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Opportunities for Expediting the Regulatory Process

Chairman: DAVID B. PINNIGER

OPPORTUNITIES FOR EXPEDITING THE U.S. REGULATORY PROCESS FOR PHEROMONES AND OTHER SEMIOCHEMICALS

S. D. JELLINEK, E.C. GRAY

Jellinek, Schwartz, Connolly & Freshman, Inc., Suite 500, 1015 15th St. NW, Washington, D.C. 20005.

ABSTRACT

The requirements for government approval of use of insect pheromones in the United States are analyzed in this paper. The data requirements imposed under U.S. regulations for obtaining experimental use permits and product registrations for pheromone products are discussed, and it is shown that a number of the ostensible data requirements are routinely waived. The paper also discusses changes to the experimental use permit program that would encourage research on additional uses of insect pheromones. Finally, it is suggested that certain categories of insect pheromones should be the subject of a categorical exemption from the requirement for a tolerance specifying an allowable level of residues on food crops.

INTRODUCTION

Semiochemicals, broadly defined, are chemical compounds that are used by organisms to transmit information between individuals of the same or different species. A subcategory of semiochemicals, insect pheromones, are volatile compounds or mixtures that are emitted by insects and are sensed by and affect the behavior of other insects of the same species, usually by functioning as attractants. Scientists have learned how to synthesize many of these compounds and how they can be used in insect control programs (Inscoe et al. 1990). A pheromone tends to be very target-specific; it has a notable effect on the behavior of members of the target species, but in most cases has essentially no effect on other insect species (including beneficial species that may be adversely affected by conventional insecticides). None of the pheromones have been shown to pose any significant human health or toxicity problem, although some of the compounds can cause temporary eye irritation or minor, temporary skin irritation.

The same narrow effect spectrum that makes pheromone products attractive from an ecological standpoint makes them more difficult to profitably develop, produce, and market. The potential market for any given pheromone product is relatively small, limited to situations where a serious problem is being caused by the particular insect species whose behavior the pheromone affects. The cost and time required to develop safety data, and the restrictions and conditions that the government places on efficacy experiments, may be perceived as too great to justify the investment needed to develop pheromones for niche markets.

Many researchers and potential pheromone registrants, and some regulatory officials as well, believe that regulation of pheromones is unnecessarily stringent in view of the apparently low toxicity of these substances, their manner of use, and the lack of significant exposure potential. These people think that regulatory programs designed with conventional pesticides in mind are not flexible enough to produce the common sense regulation of pheromones that would encourage their development and marketing. Regulators might point out in response that if they were to simply waive all rules and requirements for pheromones without sufficient justification and analysis, they likely would be accused of violating statutes that require appropriate proof of safety before a pesticide may be marketed and used. Thus, the main issue with pheromones is whether regulatory agencies will conclude that they can reach safety decisions on pheromones without requiring applicants to conduct an unaffordably large number of health and safety studies.

In this paper we examine the regulation of pheromones by the U.S. Environmental Protection Agency (EPA). Since 1979 EPA has recognized the need for a special regulatory approach to pheromone products, and since 1982 the data requirements that apply to pheromones have been considerably less stringent than those that apply to conventional pesticides. This paper discusses further steps that we think EPA could take to facilitate the registration of pheromones, including: announcing openly the Agency's policy on waiver of data requirements for pheromones; eliminating some of the current data requirements and modifying others in order to save unnecessary testing costs; and adopting new policies regarding tolerance exemptions and experimental use permits for certain pheromone products. Although this paper focuses on the United States' pesticide regulatory scheme, the issues and principles discussed here should be broadly applicable.

PESTICIDE REGISTRATION REQUIREMENT FOR SEMIOCHEMICALS

Nature and scope of registration requirement

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), a law administered by the U.S. Environmental Protection Agency (EPA), generally prohibits the sale or distribution of substances that are "pesticides" but are not registered under FIFRA, and requires that registered pesticides not be used in ways that are inconsistent with their approved labeling.

Pheromones and other semiochemicals used to prevent or control pest damage are "pesticides" within the meaning of FIFRA.[1] These compounds thus are subject to the law's premarket licensing provisions unless EPA specifically exempts them.

FIFRA section 25(b) allows EPA to issue a regulation that exempts a pesticide from FIFRA's requirements if EPA determines that regulation of the pesticide is not needed in order to carry out FIFRA's purposes. EPA has by regulation exempted certain pheromone traps from FIFRA's coverage, but this exemption does not extend to use of pheromones for

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[1] EPA has determined that a pheromone used only to help monitor or measure insect population levels is not a pesticide.

purposes such as mating disruption or attraction to limited areas where conventional pesticides can be applied to destroy the pests.

Some pheromone developers have urged that EPA greatly broaden this exemption from the registration requirement, saying that pheromones have been shown to be inherently safe and that their regulation is unnecessary. Others say in response that the data that show the safety of pheromones probably would not exist in the absence of the registration requirement. Advocates of continuing regulatory jurisdiction also point out that while some types of pheromones and use patterns have been studied enough to allow generalizations about safety, other types of pheromones and use methods have been studied less thoroughly.

It is not likely that EPA will exempt all semiochemical products--or even all pheromones--from all FIFRA requirements by use of an exemption under FIFRA section 25(b). The existence of a registration requirement for such products should make EPA more willing to adopt other regulatory reforms. The registration requirement allows EPA to require and enforce labeling language, use instructions, and composition limitations and to take prompt action to halt marketing if a problem is ever discovered. Were these safeguards not in place, it could be argued that relaxing the premarket review of pheromones would be unwarranted. Finally, exempting semiochemicals or pheromones from regulation under FIFRA would require a time-consuming and complex rulemaking under FIFRA, while other changes could be adopted and implemented more quickly.

