Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Proposal

PRO2002-02

Guidelines for the Research and Registration of Pest Control Products Containing Pheromones and Other Semiochemicals

This Regulatory Proposal outlines the requirements for research trials and registration of pest control products containing pheromones and other semiochemicals in Canada at this time. These guidelines pertain only to substances that affect arthropod behaviour.

The Regulatory Proposal reflects progress made in three important areas:

- the data requirements for these products are now harmonized among the Organisation for Economic Co-operation and Development (OECD) countries;
- the Guidelines outline a rationale for reduced data requirements developed by the OECD Working Group on Pesticides as well as the data requirements; and,
- the guidelines support effective and sustainable pest management and the introduction of new pest management technology.

Please review the document and provide your written comments within 45 days of the date of publication of this Regulatory Proposal to the Publications Coordinator.

This document replaces Regulatory Directive DIR97-02, *Guidelines for the Research and Registration of Pest Control Products Containing Pheromones and Other Semiochemicals*, dated September 29, 1997.

(publié aussi en français)

September 25, 2002

This document is published by the Submission Coordination and Documentation Division, Pest Management Regulatory Agency. For further information, please contact:

Publications Coordinator
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6605C
Ottawa, Ontario
K1A 0K9

Internet: pmra_publications@hc-sc.gc.ca
www.hc-sc.gc.ca/pmra-arla/
Information Service:
1-800-267-6315 or (613) 736-3799
Facsimile: (613) 736-3798

ISBN: 0-662-32850-7
Catalogue number: H113-8/2002-2E-IN

Foreword

A pheromone is a semiochemical produced by individuals of a species that affects the behaviour of other individuals of the same species. A semiochemical is a message-bearing substance produced by a plant or an animal or a synthetic analogue of that substance which evokes a behavioural response in individuals of the same or other species. These guidelines pertain only to substances that affect arthropod behaviour.

The data requirements, and the rationale supporting them, for these substances reflect the results of international harmonization activities involving countries in the Organisation for Economic Co-operation and Development (OECD). The data requirements for semiochemicals, including pheromones, in the United States and Canada are essentially harmonized, except in the area of efficacy. Both countries require efficacy data to be generated. Canada routinely reviews efficacy studies on all pesticides, whereas the U.S. has waived submission of these data, except in the case of public health use products. Canada will accept studies conducted according to current U.S. protocols.

Table of Contents

1.0 Introduction

This document outlines the general principles for the regulation of pheromones and other semiochemicals that affect the behaviour of arthropods and are used in pest control products. (Semiochemicals used in traps to attract and monitor arthropods are exempt from registration). The proposed data set is reduced relative to conventional pesticides. Further reductions in data requirements are proposed for the family of chemicals which make up the straight-chained lepidopteran pheromones (SCLPs). For regulatory purposes, SCLPs are pheromones with a well-defined unbranched aliphatic structure, which is characteristic of most known pheromones produced by members of the order Lepidoptera, including moths and butterflies. These data requirements reflect the result of the international harmonization activities involving countries in the Organisation for Economic Co-operation and Development (OECD). For the purposes of this document, pheromones and other semiochemicals are defined in section 3.0.

To facilitate the development, registration, and use of pheromones and semiochemicals for controlling pest arthropods, the OECD Working Group on Pesticides committed to developing guidance for registration requirements for pheromones and other semiochemicals regulated as pesticides, which includes a rationale for reduced data requirements for these products. Harmonization is critical to encourage research, development, commercialization, and use of pheromones and semiochemicals for pest control. Use of similar registration requirements by OECD countries will facilitate access to reduced risk, integrated pest management (IPM) compatible tools by making it easier for companies to submit registration applications to multiple countries and for regulatory agencies to benefit from each other's reviews.

The Canadian Pest Management Regulatory Agency (PMRA) and the U.S. Environmental Protection Agency (U.S. EPA) have established a process for the joint review of pest control products in which the new active ingredient is an arthropod semiochemical (including pheromones) and the proposed use pattern is common to both countries. The document *Updated Procedures for Joint Review of Microbials and Semiochemicals* can be found on the PMRA web site at http://www.hc-sc.gc.ca/pmra-arla/english/pdf/nafta/naftajr/nafta_jr_micro-e.pdf. The procedure entails a joint pre-submission consultation to establish specific data requirements for the product. The PMRA and the U.S. EPA are committed to joint reviews and work-sharing of pesticide evaluations on a regular basis. Joint reviews serve to increase the efficiency of the registration process, facilitate simultaneous registration in Canada and the U.S., and increase access to new pest management tools in both countries.

