopyrydine | Bird frightening agent and toxicant |
| | Aluminum Phosphide | Fumigant |
| | Chloropicrin | Fumigant |
| (Reregistration List A) | Fenthion | Bird toxicant |
| | Magnesium Phosphide | Fumigant |
| | Methyl Bromide | Fumigant |
| | Naphthalene | Repellent |
| | Rotenone | Fish toxicant |
| | Thiram | Repellent |
| | Warfarin (and its $Na^+$ salt) | Rodent toxicants |
| | Zinc Phosphide | Rodent toxicant |
| Reregistration List B | Brodifacoum | Rodent toxicant |
| | Bromadiolone | Rodent toxicant |
| | Bromethalin | Rodent toxicant |
| | Chlorophacinone | Rodent toxicant |
| | Diphacinone (and its salts) | Rodent toxicants |

Table 3. (Cont.)

| CATEGORY | COMPOUND | MAJOR VERTEBRATE USE(S) |
|---|---|---|
| List B (cont.) | Endrin | Vole toxicant |
| | Ethylene Dibromide | Fumigant |
| | Gophacide | Pocket gopher toxicant |
| | Nicotine and its derivatives | Repellent |
| | Pival (Pindone) and its salts | Rodent toxicants |
| | PMP (Valone) | Rodent toxicants |
| | Starlicide | Bird toxicant |
| Reregistration List C | Alkyl Pyridines | Repellent |
| | Bone Oil | Repellent |
| | Calcium Cyanide | Fumigant |
| | Cinnamaldehyde | Repellent |
| | Citronella Oil | Repellent |
| | para-Dichlorobenzene | Repellent |
| | Fluoroacetamide (1081) | Rodent toxicant |
| | Methyl Nonyl Ketone | Repellent |
| | Phosphorus | Rodent toxicant |
| | Scilloroside | Rodent toxicant |
| | Sodium Cyanide | Coyote, fox, and wild dog toxicant (used with M-44) |
| | Sodium Fluoroacetate (1080) | Coyote and rodent toxicant |
| | Strychnine | Rodent, lagomorph and bird toxicant |
| | Sulfaquinoxaline | Purported potentiator of Warfarin |
| | TFM | Lamprey toxicant |
| | Thymol | Repellent |
| Reregistration List D Compounds | All others (with data gaps) first registered before 11/1/84 | Various |

was assembled in 1988 for the purpose of developing data to support Strychnine Alkaloid registrations.

It is clear that pesticide manufacturers and pesticide users will have somewhat different interests regarding maintaining registrations. Pesticide manufacturers necessarily will be most interested in the fates of specific chemicals. While interested in certain chemicals, users are likely to be most interested in specific use patterns. Users may not be as concerned with which chemicals remain for the use patterns of concern as long as all chemicals are not lost. If users are able to tell manufacturers which chemicals are preferred for specific uses, they may assist manufacturers in deciding whether to pursue reregistration for those use patterns or at all. If manufacturers do not learn "where there friends are", many vertebrate pesticide compounds may be lost through the reregistration process.

## GENERAL INFORMATION ON REGISTERING PESTICIDES

To assist persons interested in applying for pesticide registrations, EPA recently has prepared the document:

> General Information on Applying for Registration of Pesticides in the United States. U. S. Environmental Protection Agency, June, 1989.

All current registrants are to be mailed a copy of this publication. Other parties interested in obtaining a copy of this volume should contact

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> Registration Support Branch
> Registration Division (H7505C)
> Office of Pesticide Programs
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## REFERENCES

This paper refers and alludes to FIFRA, its attendent regulations, and some recent Federal Register notices. These documents are cited below.


Code of Federal Regulations (CFR), Title 40, Sections 150-189, Office of the Federal Register and National Archives and Records Administration, revised July 1, 1988.

Campt, D.D. (1989a) Pesticides for which Registration Standards have been issued. Federal Register, 54:34, 7740-7750. (List A)

Campt, D.D. (1989b) Pesticides Required to be Reregistered; List B. Federal Register, 54:100, 22706-22714.

Campt, D.D. (1989c) Pesticides Required to be Reregistered; List C. Federal Register, 54:140, 30846-30855.

Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA, as amended). Public Laws 80-104 (1947); 86-139 (1959); 88-305 (1964); 92-516 (1972); 94-140 (1975); 95-396 (1978); and 100-460, 100-464 to 100-526, and 100-532 (1988).

Insecticide Act of nineteen hundred and ten. Public Law 61-192.

Reilly, W.K. (1989) Federal Insecticide, Fungicide and Rodenticide Act (FIFRA); Good Laboratory Practice Standards. Federal Register, 54:158, 34052-34074.