We do not advocate total deregulation of pheromones. We do argue that pheromones are quite different from typical pesticides, and that the regulation of pheromones should fully recognize this. The logic underlying most pesticide regulation schemes is that pesticides generally are not found in nature and are designed to kill living things, and therefore should be regarded with suspicion and given the most careful regulatory attention. Pheromones, however, lack these basic characteristics that lead us to be cautious about pesticides in general. Pheromones are not unknown in nature; manmade pheromone compounds are identical or very closely similar to naturally-occurring compounds that are produced by the very species whose behavior they control. Moreover, they are not designed to be toxic. Finally, they can replace other pesticides that are toxic by design. These differences clearly justify treating pheromones as a category differently than most pesticides. The remainder of this paper discusses several areas in which less stringent regulation of pheromones is warranted.

Data ostensibly required for registration

A person seeking a list of the EPA requirements for data to support an application for registration of a pesticide logically would turn to EPA's regulations, which are located in Part 158 of Volume 40 of the U.S. Code of Federal Regulations (abbreviatecd 40 CFR Part 158), first issued in 1984. 40 CFR 158.690 contains a detailed listing of data requirements for pheromones and other biochemical" products that is considerably less extensive than the list of studies required by Part 158 for conventional pesticides. Some requirements are conditioned on results of lower-tier studies or are waived if the application rate is very low.

For potential pheromone registrants, however, even the cost of generating the reduced set of data prescribed by 40 CFR § 158.690 can be prohibitive. For a terrestrial crop use, § 158.690 calls for applications to be supported by:

- Product chemistry information (what the product contains, how it is produced, and what its physical/chemical characteristics are). Cost: $40,000 or more, depending on the number of impurities requiring analysis and on whether the studies are performed "in house" or by a contract laboratory.

- Residue chemistry, including, at a minimum, residue analytical method and data on the nature and magnitude of residues. Section 158.690(b) says that a complete set of residue chemistry data is required to support any application for registration of any biochemical pesticide (including any pheromone) for use on any food crop used at a rate of 20 or more grams per acre of cropland per application. Residue chemistry data are primarily used to support food-crop residue clearances--tolerances or exemptions--issued by EPA under the Federal Food, Drug, and Cosmetic Act (FFDCA), discussed later in this paper. Residue chemistry data include data to characterize the nature and magnitude of any possible residues of the pesticide in crops, livestock, and processed food, and analytical methods for measuring such residues in various food commodities. These data are extremely difficult, time-consuming, and expensive to generate. Cost (if requirements are applicable): $100,000-$200,000 or more per crop, depending on the difficulty of analysis of metabolites.

- Mammalian toxicity data: This category includes a requirement for acute oral, dermal, and inhalation toxicity studies (one set of studies for each active ingredient, using that active ingredient as the test material, and one set of studies using the product as formulated for use). Also required are primary dermal irritation and primary eye irritation studies using the formulated product as the test substance, and genotoxicity, immune response, 90-day feeding, and teratogenicity studies using each active ingredient as the test substance. Minimum cost (for a product with only one active ingredient): $280,000.

- Fish and wildlife toxicity data, typically including data from avian acute oral toxicity, avian dietary toxicity, freshwater fish LC_{50}, freshwater invertebrate LC_{50}, non-target plant, and non-target insect studies. The requirements vary somewhat, depending on the physical/ chemical characteristics of the product (e.g., its volatility). Cost: $20,000-$30,000.

The total cost of all these "required" studies would be $440,000-$550,000 for the first crop,[2] and an additional $100,000-$200,000 for residue data for each of the next several additional crops (assuming that the residue chemistry requirements apply to the crops in question).

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[2] The cost of the data required to support the application of a new conventional pesticide, by comparison, would be in the millions of dollars.

Of course, these amounts do not include the cost of the research and development needed to identify a pheromone and demonstrate its potential efficacy. Nor, importantly, do they include the cost of producing the quantities of the pheromone needed for use as the test substance in the health and safety studies that EPA requires. Producing large enough quantities of a pheromone to use undiluted as a test substance can itself be extremely expensive and time-consuming at the experimental stage. For one thing, the very lack of toxicity that is typical of pheromones would require the use of relatively large doses of a pheromone in tests where it is necessary to elicit a response. Moreover, the cost of production of these complex compounds in the quantities at issue is in the hundreds of dollars per gram, and many kilograms may be needed for the required testing.

The perceived cost of data development and the time needed for the generation, submission, and review of the data thus tend to discourage prospective pheromone registrants, particularly if the data must be generated before a product has been shown to be commercially promising. (See the discussion of experimental use permits below.) The firms that face these investment decisions often are relatively small businesses that are initially unfamiliar with EPA's pesticide program and its requirements and conventions in such data-related areas as formats for reports, study design protocols, data waiver substantiation procedures, standard evaluation procedures, and good laboratory practices.

Data actually required

40 CFR § 158.45 allows EPA to waive particular data requirements for products (or categories of products) if the characteristics of the product or category are such that "the data would not be useful in the Agency's evaluation of the risks or benefits of the product." The exercise of this discretion to waive data requirements plays a very important role in EPA's approach to the regulation of pheromone products. EPA has used this authority quite wisely, for the most part; it often has approved applications to register pheromone products even though the applications were supported by considerably fewer studies than the Part 158 regulations indicate are required.[3] But EPA has not announced these decisions on data requirements, and thus other prospective registrants may not know what the real requirements are.

