Use of pheromones and other semiochemicals in integrated production
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Regulatory issues in the commercial development of pheromones and other semiochemicals

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Abstract: The regulatory issues in the commercialization of semiochemicals are addressed in the light of political and economic factors which impact the criteria on which regulatory decisions are based. Other issues affecting international harmonization of registration requirements are also discussed.

Key words: pheromones, semiochemicals, regulation, registration, lepidoptera, pesticides.

Introduction

The successful development and commercialization of any type of pest control product involves various participants, collaborators and cooperators including scientists, regulators, marketers and of course the end-user or customer. Even when all of the participants are involved from earliest stages in the development process there are still many issues to be resolved; often the scientists do not fully appreciate the regulators and the marketers, the marketers can be at odds with the regulators and the scientists, and the end-users are often perplexed by what they perceive to be weaknesses and failures in the eventual product.

Consideration of this situation leads to the realization that in semiochemical commercialization there are opportunities and constraints; these are best illustrated in a table.

Of the three main contributing factors (Table 1) only the apolitical and "a-business" factors will be discussed here as they pertain to the regulatory issues which include policies and economics.

Regulatory issues

In the U.S. the decision to approve a pest control product is based on the acceptability of data demonstrating a benefit to man and the environment while ensuring that the product use will not cause unreasonable effects on human health or the environment. In most other jurisdictions, approval is granted once the registrant has demonstrated that the product is safe to humans and the environment, and is efficacious. At the crux of the regulatory decision is the risk to human health and the environment, such risks are dependent on two parameters [a] inherent toxicity of the substance or product, and [b] the exposure to the substance or product.

Table 1. Semiochemical commercialization - opportunities and constraints

Factor	Opportunity	Constraint
Political	Environmental awareness	Lack of knowledge by policy makers, politicians, etc.
	Safer pesticide policies	*Regulatory policies*
	Mandated pesticide use reductions	Private sector/public sector cooperation
	Non-toxic mode of action	
	Private/public sector cooperation	
Technical	Target specificity	Target specificity
	Low application rates	Raw material sourcing
	Enhancement of biological control	User education
	User education	Lower efficacy
	Increasing pesticide resistance	Shorter product shelf life
	Creation of secondary pests	High product quality demands
	Compatibility with both biological and insecticide control strategies	
Business	*Regulatory policies*	Lower application rates
	Costs	Proprietary rights
	Marketing methods	Costs
		Market size
		Lack of economic incentives
		Lack of user confidence in the technology

Amongst the factors affecting the exposure to pest control products are global/individual usage (insecticide sales, currently registered active ingredients/products, properties of the active ingredient) and type of usage (in traps [releaser type, amount of active ingredient]; area-wide uses [formulation type, amount of substance]). A comparison of the insecticide sales in the years 1991, 1996 and 1997 is given in Table 2.

Table 2. Insecticide and semiochemical sales in 1991, 1996 and 1997

	1991	1996	1997
World insecticide		$8.65 billion	$9.1 billion
U.S.	$1.20 billion	$2.68 billion	$3.6 billion
Western Europe		$2.28 billion	
Rest of the world		$3.69 billion	
Pheromones/semio-chemicals	$7 - $8 million[a]	$19.8 million [a,b]	

[a] Estimated

[b] The $19.8 million value is the estimated sales in 1999 for disruption products only

The figures for pheromones/semiochemicals are estimated for 1991 and 1996, the $19.8 million in 1999 is for disruption products only, sales for all semiochemical products is estimated at about $200 million. Note that U.S. insecticide sales increased three times in the six years and the increase in disruption product sales increased accordingly. The biopesticide market segment that contains pheromones is estimated to increase 10.6% between 1999 and 2004, finishing with a value of $208 million.

Another way of comparing exposure is to consider the number of registered products for several active ingredients; this was done for several U.S. EPA registered pesticides and pheromone products and is illustrated in Table 3.