Pheromones and other semiochemicals intended for use to mitigate the effects of a pest population are within the definition of a control product in the *Pest Control Products Act* (PCPA). Therefore, these products are subject to regulation under the PCPA and, in some circumstances, it may also be required to establish a maximum residue limit (MRL) under the *Food and Drugs Act* (FDA).

In developing a regulatory approach for semiochemicals, the inherent differences between these products and conventional pesticides were taken into consideration. Semiochemicals act by modifying the behaviour of the pest species rather than killing it, are more target specific than conventional insecticides, are used at concentrations close to those occurring in nature, and dissipate rapidly. For these reasons it is expected that most semiochemical products will pose low potential risk to human health and the environment compared with conventional pesticides.

The semiochemicals that do and do not require registration under the PCPA and regulation under the FDA are listed as types 1 and 2, respectively.

Type 1: Registration not required

Semiochemicals that are used in fixed-location lures for the purpose of attracting and monitoring pests are expected to have minimal impact on either the environment or human health. Products qualify for exemption from registration when they are used as follows:

(i) Semiochemicals used in pheromone traps in which they are the sole active ingredient.

(ii) Semiochemicals used in lures attached to trap trees.

(iii) Semiochemicals incorporated into traditional chemical pesticide formulations used in fixed-location traps (the semiochemical itself does not require registration, but the pesticide formulation does).

Type 2: Registration required

For the following semiochemical-containing products, registration is required for both the technical grade of active ingredient (TGAI) and the end-use product (EP). These products may also require evaluation to determine if an MRL needs to be established under the FDA if they are used in and on food or feed crops offered for sale. The semiochemical alone or in combination with conventional pesticides may be incorporated into the following products:

(i) Semiochemicals contained in solid-matrix dispensers that are placed in large numbers by hand or machine (i.e., not fixed-location traps) for the purpose of pest control. These devices include, but are not limited to, rubber septa dispensers, trilaminate sheets, tapes, tags, wafers, macrocapillary devices such as long tubes or fibres, protected “ropes,” and twist ties. If these semiochemical dispensers are not in direct contact with a food crop, then establishment of a MRL under the FDA is not required.

(ii) Semiochemicals to be broadcast or sprayed, alone or formulated into a pesticidal bait.
These products include, but are not limited to, liquid flowables, microcapsules, microcapillary straws, granular powders, flakes, confetti formulations, cigarette filters, and unprotected "ropes."

Any uses of semiochemicals in pest management not mentioned previously will be evaluated on a case-by-case basis with the possibility of enlarging the list of products subject to, or exempt from, registration under the PCPA and MRL under the FDA. These guidelines do not pertain to personal insect repellents, which have separate regulatory requirements.

2.0 Data requirements

2.1 Rationale for reduced data requirements

These guidelines are a general guide to the data requirements for research permits and for registration of pheromones and other semiochemicals that affect the behaviour of arthropods and are used in pest control products.

The data required to chemically characterize a semiochemical pest control product and demonstrate how it is used most effectively are the same as those for conventional pesticides. However, the factors described in the *Guidance for Registration Requirements for Pheromones and Other Semiochemicals used for Arthropod Pest Control* (OECD 2001) justify substantial reductions in health and environmental data requirements, especially for SCLPs, a well-defined chemical group for which more data are available (Touhey 1990). Environmental and health studies have demonstrated that these substances pose minimal risk and provide effective pest control at low volumes, similar to that of naturally occurring concentrations. The SCLPs are defined in section 3.0.

If applicants are unsure as to the need for research permits or registration or the precise nature of data requirements to support these requests, they are strongly encouraged to consult with the PMRA **prior to** use of the product and sale of treated crops or submitting an application for a research permit or registration.

Requests for waivers for the submission of data required to support applications for research permits or registration will be considered by the PMRA. A scientific rationale must accompany each request for a waiver. For each application, and the situation presented, consideration will be given on a case-by-case basis to the nature of the product and the proposed use pattern.

The following rationale is an excerpt from *Guidance for Registration Requirements for Pheromones and Other Semiochemicals Used for Arthropod Pest Control*, part of the OECD Series on Pesticides Number 12, published February 26, 2002 (OECD ENV/JM/MONO(2001)12, pp. 12–18):

Arthropod semiochemicals are inherently different from conventional pesticides in their non-toxic, target-specific mode of action and natural occurrence. They are generally effective at very low rates, comparable to levels that occur naturally. They are generally volatile and usually dissipate rapidly in the environment. In addition, many EPs are formulated in passive dispensers (hollow fibres, tapes) that present little direct exposure to humans and nontarget organisms. All these factors effectively minimize the risk of adverse effects from the use of semiochemicals. The following paragraphs demonstrate the low exposure potential of arthropod semiochemicals in general and the low toxicity of SCLPs in particular.

Application rate is typically low and probably comparable to natural emissions

- For purposes of pest control, releases of semiochemicals (except perhaps repellents) are unlikely to greatly exceed natural emissions because their effectiveness is dependent on arthropod olfactory systems that are tuned to natural emission rates. Male Lepidoptera typically respond to a discrete range in ambient pheromone concentration, with the consequence that a high rate of pheromone release may be less effective than an intermediate rate of release. Controlled-release technology is critical to slow down and extend effective pheromone release over the flight period of the insect, which is usually 4–8 weeks (Howse et al. 1998).

- Measurements of natural releases of semiochemical components at the scale of grams per hectare per day (g/ha/d) appear to be unavailable. Estimates of emissions from individual female moths during the calling period include 8.5 ng/h for *Grapholitha molesta* and 880 ng/d for *Trichoplusia ni* (Howse et al. 1998). Natural releases within an agricultural setting may be estimated using information on population density and emissions from individual female moths. For example, the density of codling moth females in severe outbreaks in orchards was estimated, by different methods, to be 42 500 – 950 000 females/ha [(17 000 – 380 000 females/acre (1 acre = 0.4 ha)]. If all codling moth females, containing 4 ng pheromone in each of their glands, released 240 ng/h, then their total pheromone release would be 10.0–227.5 mg/ha/h (4–91 mg/acre/h). For comparison, the discrete pheromone dispensers used in mating disruption of this insect have a pheromone release rate of 32.5 mg/ha/h (13 mg/acre/h) (Touhey 1990). The recommended application rates of some pheromone dispensers (including Hercon, Ecopom, and Isomate-C Plus) used to control codling moths range from 7.5 to 410.0 g a.i./ha/year (3–164 g a.i./acre/year).

- On labels of registered products, recommended rates of application are typically about 50 g a.i./ha per application (20 g a.i./acre), and annual rates of application are typically less than 375 g a.i./ha (150 g a.i./acre). Individually placed dispensers generally give season-long control, whereas broadcast formulations are usually applied at lower rates more than once in a season.

- Considering the above, in 1994 the U.S. EPA exempted arthropod pheromones from the requirement of an experimental use permit for trials on up to 250 acres, at a rate of up to 375 g a.i./ha/year (150 g a.i./acre/year). A threshold of 375 g a.i./ha/year was established as high enough to accommodate the maximum reasonable use level that companies would require for testing. As the level is comparable to naturally occurring emissions of pheromones during an infestation, it is expected to have no impact on public health, nontarget organisms, or the environment. The U.S. EPA has received no reports of adverse effects to humans or the environment arising from this policy.

Volatility and rapid environmental transformation minimize residues in crops and exposure of nontarget organisms

- Semiochemicals are generally assumed to dissipate rapidly in the environment, primarily by volatilization and degradation; this is partly because persistence is counterproductive to a communication signal received by an olfactory system. Only the aerial compartment within and around the crop need be loaded, and concentrations in the air are unlikely to exceed several nanograms per cubic metre (see, e.g., Bäckman 1997; Koch et al. 1997).

- Many pheromones and other semiochemicals must include an ultraviolet (UV) screen (absorber) and an anti-oxidant to prevent decomposition on the shelf. Once these products are taken into the field and volatilized, they undergo photo-oxidation. SCLPs are readily transformed by oxidation of the double bonds in the carbon chain and other types of oxidative degradation. The enzymes operative during the degradation of SCLP residues are ubiquitous in nature.

- Studies of the fate of SCLPs on moistened soil and in water confirm rapid dissipation, largely due to volatilization of the parent compounds. The half-life of gossyplure (Z,Z & Z,E 7,11-hexadecadien-1-ol acetate) at 32°C was 1 d in soil and 7 d in water (Henson 1977). Similarly, the half-lives of (Z)-9-tetradecenal and (Z)-11-hexadecenal were reported to be 29 and 50 h, respectively, in soil (22°C), and 30 and 90 h, respectively, in water (24°C) (Shaver 1983).

- When lepidopteran pheromones were applied in retrievably sized dispensers, food residues from airborne transfer of pheromone were not detected; in analyses of fruit treated with 325–350 g a.i./ha (129–141 g a.i./acre), no pheromone residues could be found with a detection limit of 2–5 µg/kg (or ppb) (Spittler et al. 1988, 1992).

- Microencapsulation of pheromones can result in a prolonged release of effective levels of pheromones at application rates that leave little, if any, food residues. In a laboratory study of volatilization from an SCLP (tridecenyl acetate) formulated in ~35-µm microcapsules, about 70% of pheromone remained after 30 d, a slower rate of loss than anticipated. Residues of the same pheromone were analyzed from

unwashed tomatoes from field-treated plants, with the following results: 21–72 µg/kg on the day of application, 0.9–6.8 µg/kg on day 15, and 0.29–1.2 µg/kg on day 30. Washing the tomatoes brought all the residues below the level of detection. This study demonstrates pheromone residue levels in tomatoes which are several orders of magnitude lower than those previously estimated. The process of application, weathering, and other environmental transformation processes lead to a reduction in the active ingredient which approaches the system limit of detection in the expected 3-week lifetime of the raw agricultural product (United States Federal Register 1995).

SCLPs are of low toxicity to mammals

- The United States EPA, the PMRA, and the European Union regulatory authorities have received no reports of adverse effects to human health or the environment associated with semiochemicals registered for use in mating disruption of arthropods and other applications. Most registered products are SCLPs.

- The data submitted for registering semiochemicals in the U.S. (most are SCLPs) have indicated no mammalian toxicity when mammals are exposed to high doses. Available data indicate acute oral toxicity (median lethal dose LD_{50} > 5000 mg/kg; U.S. EPA category IV, nontoxic), acute dermal toxicity (LD_{50} > 2000 mg/kg; U.S. EPA category IV, nontoxic), acute inhalation toxicity (median lethal concentration LC_{50} generally >5 mg/L; U.S. EPA categories III–IV, practically nontoxic), no evidence of mutagenicity (Ames Salmonella assay), and minimal eye and skin irritation (United States Federal Register 1994a). Published mammalian toxicity data on SCLPs indicate no significant acute toxicity to humans (Inscoe and Ridgway 1992).

- SCLPs are biodegradable by enzyme systems present in most living organisms and should present no problems with their normal physiology. For example, the known metabolism of long-chain fatty acids predicts that SCLPs would be metabolized either by β-oxidation, yielding a series of paired carbon losses, or by complexing with glucuronide and excretion by the kidneys (United States Federal Register 1995).

- The U.S. EPA has used the results of two subchronic toxicity studies as bridging data for the safety assessment of other structurally similar SCLP products submitted for registration. Published results of these studies indicated no significant health effects. A 90-d feeding study (using rats) was conducted at doses up to 1 g/kg of a commercial blend of branched acetates with an aliphatic chain length between C_{10} and C_{14}. The results indicated no significant signs of toxicity other than those expected with longer term exposure to high doses of a hydrocarbon, namely, histopathologic evidence of nephropathy in males and increased liver and kidney weights in both sexes (Daughtrey et al. 1990). A

developmental toxicity study (using rats) involving inhalation exposure to unbranched, primary alcohols with chain length C_8 to C_{10} indicated no detectable developmental toxicity (Nelson et al. 1990).

2.1.1 Data requirements

The data required to chemically characterize a semiochemical pest control product and demonstrate how it is used most effectively are the same as those for conventional pesticides.

However, the factors described in this document justify substantial reductions in health and environmental data requirements, especially for SCLPs, a well-defined chemical group for which considerable data are available (Touhey 1990). For other classes of semiochemicals, it may also be justified to waive certain required studies if the registrant can provide an adequate rationale.

Compliance with good laboratory practice (GLP) is required for testing of pest control products to obtain data on their properties and safety with respect to human health or the environment in accordance with the Regulatory Directive DIR98-01, *Good Laboratory Practice*.

2.1.1.A Data Required for Product Analysis

Product analysis information should be sufficient to identify the active ingredient, formulants, and impurities of toxicological concern in the pest control product and provide specific physical and chemical characteristics.

For TGAIs, identity data are used to determine whether an active ingredient is identical or substantially similar to another active ingredient or a naturally occurring substance. Required elements include a description of starting materials and the manufacturing process, a discussion of the possible formation of impurities, upper and lower certified limits for each AIC with upper limits for impurities, and supporting analytical data including component identity confirmation.

For EPs, required elements include a description of starting materials and the formulation process, upper and lower certified limits of TGAI and formulants, and an enforcement analytical method for each active ingredient component (AIC). If the formulation process introduces or enhances the presence of impurities of toxicological concern, this must be identified along with upper limits and a corresponding enforcement analytical method.

2.1.1.B Data for assessment of human health and safety

Toxicology
Sufficient information to identify potentially hazardous products is always required. Studies of teratogenicity and subchronic exposure can generally be waived if long-term

exposure above background levels can be excluded or if a substance is a member of a well-characterized group, such as SCLPs, for which toxicological concerns have already been addressed. In general, the possibility of irritation, dermal sensitisation, acute toxicity, and mutagenicity and the latest medical data should be taken into account.

Less information is available on the toxicity of other forms of semiochemicals that may contain ketone, epoxide, lactone, terpenoid, pyrazine, pyran, and other aromatic structures. If they have the toxicity characteristics of other chemicals with these substructures or functional groups, they may be more toxic than the SCLPs and might potentially require long-term tests (United States Federal Register 1994a; Inscoe and Ridgway 1992).

Dietary, occupational, and bystander exposure

Metabolism and residue chemistry data are designed to provide the information necessary to determine the site, nature, and magnitude of residues in or on food, feed, and tobacco so that the acceptability of crops that have been treated with a pest control product can be established. For semiochemicals, residue data may not be required if it has been determined that detectable residues on the consumable commodity are unlikely to occur, or that residue levels are unlikely to exceed natural background levels during outbreaks of the pest, and that the residues are not toxic.

In Canada and the European Union, applicants are encouraged to provide a scientific rationale for waiving residue data based on the low potential risk of any residues on a treated crop. The U.S. EPA has established an exemption from the requirement of a food tolerance (i.e., MRL) for most uses of arthropod semiochemicals, namely (i) in retrievably sized polymeric dispensers used at a rate no more than 375 g a.i./ha/year (150 g a.i./acre/year); (ii) at a rate of no more than 50 g a.i./ha (20 g a.i./acre) per application regardless of formulation, provided no potentially adverse effects are observed during the tier I toxicity testing; and (iii) SCLPs at rates up to 375 g a.i./ha/year, regardless of the mode of application.

Sufficient information is required to characterize occupational–bystander exposure potential. This would include consideration of application method and rate and appropriate physical–chemical properties. For those substances with significant exposure potential and those with toxicological concerns, additional exposure data would be required.

2.1.1.C Data for assessment of environmental risks

Sufficient information is required to assess the hazard potential of pheromones and other semiochemical pest control agents to terrestrial wildlife, aquatic animals, plants, and beneficial insects. The European Commission also requires that the environmental fate of a semiochemical (e.g., stability in air and water) be assessed, based on available information. Test data on a compound will only be required if its use will result in environmental contamination exceeding natural background levels. