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REGISTRATION REQUIREMENTS FOR NON-TOXIC NATURAL PRODUCTS AS ANIMAL DAMAGE CONTROL AGENTS

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ABSTRACT: Plant extracts, animal glandular secretions and excretions, and natural food flavoring agents are common sources of natural products that can be used in animal damage control applications. Such products can be used either by themselves (e.g., coyote urine as a rodent repellent), or in combination with other control agents (e.g., food odor or flavor enhancer at baiting sites). The Environmental Protection Agency registration requirements are described for a variety of potential applications of natural products including bird and rodent repellents. In some applications, the product chemistry or other data requirements could make the registration process prohibitive due to the cost of chemical identification and quantification of compounds. Under a new Reduced Risk Pesticide Program, however, many data requirements for registration of natural products can be waived by EPA with the exception of some toxicology and efficacy studies.

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INTRODUCTION

A variety of natural products either in their natural or synthesized forms have been used to reduce damage by vertebrates for well over a hundred years. Some of the products are naturally occurring toxicants (e.g., red squill, strychnine, sodium monofluoroacetate-1080) derived from plants and are used for reductional control of vertebrate pests. Other products could be considered relatively non-toxic and are used as attractants (e.g., synthetic fermented egg scent as a coyote survey tool; Bullard 1982). There are also hundreds of natural odor lure products sold to hunters, photographers, and wildlife enthusiasts that are not regulated. Some agents in this latter category, when used in animal damage control applications, will be discussed in this report in terms of registration requirements imposed by the Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA). EPA has begun to establish general exemptions from regulation under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) for some natural product pesticides that are considered to be non-toxic (Environmental Protection Agency 1993a).

Most non-toxic natural products in this category are labelled as semiochemicals capable of information transfer or a signalling function from one organism to another (Albone 1984; Acree and Soderlund 1985). Pheromones are defined as a category of substances that are emitted to the air by an individual and then detected by a second individual of the same species that responds behaviorally (e.g., a male insect moves toward the scent of an ovulating female) or physiologically (e.g., female mice synchronize their estrus cycles in the presence of male mouse urine odor). These pheromone sub-categories are sometimes referred to as releaser and primer pheromones, respectively. That is, the releaser pheromones effect an immediate and observable response in the receiving insect, where as the primer pheromone produces a change in hormone output level or modulates some other neuro-humoral change in the receiver. These definitions, derived mainly from insect research, do not strictly adhere to analogous categories in vertebrates (Beauchamp et al. 1976), particularly when referring to mammals. In terms of their response to pheromones, the higher vertebrates are probably influenced by a variety of other sensory inputs as well as by experiential-learning factors (Shumake 1977). Three other less frequently used terms that describe semiochemicals are closely related to pheromones. These are the allomones or odor stimuli that transfer information from one species to a different species (Albone 1984); the kairomones or odors used by predators or parasites to locate prey or hosts (Burke 1992); and synomones or chemicals that are emitted by one species that can affect the behavior of a second species to the mutual benefit of both species (Tinsworth 1990).

A sub-category of semiochemicals includes flavoring agents, defensive insect or plant secretions, or other irritants that are relatively non-toxic, but capable of producing repellency by means of unpalatable properties (e.g., bitter taste, pungent odor) or pain-irritability properties (e.g., capsicum) affecting the oral, ocular, or dermal areas of the target animal. Natural products that produce conditioned flavor aversion or mimicry effects (e.g., cardiac glycosides, anti-metabolites) are relatively more toxic, and are therefore outside of the realm of the agents examined in this report.

Relatively innocuous natural products such as garlic, predator urine, and protein fermentation products as animal repellents are probably regarded by users and the general public as substances that are excluded from the pesticide regulation and registration requirements. However, 40 CFR 152.3 Subpart A (July 1, 1993c) defines a pesticide as ... "any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest, or intended for use as a plant regulator, defoliant, or desiccant" .... A further distinction is made for a sub-class called biochemical and microbial "pesticides" under section 158.65 "Biochemical and microbial pesticides are generally distinguished from conventional chemical pesticides by their unique mode of action, low use volume, target species specificity or natural occurrence" ... "Biochemical

pesticides include, but are not limited to, products such as semi[o]-chemicals (e.g., insect pheromones), hormones (e.g., insect juvenile growth hormones), natural plant and insect regulators, and enzymes. When necessary the Agency will evaluate products on an individual basis to determine whether they are biochemical or conventional chemical pesticides."

By the above definitions, semiochemicals have to be included uT the registration process when used for controlling vertebrate pest damage. These agents are labelled as biochemical pesticides under the EPA regulations. Microbial pesticides will not be examined in this report; the reader is referred to 40 CFR Part 158.740 for an outline of data requirements for this category (Environmental Protection Agency 1993c). For semiochemicals, Lindsay (1992) has indicated that the only circumstance under which the provisions of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) do not apply occurs when the natural agents are to be used solely for survey or detection purposes. In insect integrated pest management (IPM) programs, for example, pheromone traps often form an integral part of the overall program, but the trap data are used to determine correct timing and applications rates for conventional insecticides. This application of pheromone traps tends to minimize the use and to maximize the effectiveness of conventional insecticide treatments (Phillips 1976). The pheromone attractant traps, when used to detect invasions or upsurges in the populations of certain insect species, are not being used to reduce the population density or to repel the insects. Thus, this use of semiochemicals does not fall under the mandated EPA registration requirements for biochemical pesticides.

Conversely, when pheromones and other biological product pesticides (Lindsay 1992) are used to directly reduce crop damage, they are included under the FIFRA registration requirements but with reduced data submission requirements compared to those needed for conventional pesticides. The requirements have been reduced in view of the fact that these natural products normally have: 1) low toxicity; 2) limited application rates generally <20 g per acre; 3) target species specificity; 4) use potential mainly on terrestrial (nonaquatic) sites; 5) a high volatility; and/or 6) minimal or low residue levels due to rapid biodegradation in soil, water, and air. Some calculations designed to estimate residue levels after insect pheromone applications for control (Jellinek and Gray 1992), for example, have indicated that the levels may often be below chemical analytical detection limits in the parts per billion (ppb) range. When the natural product is to be used on a food crop, the regulations contained in the Federal Food Drug and Cosmetic Act (FFDCA) which is administered by EPA, FDA and the U.S. Department of Agriculture (USDA) are also applicable. These FFDCA regulations are discussed in detail elsewhere (Jellinek and Gray 1992).

REGISTRATION UNDER FIFRA: BRIEF HISTORY

The EPA data submission requirements for registration of biological product pesticides or semiochemicals have been reduced compared to those required for registration of conventional pesticide products over the past two decades. Separate registration guidelines for pheromones and insect growth regulators were issued by EPA in 1974. In 1979, a policy statement was published by EPA in the Federal Register encouraging development and registration of pheromones and other biochemical agents as safer products compared to most of the conventional pesticides. These reduced registration requirements have substantially shortened the time required for registration of most relatively non-toxic natural products. Guidelines for microbial and biochemical pesticide registrations requirements were later revised and issued in 1982. By late 1990, EPA had granted 41 biochemical and 21 micro-organism product registrations (Tinsworth 1990; Lindsay 1992). By 1993, EPA had initiated a Reduced Risk Pesticide Program (EPA 1993a; Culleen 1993) that enabled some non-deleterious pesticidal agents to be exempted from many data requirements for registration. Some recently registered natural product pesticides are cedar wood used as a moth repellent, capsicum used as a dog repellent, and garlic used as a deer or rodent repellent (Anonymous 1993).