Table 3. Number of U.S. EPA approved labels for various pesticide active ingredients

Material	Active ingredient	#Approved labels
Pesticide	Permethrin	730
	Lambdacyhalothrin	28
	Glyphosate	87
	Phosmet	17
	B.t. var.Kurstaki	74
Pheromones	Gossyplure	13
	Codlemone	14
	OFM pheromone	13
	Tomato pinworm pheromone	13
	Muscalure	12

From the data in Tables 2 and 3 it can be seen that the exposure to the pheromone active ingredients and products is very much smaller than to the other types of pest control agents.

A comparison of registered "biochemical" pest control agents in the U.S. and in the European Community is given in Table 4, and illustrates both a more advanced understanding of these types of product by the U.S. regulatory community and a greater cooperation between the public and private sectors.

As of February 1999 the pheromone/attractant authorizations in the European Community member states were 27 in Spain, 18 in Greece, 5 in France, 2 in Germany and Austria, and one each in Netherlands, Luxembourg, Poland and Italy. Note that the following member states have no pheromone/attractant approvals, Finland, Sweden, Denmark, Ireland, Belgium and the United Kingdom. The high number of approvals in Greece and Spain reflect the need to register monitoring in addition to area-wide disruption products.

A review of several semiochemical databases [including those of the Pherolist and Tohoku University] presents information that there are over 500 known pheromones and attractants for lepidopteran insects and that there are 193 semiochemicals belonging to 11 orders which begin with the letter 'D' (*eg.* from danaidal and (2,6-Z,E)-7-methyl-3-propyl-2,6-decadien-1-ol to (Z)-3-dodecenolide and dopamine). The number of arthropod pheromones and attractants whose structures are known is staggering but it must be noted that only an extremely small percentage of these materials will ever be considered for commercialization, and only a small percentage of those will be used in area wide control products, most being incorporated into monitoring and other trapping products.

Table 4. Registered "biochemical pest control agents" in the U.S. and European Community [active ingredients/products]

U.S. EPA	
Biochemical active ingredients	
Pheromones	[31/157]
Floral attractants/plant volatiles	[18/74]
Repellents	[18/64]
Miscellaneous (from plant and insect sources)	[6/11]
European Community	
Attractants [includes hydrolyzed protein]	[41]
Repellents	[8]

Another aspect of exposure relates to properties of the semiochemical such as ubiquity, non-semiochemical uses, stability, non-toxic mode of action, *etc*. For example geraniol occurs in over 250 essential oils in addition to having been isolated from 14 insect species from seven families in five orders. It is commonly used in the fragrance industry and as a flavoring for alcoholic and non-alcoholic beverages, ice cream, candies and baked good, *etc*. Annually, over 800,00 lbs are used in cosmetics, soaps and detergents. In the U.S. geraniol is classified by the Food and Drug Administration as being GRAS [Generally Regarded As Safe] and may be added directly to food for human consumption as a flavoring, adjuvant or additive. It is also well known that many of the lepidopteran pheromones, especially those containing multiple double bonds and/or other labile functional groups such as the aldehydic group are very susceptible to UV catalyzed oxidative degradation.

Table 5. Acute toxicity of several semiochemicals

Compound	Oral LD_{50}	Dermal LD_{50}	Inhalation LC_{50}
Acetate[a]	>5 - 34.6 g/kg [b] [10]	>2 - 20.25 g/kg [b] [9]	>3.3 - 32 mg/l [b] [5]
Alcohol[a]	>3 - >50 g/kg[b] [7]	>2 - 5 g/kg [b] [4]	5.26 mg/l [b] [1]
Aldehyde[a]	> 5 mg/kg [b] [3]	>2 - >5 g/kg [b] [3]	>5 - 16.8 mg/l [b][3]
Muscalure	> 5 mg/kg [b]	> 2 mg/kg [b]	>5.0 g/ m^3 [b]
Citronellol	3.45 g/kg	2.65 g/kg	
Geraniol	3.6 - 4.8 g/kg	>5 g/kg [b]	
Farnesol	>5 g/kg [b]	>2.01 g/kg [b]	0.917 mg/kg
Hexyl butyrate	>5g/kg [b]	>5g/kg [b]	
Linalool	2.79 g/kg	5.61 g/kg	

[a] the asterisk denotes saturated and unsaturated compounds of 11 to 18 carbons chain length. The numbers in parenthesis after the values for these compounds represents the number of compound included in these data.