A person who is considering filing an application for a pheromone registration needs to know what data are required well before the application is filed (so that the data can be timely generated) as well as what data are not required (to avoid unnecessary testing costs and wasted time). If such a person submits an individual request for a waiver of a data requirement, the request is evaluated by EPA scientists from the relevant discipline(s). These scientists are extremely busy. To them, evaluating an individual advance request for the

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[3] In this context, it is worth noting that most of the pheromone products approved in recent years are intended to control *Lepidoptera* species and have been designed to prevent the pheromone from contacting the food plant until after the pheromone has volatilized and dispersed from the dispensing device. It is altogether possible that EPA would demand a greater amount of data for products containing categories of semiochemicals about which much less is known, or for products whose design would allow the active ingredient to come in contact with food in a more concentrated form.

waiver of a data requirement is apt to have a lower priority than evaluating actual data. It may take EPA several months to respond formally, and the response may be that the waiver request cannot be evaluated in the abstract and can only be considered as part of an application for registration.

On the other hand, if EPA has already decided categorically to waive certain data requirements for the kind of product in question, no delay should be involved. Such waiver decisions do exist, but applicants may not be aware of them. Over the years EPA has decided internally, without announcement, that some of the studies that the regulations list as required need never be required for some kinds of pheromone products. For instance, the Toxicology Branch of EPA's Office of Pesticide Programs (OPP) determined in 1986 that there was no need for teratology or subchronic dietary exposure studies for pheromone products in which the active ingredient is so formulated that it is contained in a plastic matrix, used in a solid state, and contained in some sort of dispenser, and furnished OPP's registration officials a memorandum to that effect dated November 24, 1986. Likewise, in December 1986 OPP's Ecological Effects Branch issued a policy memorandum stating that the Branch had determined that the avian dietary LC_{50} study need not be submitted "when the pheromone is impregnated in a non-biodegradable medium, such as plastic." Those decisions have not been published, although publication would be useful and is provided for expressly by 40 CFR § 158.45(c), which states (emphasis added):

> *Notification of waiver decisions.* The Agency will review each waiver request and inform the applicant in writing of its decision. In addition, for decisions that could apply to more than a specific product, the Agency may choose to send a notice to all registrants or to publish a notice in the Federal Register announcing its decision.

Based on the discussions of available data contained in the Federal Register documents published by EPA between 1981 and mid-1990 establishing clearances for pheromone pesticide residues under the Federal Food, Drug, and Cosmetics Act, and on discussions with members of the EPA staff and with employees of pheromone registrants, the data requirements that EPA actually imposes for food-crop products seem to be as follows:

- As to product chemistry data, EPA actually requires essentially all of the information described in 40 CFR § 158.690, and few waivers are sought or granted.

- With respect to mammalian toxicity data, EPA apparently always requires the acute inhalation toxicity study and the eye irritation study. EPA usually (but not always) requires acute oral toxicity, acute dermal toxicity, and primary dermal irritation studies as well. EPA ordinarily requires genotoxicity data but usually will allow the product to be marketed under a conditional registration while the data is being generated; the Agency does not require the immune response study unless it appears that there will be particularly high exposure. No instance was found where the Agency required either a teratogenicity or subchronic feeding study, each of which is considerably more expensive and takes much longer to conduct than an acute toxicity study. As already noted, since 1986 EPA's policy has been to not require

these studies for matrix-formulated pheromones. Moreover, while the mammalian acute oral, dermal, and inhalation toxicity studies ostensibly must be performed separately for each active ingredient as well as for the end-use formulation, EPA typically has required only one study of each type per product. Cost of the actual requirements (including associated chemical analyses): $30,000-$75,000.

- None of the notices indicated that any residue chemistry data were submitted, evaluated, or relied on by EPA. We do not know whether this is because none of the products were to be applied in excess of 20 grams per acre, or because the data requirements were waived by EPA.[4] Cost of the actual requirement: zero.

- As far as ecological effects data are concerned, EPA typically has required most of the first-tier avian, fish, and aquatic invertebrate toxicity studies. (As already noted, EPA has waived the avian dietary study for the typical dispenser/matrix formulations.) The nontarget plant and insect data requirements are imposed rarely, if ever. Cost: $16,000-$22,000.

This survey shows that EPA systematically has used its authority to waive many of the most expensive and time-consuming data requirements that EPA's regulations say are required to support a pheromone registration. The cost of the studies actually required is in the range of $85-140,000, rather than the $440-560,000 suggested by EPA's regulations. This would not necessarily be obvious to a prospective investor, however, particularly since both government officials and private industry advisors continue to indicate that the full set of Part 158 data normally is required. For instance, a recent article by a senior EPA official (Tinsworth 1990) set forth the data requirements of Part 158 and gave no indication that any of those requirements had been or might be waived for whole categories of products. Another recent article (O'Connor 1990) states flatly that teratogenicity and subchronic toxicity studies are required, and that waivers are issued on a case-by-case basis in response to substantiated written waiver requests submitted by applicants. EPA should further encourage the development and use of pheromones by announcing its policies regarding waivers of data requirements.

The logic underlying the data waivers that have been granted by EPA would seem to call for further data waivers. For example, if an avian dietary LC_{50} study is not needed for impregnated pheromone formulations because avian dietary exposure is unlikely, why should there be a need for an avian acute oral LD_{50} study either? Is there really any serious possibility that a bird is going to devour a pheromone dispenser, or is this requirement being applied in a purely rote fashion? Moreover, if birds are unlikely to be exposed to such a pheromone product, it would be even less likely that fish or other aquatic organisms would be exposed. But as far as can be determined, EPA has not contemplated waiving the fish and aquatic invertebrate toxicity studies.

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[4] Residue data were required for one pesticide, gossyplure, first registered before the 1982 guidelines were issued.