The EPA Office of Pesticide Programs (OPP) has amassed, assembled, and evaluated a large amount of information and technical data on different classes of primarily insect pheromone products that have been chemically identified and synthesized (e.g., several straight chain alcohols, aldehydes, and acetates). There are as yet no general exemptions to many of the data submission requirements (Lindsay 1992) for pheromone products falling under these classes. However, assessment of the toxicity and ecological effects of different classes of chemicals may eventually help to further reduce some of the regulatory burden imposed on new registrations.

DATA REQUIREMENTS FOR BIOCHEMICAL PESTICIDES

For biochemical pesticides, there are six main testing areas to be considered on a product-by-product basis: 1) product chemistry; 2) toxicology; 3) residue chemistry; 4) hazards to non-target organisms; 5) environmental fate effects; and 6) product efficacy (Tinsworth 1990). The second, fourth, and fifth testing areas involve a tiered approach where by some products may require more extensive testing than others based upon initial results. The approach is to have the Tier I studies provide a maximal challenge. If results indicate minimal toxicity, other studies (Tier II or III) are not required. Detailed data requirements for registration of biochemical pesticides have been listed in 40 CFR 158.690 (Environmental Protection Agency 1993c). In brief, the data requirements cover the following types of studies.

Product Chemistry

The identified chemical structure of each active ingredient (a.i.) needs to be provided as well as a description and discussion of the inert ingredients in the technical or end-use product. If not under patent protection, the process used to manufacture the synthesized natural ingredients, purification procedures, and impurities generated by the process need to be fully described using flow charts and diagrams if necessary for

clarity. Sample analysis of the manufactured product for each a.i. may be conditionally required as well as the submission of a product sample. A validated analytical method for detecting and quantifying concentrations of each a.i. as well as test data on several physical/chemical properties (e.g., color, physical state, odor, density, etc.) are normally required.

Toxicological Evaluations

The first tier of tests required normally involves evaluations of acute oral, dermal, and inhalation toxicity effects; primary eye and skin irritation effects; and mutagenicity/gene mutation effects. Some of the data requirements may be waived by EPA if a sufficient rationale is presented by the applicant indicating that the natural product possesses low or no toxicity (Tinsworth 1990). If, on the other hand, the Tier I toxicological or residue data indicate significant adverse or persistent effects, Tier II or III data submissions may also be required for registration. The latter involve subchronic and chronic exposure tests in animals to further evaluate mutagenic, immunogenic, and oncogenic effects. When the product is to be used on a food or animal feed crop, 90-day feeding tests are normally required. However, the currently registered food crop use of semiochemicals have been routinely exempted from this requirement based upon Tier I test results. This often occurs when the manufactured product is chemically identical to the natural product as is the case with many commercially synthesized insect pheromone products.

Residue Chemistry

Whenever residues are expected to be present on harvested food or an animal feed commodity and the rate of application exceeds 20 g (0.7 oz) per acre per application, residue chemistry data may be required (Lindsay 1992). EPA has to either establish an allowable residue level or can exempt the product from this data requirement if the Tier I toxicity data indicate essentially no hazards. If other factors, such as rapid volatization or biodegradation, result in no measurable residues above the background levels of the natural product, these factors need to be fully described and documented by the applicant as a rationale for waiving the residue chemistry data requirement.

Hazards to Non-target Organisms

Avian, fish, and aquatic invertebrate toxicity data are usually required by EPA. Other concerns are those directed toward plants and beneficial insects. Again, it is up to the applicant to determine what risks might be expected to non-target organisms based on the intended use pattern of the product. If, for example, the natural product pesticide is to be contained within a holder or matrix, there may be a greatly reduced risk to non-targets and some of the tests could be waived. The Tier II testing in this area consists of an evaluation of those environmental fate effects that could affect non-targets. The Tier III testing is designed to reveal risk potential to non-target species and to quantify the extent of this potential for each given use of the product.

Environmental Fate Effects

These studies are designed to evaluate and monitor the movement, degradation, and metabolism of the product in soil, water, and air. Hydrolysis, photodegradation measurements in the three listed media, aerobic and anaerobic metabolic monitoring, soil leaching, adsorption/desorption, ground water migration, and bio-accumulation in fish and aquatic ecosystems are some tests that may be required for certain pesticide products in this category depending upon the volatility, the degree of toxicity, and persistence of the natural product or metabolites.