[b] denotes limit testing, the guidelines of the U.S. EPA for acute toxicity testing contain "principles which provide that if no mortality is produced by administration of a specified dose level, no further testing is required".

Consideration of the various ways in which pheromones are used, and of the formulations used leads to the conclusion that while area-wide use of semiochemical products would generally lead to a greater exposure than use in traps, such exposure is likely to be insignificant. In the U.S. the regulatory agency believes that with the majority of lepidopteran pheromones there is no evidence of risk when the use does not exceed 150 grams of active ingredient per acre per year. In reality, this level is rarely reached when pheromones are used commercially. It is of interest to note that no residues of lepidopteran pheromones have been detected on fruit [grapes, apples and peaches] from the use of pheromones on fruit from distinct point source formulations at application rates from 5.0 to 126.4 grams per acre. In the case of tomato pinworm pheromone, residues on unwashed fruit ranged from 21 - 72 ppm on the day of application, and 0.29 - 1.2 ppm on day 30 however washing the tomatoes at anytime brought the residues below the level of detection.

Focusing on the second component of the risk equation, namely inherent toxicity of the of the semiochemical, some acute toxicity data are reviewed in Table 5.

Table 6. Toxicity of acetate and aldehyde lepidopteran pheromones to non-target avian, fish and aquatic invertebrate organisms

Toxicology Test	Acetate	Aldehyde
Avian acute oral [mallard]	LD_{50} >2 - >10 g/kg [3]	LD_{50} > 2 g/kg [1]
Avian acute oral [quail]	LD_{50} >2 - >2.25 g/k [2]	LD_{50} > 2 g/kg [1]
Fish toxicity [bluegill sunfish]	LC_{50} >100 - 540 ppm [4]	
Fish toxicity [rainbow trout]	LC_{50} >100 - 270 ppm [3]	LC_{50} 320 ppm [1]
Aquatic invertebrate toxicity [*Daphnia magna*]	LC_{50} 1.30 - 6.80 ppm [3]	LC_{50} 0.45 - 2.23 ppm [2]

For avian acute toxicity studies U.S. EPA guidelines state that "satisfactory data should establish that the avian single dose oral LD_{50} is greater than 2 g/kg". For fish and aquatic invertebrate toxicity, satisfactory data must establish an LC_{50} greater than 100 ppm or >100,000 times the maximum expected environmental concentration or estimated environmental concentration when the end-use product containing the active ingredient is used as directed.

Discussion

From the information presented above, the rational conclusions which may be drawn are: (1) the use of semiochemicals in pest management presents far less risk to humans, other mammals, non-target organisms and the environment that conventional chemical insecticides; (2) the burden of demonstrating that use is safe or will not cause unreasonable effects of health and the environment should be significantly less than for conventional chemical insecticides; (3) semiochemical products are capable of surviving in markets where both the size and profitability does not interest the major pesticide manufacturers. In this regard the need for, and the cost of expanded requirements is not likely to be offset by larger, global markets; (4) in the U.S., agriculture has benefitted from the evolution of a regulatory process which first recognized the differences between chemical pesticides and biopesticides [including pheromones and semiochemicals], and then the responsible agency [U.S. EPA] worked in concert with stakeholders to develop a reasonable and reduced set of data requirements for the registration of such materials.

Amongst the countries which have adopted regulatory policies for semiochemical pest management products, the most progressive is in the U.S. The current status of semiochemical regulation is illustrated in Tables 7 and 8.

Table 7. Regulatory/Registration status of semiochemicals in U.S. based on formulation and use

Monitoring/Survey	Arthropod pheromones, attractants and minimum risk pesticides can be used and be *exempt* from registration
Mass trapping	Arthropod pheromones can be used for pest control and be *exempt* from registration
Kairomonal use	of a semiochemical in pest control strategies is *exempt*
Disruption	All pheromones, irrespective of formulation require to be registered, but when used on food and feed crops certain lepidopteran pheromones are *exempt* from the requirement of a tolerance
Attract & kill	Pheromones used in conjunction with an insecticide in a formulated product require to be *registered*, and although the pheromone may be exempt from tolerance for food and feed crop use the insecticide and inerts must either have a tolerance or an exemption from tolerance

Although the EPA has stated that at this time it does not intend to grant any further regulatory relief to pheromones and other semiochemicals it will [a] on a case by case basis consider any reasonable proposal an applicant/registrant wishes to make regarding registration requirements and work with the applicant/registrant, and [b] as the database of information on other types of pheromones and semiochemicals grows it will then consider further regulatory relief.