Time required to process applications

It is EPA's policy to give priority treatment to applications for pheromone registration, and its staff seems genuinely interested in moving applications promptly through the process. Despite this, however, several kinds of problems can cause long delays. First, data submitted to EPA in support of an application might not comply with the strict EPA formatting requirements, causing a rejection of the data after a front-end review. Getting past the initial format review can by itself be a frustrating experience. Second, if scientific review of data is needed, or if waiver of a data requirement is requested, there will generally be a delay of some months before the study or waiver request can be reviewed. Finally, after all the scientific reviews are finished, it often takes several more months for EPA to prepare and publish a Federal Register document establishing an exemption from the need for a tolerance.

In most cases, the delays are due primarily to backlogs caused by resource shortages rather than the need to resolve any substantive issues. We should emphasize that pheromones are not being denied registration because of any substantive risk concerns. But studies on pheromones are being reviewed despite the lack of meaningful scientific issues, and the delays attributable to obtaining those essentially meaningless reviews are substantially hindering the development of a new generation of safer pesticides. EPA should consider seriously whether a more environmentally protective approach might be to waive generically many of the requirements for data generation and streamline the process for regulatory approval of pheromones.

Reregistration and fees

Several pheromones were first registered before 1984 and thus are subject to the reregistration requirements that the 1988 FIFRA amendments imposed. A listing of these substances has been published (USEPA 1989). The registrants of products containing these pheromones are subject to substantial reregistration fees (one firm has been billed a total of $180,000 for two of its pheromone products), although they may be eligible for fee discounts or exemptions. They also may be required to spend a considerable amount of time arguing for waivers of data requirements; unfortunately, if data requirements were waived when the product was first registered, those waiver decisions probably were not reduced to writing, and probably were made by a different set of staffers than those who will conduct the reregistration review.

FOOD RESIDUES AND PHEROMONES

In addition to FIFRA registration, persons interested in marketing a pheromone or other semiochemical product for use on food crops must cope with another regulatory requirement. Food sold in interstate commerce in the U.S. may bear a pesticide residue only if there exists a clearance established by EPA under the Federal Food, Drug, and Cosmetic Act (FFDCA) that permits the residue. The U.S. Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA) enforce this requirement by inspecting food and analyzing for residues. An FFDCA clearance for an active ingredient of a pesticide can take the form of a regulation setting a tolerance (a finite authorized residue level) or a regulation

exempting the residue/crop combination from the need for a tolerance. Each pheromone that has been approved under FIFRA for use on food crops has first been the subject of an exemption regulation issued under FFDCA; no tolerance for a pheromone ingredient has been requested or issued. An FFDCA tolerance or exemption must also exist for each intentionally added inert ingredient (such as a polymer compound used as a controlled-release dispenser or encapsulator) before the product will be registered.

Section 408(c) of the FFDCA states that EPA may issue a regulation

> exempting any pesticide chemical from the necessity of a tolerance with respect to use in or on any or all raw agricultural commodities when such a tolerance is not necessary to protect the public health.

In its implementing regulations, EPA has expanded on this criterion (40 CFR § 180.1001(a), emphasis added):

> An exemption from a tolerance shall be granted when it appears that the total quantity of the pesticide chemical in or on all raw agricultural commodities for which it is useful under conditions of use currently prevailing or proposed will involve no hazard to the public health.

Pheromones are identical or extremely similar in composition to naturally produced substances that may appear on food but are totally unregulated. None of the pheromones tested so far have given any reason for concern about dietary toxicity.

The amount of a pheromone active ingredient released per acre is very small (a few grams to a few tens of grams per acre) and the maximum residue levels that reasonably could occur on crops are therefore very low. For example, a commercial U.S. tomato farm typically produces about 40,000 pounds of tomatoes per acre (USDA 1989). If 50 grams of pheromone (approximately 0.1 lb) were applied to that acre, and if every molecule of the pheromone used on that acre became a residue on those tomatoes (which would never occur in actuality), the resulting theoretical maximum residue would only be about 2.5 parts per million (ppm). If 5 grams per acre (a much more typical rate) were applied, the highest possible residue would be about 0.25 ppm. Degradation and volatilization during the growing season are likely to be substantial and the likelihood of detectable residues on harvested food is small.

Indeed, when a residue detection method for a pheromone was developed and used to analyze crops grown in fields where the pheromone was used, no residue could be detected, although the method was extremely sensitive. In a recent publication (Spittler et al. 1988), researchers describe the results of an experiment using an impressive method they developed for detecting and measuring residues of the grape berry moth pheromone. The method was sensitive to 2 parts per billion (ppb) and could quantitate residue levels above 5 ppb. The pheromone was applied in the field using hollow polyethylene tie-on dispensers at rates up to 140 grams/acre. Thirty-six food samples were analyzed; no residues were detected.

It is highly unlikely that FDA or USDA ever will devote any resources to attempting to detect residues of pheromones on food. Realistically, officials of these agencies can be expected to decide that there are better things to do with their limited inspection and analytical resources than to look for incremental residues of naturally occurring substances from a family of compounds known for their low toxicity. Moreover, it is very unlikely that FDA or USDA analysts could ever find a pheromone residue were they to look, simply because the residue levels are so low. Finally, even if a detectable level of a pheromone were found on a food, FDA could seize the food as "unsafe" only if it could make the finding that the pheromone was "added" to the food by human activity, rather than resulting from natural occurrences. For pheromones, making this finding would be virtually impossible.

As already discussed, the time that EPA takes to process an individual exemption request can be considerable.[5] EPA could lessen the impact of such delays by issuing a broad exemption for all pheromones or for a large subset of pheromones. Exemptions for entire broad categories of other kinds of compounds often have been issued where there was little concern about dietary health effects of the entire category. For instance, 40 CFR § 180.1001(c) (1989 ed.) lists the following categorical exemptions, among others: "methyl esters of fatty acids derived from edible fats and oils;" "fatty acids" conforming to certain regulations; "methylated silicones;" "mono- and diglycerides of C_8-C_{18} fatty acids;" "polymers derived from the following monomers: acrylic acid, sodium form; butyl acrylate; ethyl acrylate; methacrylic acid and its ammonium and potassium salts; and methyl methacrylate;" and "soap (sodium or potassium salts of fatty acids)." EPA could speed the process of allowing pheromone testing and marketing by issuing a similarly broad exemption for pheromones that are aimed at *Lepidoptera* species and are registered in the form of products that present little dietary exposure potential. As sufficient information becomes available for other semiochemical categories, they should be similarly exempted from the need for a tolerance.[6]

EXPERIMENTAL USE PERMITS AND PHEROMONES

In order to know what specific types of uses of a pheromone pesticide to propose for registration, the manufacturer needs to perform field tests to determine its efficacy under various growing conditions. FIFRA does not prohibit the testing, as such, of an unregistered pesticide. But FIFRA generally does prohibit the shipment of substances that are pesticides

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[5] Applicants should be aware that the inert ingredients of a food-use pheromone product also must be cleared under the FFDCA before the product can be approved for use in crop production. If a product is to contain an inert ingredient that has not already received an exemption, the applicant should apply for an exemption early in the process and should assume that at a minimum several months will be required for approval.

[6] Some exemptions for inert ingredients used in pheromone dispensers are worded to allow use only with specific pheromones. EPA should investigate whether these exemptions could be broadened to allow use of the inert ingredients with all pheromones.

but that are not registered, and it usually is necessary to ship the test material to a use site before conducting tests.

Two FIFRA provisions afford relief from this general shipment ban. First, FIFRA section 12(b)(5) says that no penalty shall apply to

> any person who ships a substance or mixture of substances being put through tests in which the purpose is only to determine its value for pesticide purposes or to determine its toxicity or other properties and from which the user does not expect to receive any benefit in pest control from its use.

Second, FIFRA section 5 authorizes EPA to grant an experimental use permit (EUP)

> if the Administrator determines that the applicant needs such permit in order to accumulate information necessary to register a pesticide under section 3.

FIFRA section 5 contemplates the submission of an application for an EUP with supporting data, and review by EPA before approval. Section 3(b)(2) of FIFRA authorizes the transfer of an unregistered pesticide in accordance with the terms of an EUP.

The statute thus differentiates between those experiments that require an EUP and those that are covered by the section 12(b)(5) exemption on the basis of the intent or expectations of the experimenter, not on the basis of the area involved in the experiment. However, EPA claims to have created an acreage-based distinction in its EUP regulations, 40 CFR Part 172. The regulation says that EPA will "presume" that terrestrial testing of a substance on a cumulative total of 10 acres or less is for a purpose that falls within the exemption, and similarly will "presume" that testing on a cumulative total of more than 10 acres is not covered by the exemption and is permitted only if an EUP has first been obtained. These presumptions evidently are designed to be used to help EPA carry its burden of showing the inapplicability of the exemption in enforcement actions brought by EPA against alleged violators. Although it is far from clear that EPA could prevail on its 10-acre theory if challenged, persons in the pesticide business are unlikely to risk prosecution by ignoring EPA's approach.

Pheromone experimenters argue that an individual test site for determining pheromone efficacy often must be much larger than 10 acres to be useful. In mating disruption studies, for instance, treating more than 10 acres may be needed in order to avoid the confounding results that would obtain if already-mated insects from nearby untreated sites flew into the test area. A large treatment area provides a kind of buffer around the central part of the treatment area where the efficacy will be measured.

If the test is to be conducted on a food crop site, another precondition is the FFDCA requirement, already discussed, for a tolerance or exemption for the residue of the pheromone on the resulting harvested food. EPA regulations preclude the issuance of an EUP for a food crop unless either (1) a tolerance, exemption, or temporary tolerance for the pesticide/crop combination is in effect under the FFDCA, or (2) the food or feed derived

from the crop will be destroyed instead of being marketed or used for human or animal consumption. Destroying the crop means that the experiment must cost much more than it otherwise would. A crop-destruct permit might be feasible for tests involving small sites and crops of low per-acre value, but may be prohibitively expensive for high-value crops such as fruits or vegetables, or for the large-acreage sites sometimes needed for pheromone experiments.

Another problem for pheromone developers is the narrowness and specificity of the EUPs that EPA issues, in terms of duration, application methods, and precise ingredient content. The regulations (40 CFR § 172.5(b)) say that the duration of an EUP is

> normally one year, depending on the crop or site to be tested and the requirements of the testing program submitted. The applicant should propose a suitable duration of the permit commensurate with the program submitted. Permits and associated temporary tolerances may be renewed, extended, or amended upon request if circumstances warrant.

EPA regulations also require that the testing program be described quite explicitly, with detailed use instructions that must be followed, and require "a complete confidential statement of composition for the formulation to be tested giving the name and percentage by weight of each ingredient, active and inert." See 40 CFR § 172.4(b)(3).

Pheromone developers argue that these provisions conflict with their need to be able to conduct experiments designed to conduct large numbers of efficacy studies using variations in formulations and application methods, and that the delays associated with the need to obtain repeated EUP approvals exacerbate this problem. They stress that in order to encourage the development of pheromone pesticides, EPA must find ways to make it easier to get approval to conduct a range of tests in a relatively inexpensive manner without having to repeatedly request EPA approval and wait until it is granted. This could be done by exempting more testing from the need for an EUP, increasing the scope and duration of EUPs, speeding up the review and approval of EUPs, or some combination.

Recently a developer obtained an EUP for a multi-year period that authorizes experiments with different application techniques, and with different formulation types and active-ingredient ratios. Similarly, in at least one case EPA granted a request for an FFDCA exemption that covers all food crops, rather than naming specific crops. Thus, there are signs that EPA recognizes the need to allow significantly more flexibility to pheromone experimenters than is afforded to experimenters using conventional pesticides.