Efficacy Evaluation

Efficacy test data are generally required for each intended use of the product. These data are critical for registration decisions, even for products that have been granted waivers for the rest of the required tests. These evaluations may involve laboratory, enclosure, or field test protocols that are sensitive to indicating the degree to which the product reduces the pest problem through repellency, population reduction, mating disruption, or other means. Strictly speaking, it is illegal to market, sell, or distribute natural products that have not been reviewed and assessed through the EPA pesticide registration process. Application should be made for registration of the natural product for each intended use and/or target species to be controlled.

EXPERIMENTAL USE PERMITS

These are required prior to registration data collection whenever the treated field test site exceeds 10 acres in size. Field tests are usually conducted to establish efficacy of the product and to obtain residue data when food or feed crops are involved. Unless the applicant agrees to destroy the crop upon completion of the test, a temporary tolerance or an EPA exemption from a tolerance level has to be obtained before the Experimental Use Permit (EUP) is issued (O'Connor 1990).

For field test areas that involve fewer than 10 acres, these FIFRA requirements do not apply and no EUP is required of the applicant. The EPA makes the assumption that no benefit in pest control will result from the test and that the product is not within the legal definition of a pesticide under the language used in FIFRA. These small field tests then fall under the jurisdiction of the Toxic Substances Control Act (TSCA) that requires EPA to maintain a listing of all commercial chemical products manufactured, imported, or processed in the United States. Generally, when intended for research and development as a pesticide, EPA exempts both the pre-manufacturing notification, reporting, and record keeping requirements for new chemical products under TSCA. Manufacturers, processors, and distributors of pheromone products must, however, maintain records regarding adverse environmental or health effects posed by the product. This information must also be made available to EPA along with any other information regarding potential adverse effects of the technical or end use product.

DATA WAIVER REQUESTS

Some data requirements may be deemed inappropriate by the applicant for the use pattern needed to effect control. In other instances, EPA may deem the normally required data not useful in the Agency's risks:benefits analysis of the product.

Certain data items and evaluations can be waived by EPA but this action must first be initiated by the registrant by way of formal written requests. Registrants should discuss with an EPA Product Manager the data requirement and the feasibility of obtaining a waiver given an adequate rationale or alternate available data. A specific scientific rationale must be developed by the registrant to waive each data requirement. General assumptions and statements about the human safety and target species specificity of using semiochemicals are not accepted by EPA as justification for summarily waiving all registration data requirements.

Each biochemical pesticide application is evaluated on a product-by-product basis in terms of data needed for registration. The time required to register semiochemicals depends upon several factors: how many data requirements are granted waivers, the proposed use(s) of the product, the description of instructions for use and cautionary statements to be included on the label, the preliminary product analysis, and the hazard evaluation studies required by EPA beyond the Tier I levels.

Waivers to the registration process have been granted by EPA for insect pheromone products labeled for pest control purposes, but only when they are contained in traps that contain no other active ingredient (e.g., conventional insecticide) and where use of the product is predicted to add no significant increase in the background concentration of the pheromone in the environment (Tinsworth 1990; Lindsay 1992). Similarly, predator odor lures of natural origin can be used in traps, snares and other control devices with the registration requirements waived by EPA (Fagre et al. 1983). This is specifically the case where a rationale can be made for increasing the selectivity/species specificity when an odor lure or pheromone is added to the device.

FACILITATED REGISTRATION UNDER THE REDUCED RISK PESTICIDE PROGRAM

Under the OPP Reduced Risk Registration Program of EPA, a proposed rule was recently published (Federal Register 40 CFR Part 152 1993b) requesting public comment on the exemption from FIFRA regulations for natural cedar wood when used for pesticidal repellent control of arthropods or to retard mildew growth. EPA was of the opinion in this proposal that the regulatory burdens imposed by registration of this product (cedar wood) as a pesticide could not be justified in view of the negligible risk associated with it. It should be emphasized, however, that this exemption was proposed for the natural wood product, and not for extracted cedar wood oil. Other natural products that have been considered for exemption from FIFRA regulations include: dried blood, pine oil, garlic, capsicum, iron salts, and soaps (Anonymous 1993).

In vertebrate pest control, predator urine can be similarly regarded as a relatively risk-free natural product for effectively protecting Douglas fir tree seedlings from damage by small rodents, mountain beavers, or ungulates. When applied in a non-food crop application, only efficacy data would be required by EPA to develop a use label for these particular applications (W. Jacobs, U.S. Environmental Protection Agency, Washington, D.C., personal communication 1994). Urine biodegrades rapidly and any nitrogenous residues would serve as fertilizer for the growing seedlings. Again, the product identification of the active ingredients, inert ingredients, and other trace compounds contained in predator urine would pose an extreme burden on a registrant. There are literally thousands of chemical components in mammalian urine that will vary with diet, season, metabolic function, and kidney efficiency of individual predators. Eventually, it may be possible to isolate and synthesize the a.i.(s) that produce the repellency effect, but such an undertaking would take many years at great expense. In the interim, the natural product could be used to replace more toxic repellent alternatives.

There are a variety of other natural products that may prove to be useful for reducing damage posed by problem vertebrate species. Powdered egg product, previously registered as Big Game Repellent (BGR), could probably be used in its natural state with only efficacy data required unless extremely high concentrations are needed to deal with heavy feeding pressure from deer and elk in newly reforested areas in the Pacific northwest. Capsicum, the a.i. in hot red peppers, is already registered as a dog repellent and as an agent for personal protection against would-be assailants. This material may have applications in some vertebrate damage control situations and could probably be registered with minimal data requirements under the EPA Reduced Risk Pesticide Program.

Methyl anthranilate, a natural grape flavor agent that has been on the FDA Generally Regarded As Safe (GRAS) list as a food additive ingredient, has many applications in repelling birds from airports, feedlots, and some crops. As indicated in Table 1, EPA has waived all of the residue and non-target plant hazard data requirements for this compound even though it may be used at application rates above 20 g per acre because the material biodegrades very rapidly into natural sugar compounds (J. Hushon, ERM Program Management Co., McLean, VA, personal communication 1994). Minimal data were required for the non-target hazard evaluations and no field tests were required for environmental fate evaluation since the material breaks down within 48 hours when exposed to soil and air. The Tier I toxicology data indicated essentially no toxic effects on albino rats and mallard ducks (LD^, >2000 mg/kg) and these data are supportive of the reduced data submission requirements for the rest of the areas of human health and safety concerns.

Official field efficacy studies required for end use product registration of this repellent are still in progress. Overall, data submission requirements have been reduced by approximately one-half for this synthesized natural product when compared to those required for conventional pesticides.

A Pesticide Regulation Notice (PR-No. 93-9) was issued by EPA to manufacturers, formulators, producers and registrants of pesticide products on July 21, 1993

Table 1. Data requirements for registration of methyl anthranilate as an avian repellent.[1]

Product Chemistry		
61-1[2]	Product Composition	63-7 Density
61-2	Materials for Product Formulation	63-8 Solubility
62-1	Preliminary Analysis	63-9 Vapor Pressure
62-2	Certifiable Limits	63-10 Dissociation Constant
62-3	Validated Analytical Method	63-11 Octanol/Water Partition Coefficient
63-2	Color	
63-3	Physical State	63-13 Stability
63-4	Odor	63-14 Oxidizing/Reducing
63-5	Melting Point	Reaction
63-6	Boiling Point	63-17 Storage Stability
		63-18 Viscosity
		63-20 Corrosive Characteristic
Hazard Evaluation: Human and Domestic Animals (Toxicology)		
81-1	Acute Oral LD_{50} - Rat	
81-2	Acute Dermal LD_{50} - Rabbit	
81-4	Primary Eye Irritation - Rabbit	
81-5	Primary Dermal Irritation - Rabbit	
81-6	Dermal Sensitization - Guinea Pig	
Hazard Evaluation: Wildlife and Aquatic Organisms		
71-1b	Avian Oral LD_{50} - Mallard	
71-2b	Avian Dietary LC_{50} - Mallard	
72-1a	Freshwater Fish LC_{50} - Bluegill	
72-1c	Freshwater Fish LC_{50} - Trout	
72-2a	Freshwater Invertebrate LC_{50} - *Daphnia*	
72-3a	Estuarine/Marine Organisms LC_{50} - Atlantic Salmon	
72-3b	Estuarine/Marine Organisms LC_{50} - Channel Catfish	
Hazard Evaluation: Non-Target Plants[3]		
Product Performance		
96-Series	Field Efficacy	
Environmental Fate		
161-1	Hydrolysis	
161-2	Photodegradation - Water	
Residue Chemistry[3]		

[1]Information on registration studies required for this product was kindly supplied through Cathy Shea, ERM Program Management Co., McLean, VA.
[2]Guideline Reference Numbers. For more details regarding specific procedures needed to obtain the required registration data consult the reference source--Environmental Protection Agency. 1993c. Code of federal regulations 40 CFR (Parts 150-189).
[3]Data requirements waived.

inviting applicants to submit rationales for exemptions from FIFRA, or for special consideration under the Reduced Risk Pesticide Product Program for natural products and other agents that pose a lower hazard and exposure potential when compared with existing conventional pesticides. Specific guidelines for the content to be included in these rationales included the five categories of: a) human health effects; b) environmental fate and effects; c) other hazards; d) risk discussion; and e) pest resistance and management. Other supporting information beyond these five categories can be included by the applicant to support the thesis that the a.i. should be considered as a reduced-risk pesticide. In the notice, applicants were also encouraged to compare properties of the product with alternative registered products intended for the same use pattern. Applicants are not expected to generate new data to cover these rationales; citation of existing data is sufficient.

More specifically, the Human Health category should include discussions of acute toxicity; reproductive, developmental, mutagenic and neurotoxic properties; and any other known oncogenic and chronic effects. An Environmental Fate and Effects category requires the applicant to address 13 sub-categories including: toxicity in mammals, avians, fish and invertebrates; toxicity to plants and potential exposure to non-target animals; potential environmental persistence and mobility; and potential for bioaccumulation. The Other Hazards category includes a discussion of potential hazards due to storage, mixing, transportation, use and disposal of the agent. A Risk Discussion category involves discussion of reduced toxicity, exposure potential, or environmental burden of the product with comparisons made to existing registered pesticides for the same intended use(s). Pest Resistance and Management requires a rationale to address questions in regard to pest resistance and potential use of the new agent in Integrated Pest Management (IPM) programs. Effects of the new product on natural predators of the target pest species should also be included in this discussion.

This information contained in the five Reduced-Risk Rationales should be addressed and specifically identified on all correspondence to facilitate review by the EPA-OPP. This standardization of categories for rationales was developed to expedite the EPA review process in terms of determining data requirements verses data waivers under FIFRA.

These reduced data requirements have been purposely promulgated by EPA to encourage more applicants to pursue natural product registrations. Use of the whole natural product in animal damage control applications appears to be the least time-consuming and least expensive way to obtain a registration if the product is readily available in quantity at low cost (e.g., predator urine). The identification of the a.i.(s) and inerts in the natural product semiochemicals can sometimes involve years of research and development. EPA is continuing to examine classes of insect pheromone chemicals that may be reviewed for data requirements more quickly than in the past. Hopefully, this trend toward minimizing the data requirements on these relatively innocuous natural product pesticides will continue during this decade.

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