In order to facilitate development, registration and the use of semiochemicals in other areas of the world the OECD through its Working Group on Pesticides is committed to harmonizing the regulation of semiochemicals.

Table 8. Regulatory/Registration status of semiochemicals in the U.S. based on chemical type

Arthropod pheromones	Lepidopteran pheromones	Arthropod semicochemicals
Exempt - sole active ingredient when used in a trap for monitoring or control	Certain lepidopteran pheromones[a] are *exempt* from the requirement of a tolerance, irrespective of formulation provided the use rate does not exceed 150 g/ai/acre/year	Attractants, certain miscellaneous semiochemicals when used only to attract pests, and labeled accordingly are *exempt* from regulation under FIFRA[b] "not deemed to be used for pesticidal purposes"
Exempt - when acting as a kairomone for a beneficial arthropod	Certain lepidopteran pheromones[a] are *exempt* from the requirement of an experimental use permit for testing on acreage up to 100 hectares [250 acres]	Semiochemicals which are used to behaviorally manipulate beneficial arthropods *eg.* Honey bees are *exempt* from regulation under FIFRA[b]
Exempt - when used in "retrievably sized polymeric matrix dispensers" when applied to growing crops only at a rate not exceeding 150 g/ai/acre/year		
Registration - products used in area-wide pest control strategies		

[a] "certain lepidopteran pheromones" is an EPA designation for straight chain aliphatic (9 - 18 carbons) alcohols, aldehydes or acetates with up to three double bonds.
[b] FIFRA is the acronym for Federal Insecticide, Fungicide and Rodenticide Act.

As a first step OECD is attempting to establish a common core of data requirements for pheromones and other semiochemicals and most recently a PMRA sponsored workshop held in Ottawa in September 1999 made recommendations to the OECD Secretariat concerning core requirements. A review of the recommendations, which propose separate data requirements for straight chain lepidopteran pheromones and other semiochemicals, give the impression that there is a common core of data requirements with a high degree of commonality and there could be multi-countries data reviews with exchange of information and data. At the OECD Biopesticides

Steering Group in February of this year, although the name of the Ottawa document was changed to "Guidance for registration requirements for pheromones and semiochemicals" there was general agreement regarding the content of the document. There was also agreement that no further work on the harmonization would take place for three years until the member countries gain experience in the registration process and worksharing.

At the same time that the Workshop was being held in Ottawa, the AgNet list server of the University of Guelph carried a statement on pesticides, by Dr. Bruce Ames, Professor of Biochemistry & Molecular Biology, and Director of the National Institute of Environmental Health Sciences Center at the University of California at Berkeley, in which he said "Scares about tiny traces of synthetic chemicals, such as pesticides, are a distraction from important risks. The amount of pesticide residues ingested are so small, relative to levels that have been shown to have toxicological effects, they are toxicologically implausible as health risks".

On the other hand, there is the alarming trend of almost universal adoption of the Precautionary Principle in Europe in regard to the use of any new technology, process, chemical or any new activity whatsoever. The differences in these two philosophies illustrates why harmonization although desirable will be most difficult to achieve, proponents of the approach represented by the views of Dr Ames will continue to want semiochemicals regulated on presumption of negligible risk while the adherents of the Precautionary Principle will maintain that an examination of the full range of alternatives must be examined, including the alternative of doing nothing, and that the registrant must accept the "burden of proof of harmlessness".

It took seventeen years from the proof of the structural elucidation of the first pheromone [bombykol (1961)] to the granting of the first registration of a pheromone for broadcast use in crop protection [gossyplure (1978)], hopefully there will not be such a time lag in expediting the introduction of semiochemicals in to the global market-place through regulatory harmonization.

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