CONCLUSION

Many of the regulatory requirements that apply generally to pesticides are unwarranted in the case of pheromones because of the unique nature of pheromones. Relaxing those requirements for pheromones is actually environmentally beneficial. If EPA continues to recognize these principles, and consistently and publicly applies them, more

pheromone products can be developed and registered and their use can decrease the need for less specific, more toxic pesticides.

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FUTURE REGULATION OF PHYTOPHARMACEUTICAL PRODUCTS IN THE EEC

N.M. VERBIESE

DOW CORNING EUROPE, Rue General de Gaulle 62, B-1310 La Hulpe

ABSTRACT

The proposal of a future Directive regulating marketing of phytosanitary products in the European Economic Community (EEC) is presented. As for the time being fundamental principles are still under discussion, to come to a global compromise, there are opportunities for being proactive and to suggest guidelines for the registration of products like pheromones and insect behaviour-modifying chemicals. It is a challenge to industry to demonstrate that those chemicals are different from conventional pesticides and should be considered appropriately.

INTRODUCTION

EEC is presently working on a Directive proposal to regulate the introduction on the market and the use of phytopharmaceutical substances and preparations.
The content of the future Directive is still being examined at a very general level and topics such as semiochemicals are not specifically covered. The absence of regulation is not an ideal situation as it admits different national interpretations and requirements.
Therefore, there is a need for harmonization and development of an appropriate regulation allowing some flexibility in the approval procedure for the use of pheromones and other insect behaviour chemicals.

We want to emphasize that the information given in this paper is presented to describe the regulatory climate of the future Directive and is still likely to be modified.

CONTENT OF THE FUTURE DIRECTIVE

The following subjects will be covered by the future Directive:

- Definition of phytopharmaceutical products and role.
- Definition of active substances and preparations.
- Conditions and validity of authorizations.
- Conditions of experimental use.
- Identification and analysis of active substances, preparations and residues.
- Content of the registration file of active substances and preparation.
- Possibility of simplification of registration requirements.

Only registered products will be authorized in the phytosanitary applications.

To be admitted on a list of permitted substances, a set of data on the active ingredient must be provided. When a substance will be included in a phytopharmaceutical preparation, as it is usually the case, additional data on the final product must be provided.

Pheromones and other insect behaviour-modifying chemicals used to protect plants by controlling or preventing pest damage, will not be considered differently from conventional pesticides within the definition of the future Directive. However, it is anticipated that some simplification of the approval procedure will be possible under the following conditions:

- provided that adequate scientific rationale is given, the requirements of the registration file can be reduced.

- For certain categories of products, some fundamental principles for a uniform simplication procedure could be defined in the future Directive. This would avoid a case by case examination of the file and minimize the risks of having a long delay for the approval procedure.

- There will be a mutual recognition of competence in member countries for approvals and experimental use permits.

CONTENT OF THE REGISTRATION FILE

1. Identity of the substance/*preparation

Manufacturer	CAS nr	Purity
Trade name	Formula	Impurities
Chemical name	Manufacture	*Composition

2. Physico-chemical properties

Melting point	Spectra (UV,IR,RMN)	Reactivity
Boiling point	Solubility	Surface tension
Density	Partition coeff.	Flash point
Vapour pressure	Water/air/light stability	Viscosity
Colour/odour	Thermal stability	*Wetting properties
Granulometry	*Emulsion stability	

3a. Action of the active substance

Function	Information on resistance
Effect on pests	Application scope (green house, field, garden)
Use	*Method of application

3b. Storage, handling, transportation recommendations

Emergency procedures (accident, spill)
Cleaning of the material used for the application.

4. Method of analysis

Analysis of the active substance
Detection of residues on the treated plants, soil, air, water, living organisms.
*Analysis of the ingredients

5. Toxicological data

Acute toxicity (oral, sub-cut,inhal,i.p.)	Chronic toxicity	Medical aid
Irritation (eye, skin)	Mutagenicity	Epidemiology
Sensitization	Reproductive tox	NOEL/DTA
Repeated exposure	Metabolism	Complementary studies

6. Determination of residues

Residues on treated plant	Effect of industrial process
Fate of the residues	*Modification of organoleptic characteristics
Absence of adverse effects	

7. Behaviour and fate in the environment

Degradation in soil (3 types)	Degradation in water
Adsorption/desorption (3 types)	Sedimentation (adsorption/desorption)
Mobility	Degradation in air

8. Ecotoxicological studies

Effects on birds (acute/long term toxicity)
Effects on fish (acute/long term, bio-accumulation)

Toxicity to daphnia	Effect on soil microorganisms
Toxicity to algae	Effect on waste water treatment
Toxicity to bees	Effect on surface water
	Effect on non target organisms

9. Labelling

Symbols
Risk and Safety phrases

10. Efficacy data

Preliminary use
Side effects on treated plants and on organisms.

*Concerning preparation

COMMENTS AND RECOMMENDATIONS

For the evaluation of the toxicological and environmental impact of chemicals, different parameters should be considered: physico-chemical properties, intrinsic toxicity, exposure, presence and persistence.

In view of the following very specific properties of semiochemicals:

- target action on insect species
- small amount of pheromone active ingredient released per agricultural surface
- volatile compounds
- readily degradable molecules
- no known adverse effect on plants, vegetables, crop
- no known adverse effect on human health
- very small amount of residue (ppm range or less)

Special provisions should be established in the frame of the future European Directive establishing less stringent data requirements for their registration and allowing more flexibility for obtaining experimental use authorizations.

6.
Workshop

Chairman: FRED C. SAUNDERS

Workshop Report

INTRODUCTION

A regulatory workshop on pheromones and other behaviour-modifying chemicals was held in Brighton on November 18, 1990, the day prior to a symposium on the same subject, to provide an opportunity for the symposium speakers to develop some common understanding of the knowledge and views that were likely to be represented at the symposium. The workshop also provided an opportunity to identify expertise, particularly from the European Community (EC), that was not well known to the organizers and to identify areas of common interest and agreement on regulatory guidelines and procedures.

The workshop was attended by 35 people from 9 countries [Belgium, Canada, France, Ireland, Italy, The Netherlands, Switzerland, United Kingdom, and United States of America (US)]. Attendees represented 14 commercial companies (Agrimont/Donegani, AgriSense–BCS, AgriSense USA, BASF, Bedoukian Research Inc., Ciba-Geigy, Consep Membranes Inc., Cooper France, Dow-Corning Ltd., ICI Agrochemicals, Phero Tech Inc., Phillips Petroleum Inc., Siber Hegner, Trécé Inc., and Yellowstone International) and 10 governmental and academic institutions. Particularly helpful was the presence of regulatory officials and other persons familiar with the status of regulations in North America and the Proposed EC Pesticide Registration Directive. A complete list of workshop participants follows this report.

Informal presentations were made at the workshop on use patterns, non-target effects, potential exposure and residues, tier-testing and "decision-tree" schemes, and status of regulations in Europe and North America. Participants exchanged views following each presentation, with the understanding that these views did not necessarily represent the policy of any particular agency, company, government, or organization.

During the workshop discussions, many participants expressed the view that the present regulatory process for pheromones and other semiochemicals is often unduly long and that in many countries a clear policy is lacking. Although the workshop was not held with the intent of establishing regulatory policy, a number of principles or collective judgments were identified that should be useful for follow-up discussions and action by various regulatory agencies.

PRINCIPLES FOR FACILITATING THE REGULATORY PROCESS

The principles or collective judgments for facilitating the regulatory process were drafted with the intent of representing the consensus views of the workshop participants. In those instances where differences of opinion were identified, efforts were made to reflect these in the discussion highlights. The following principles are suggested for consideration by regulatory officials and other interested parties:

- Semiochemicals used in traps for monitoring should be regulated primarily under laws ensuring safety in manufacturing and handling.
- Semiochemicals used for pest control should be regulated.
- Semiochemicals are different from conventional pesticides and should be subject to adjusted and less stringent regulation.
- A tier-testing or decision-tree scheme can provide a logical scientific approach to establishing the regulatory requirements for semiochemicals while maintaining the critical regulatory procedures necessary to ensure minimum risk.
- Scientific advisory groups should be consulted to facilitate the development of criteria for use by regulatory agencies.

- Rationale for regulatory decisions, including case-by-case decisions on data requirements, should be made readily available to the public.
- Regulatory procedures imposed and data requirements for semiochemicals should be adjusted to be consistent with the potential risk associated with the use and the rate and method of application; data requirements could be reduced for:
  - semiochemicals applied to non-food crops as compared to those applied to food crops or to stored foods.
  - semiochemicals delivered by techniques in which the chemical or its formulation does not come in contact with the edible portion of the crop.
  - semiochemicals that are applied at very low rates
  - semiochemicals that are applied for small-scale experimental purposes when compared to those for commercial use.
- Requirements for data on the active ingredient versus the end-use product should be clarified.

The application of these principles to the regulatory situation in specific countries was not addressed in the workshop. However, those wishing to apply these principles in the development or modification of policy or regulations may find it helpful to review some specific suggestions that have been made in relation to the situation in the US. These suggestions include expansion of the exemption for traps (O'Connor 1990), permission for use of data obtained for chemically similar pheromones (Kennedy 1985,1986, O'Connor 1990), relief from the acreage limit for experimental use permits (Cook 1989), exemptions for non-sprayable formulations (Roelofs 1989), exemption from the requirements of tolerance for a class of pheromones formulated in non-sprayable formulations (Kirsch 1989), exemption of a class of nontoxic pheromones (Roelofs 1989), exemption from requirements of registration for some non-food uses (Kennedy 1989), modification of experimental use permit requirements (Kennedy 1989), and application of structural analysis procedures (Weatherston 1990). A recent review of the USA regulations as they relate to pheromones and other semiochemicals (Tinsworth 1990) and an analysis of the proposed EC Directive (Thomas 1990), together with a number of reviews and papers that reflect the evolution of regulations in USA (Djerassi et al. 1974, Beroza et al. 1975, EPA 1975, Engler and Rogoff 1976, Knipling 1976, Phillips 1976, Siddall and Olsen 1976, Siddall 1979, Roelofs 1980, Dover 1981, Plimmer 1981, Plimmer et al. 1981, Zweig et al. 1982, Upholt 1985, Hodosh et al. 1985, Booth 1988, Kirsch 1988, Punja 1989, Roelofs 1989, O'Connor 1990) and that describe the European situation (Anonymous 1979, NATO 1983, Minks 1990) may also be useful.

DISCUSSION HIGHLIGHTS

Discussions associated with the collective opinions consumed a major portion of the half-day workshop. These highlights are an attempt to document those discussions, summarizing some of the various opinions expressed.

Definitions and characteristics

The word "semiochemicals", coined by Law and Regnier (1971) for chemicals transmitting messages between living organisms, was adopted by the workshop participants, with the understanding that at present only those chemicals acting as releasers of behavioural responses are under consideration. The term "behavior-modifying chemicals" was also considered to be acceptable as long as a restriction is made to include only chemicals used in the same way as they function in nature. Among the pheromones, which make up the majority of semiochemicals identified, to our knowledge only "releasers", which have an immediate effect on behavior, have been used for pest control.

Need for regulation

That semiochemicals should be subject to regulation was not questioned by any of the workshop participants. However, in previous meetings, some speakers have expressed the view that pheromones should be exempted from pesticide regulations "because they are not pesticides".

Regulation when used in traps

Workshop participants were in general agreement that semiochemicals used in monitoring traps should be exempt from strict regulation as pest control agents and that current policy in most North American and European countries is consistent with this view (Tinsworth 1990, Minks 1990). A counter view held that any product that directly controls an insect population should be registered. Another opinion that was expressed held that semiochemicals used in mass trapping should be subjected to reduced testing requirements, particularly in those cases where the use of mass trapping does not increase the level of semiochemical in the environment above that known to occur as a result of natural infestations of the pest insect.

Semiochemicals vs. conventional pesticides

The prevailing opinion at the workshop was that semiochemicals require an appropriate degree of scrutiny for possible unwanted side effects, just as do conventional pesticide chemicals. However, participants recognized that such scrutiny does not necessarily mean that identical procedures and data requirements are necessary. The idea underlying most pesticide regulation schemes is that pesticides are designed to kill living things and therefore deserve the most careful regulatory attention. Semiochemicals may be pesticides in a legal sense, but generally they clearly lack the basic characteristics that lead us to be cautious about pesticides. Semiochemicals are identical or closely similar to compounds that are found in nature and are often produced by the very species whose behavior they control. Their mode of action is not through toxic action. Finally, they can replace other pesticides that are toxic by design. Thus, there are good reasons for treating semiochemicals as a category of chemicals for which data requirements to adequately assess risk can be less than for most pesticides.

Some discussion arose over the question as to whether semiochemicals should receive preferential treatment in the regulatory process. The opinion was expressed by some participants that this would be unfair to developers of other pest control agents.

Tier testing and decision trees

The pesticide regulations in the USA make a special provision for microbial and biochemical pesticides in which three tiers of data requirements are identified (Tinsworth 1990, Lindsay, this volume). Even the Tier 1 data requirements can be, and often are, reduced through waivers (Tinsworth 1990, Jellinek and Gray, this volume). This combination of tiered data requirements and waivers of inappropriate requirements can provide an effective mechanism for treating semiochemicals differently from conventional pesticides. The flavour and fragrance industry in the USA utilizes a decision-tree process to assist in identifying the appropriate numbers of safety tests that are conducted with a specific flavour or fragrance chemical and whose results are submitted to the concerned regulatory agencies (Cramer et al. 1978, Ford 1989, Bedoukian, this volume). That approach was deemed to be relevant to the control of semiochemicals. These procedures could provide a basis for regulating semiochemicals worldwide.

Differential Data Requirements

The logic behind substantial differences in data requirements for different semiochemicals and for different methods of use is associated with differences in the expected toxicities, levels of exposure, and non-target effects. Some judgments probably can be made on groups of

compounds of similar chemical structure, particularly where considerable information is available on the non-target effects of a number of representatives of a group or class. Knowledge of physical properties of chemicals will be helpful in assessing potential exposure. However, the scientific rationale supporting the case for judgments on differential data requirements must be documented and defended. The data presented in this volume (Minks, Ridgway and Inscoe, Inscoe and Ridgway, Burke, Bedoukian, and Spittler et al.) on use patterns and non-target effects should be useful in that regard.

Perspectives from regulatory officials

Regulatory officials from Europe and North America responded favorably to the dialogue that occurred at the workshop. Representatives from both sides of the Atlantic encouraged the semiochemical community (industry and public sector) to continue to work together to influence the regulatory process, emphasizing that interested parties should act now. European interests were encouraged to state their arguments and transmit them to the appropriate EC officials in order to influence the proposed EC Pesticide Registration Directives. Some European regulatory officials recognized that semiochemicals should be regulated differently, but the need to maintain high standards in the regulation of all pest control agents was stressed and the fact that "naturally occurring" does not necessarily mean "safe" was emphasized. It was also recognized that persons that handle these chemicals would be subject to greater exposure than would those that consume treated crops.

North American regulatory officials emphasized that general public interest in alternative pest control methods was now higher than ever before. Therefore, the opportunity to seek change is great.

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Workshop Participants

M. Angst
Ciba-Geigy, Switzerland

H. Arn
Fed. Res. Stn., Wädenswil, Switzerland

D. Banasiak
AgriSense, US

R. Bedoukian
Bedoukian Research Inc., US

S. Burke
Phero Tech, Canada

A. Carter
Agriculture Canada, Canada

E. Casagrande
AgriSense-BCS, UK

S. Clayton
Yellowstone International., US

R. Cook
Phillips Petroleum, Inc., US

W. de Raat
TNO, The Netherlands

K. Farminer
AgriSense, US

H. Fontier
Ministry of Agriculture, Belgium

R. Griggs
ICI Agrochemicals, UK

O. Grosjean
BASF, UK

U. Heilig
Cooper-France, France

R. Hotz
Siber Hegner, Switzerland

M. Inscoe
Advisor, US

S. Jellinek
Consultant, US

S. Jenkins
AgriSense-BCS, UK

O. Jones
AgriSense-BCS, UK

A. Lindsay
EPA, US

B. Lingren
Trécé, US

M. Lynch
Department of Agriculture & Food, Ireland

R. Matt
Siber Hegner, Switzerland

L. McVeigh
NRI, UK

A. Minks
Wageningen Research Institute for Plant Materials, The Netherlands

V. Oakey
Consep Membranes, Inc., US

F. Rama
Agrimont/Donegani, Italy

G. Price
Consultant, UK

B. Pye
Rothamsted, UK

R. Ridgway
USDA, ARS, US

F. Saunders
Dow Corning, UK

T. Spittler
Cornell University, US

N. Verbiese
Dow Corning, Belgium

L. Wadhams
Rothamsted, UK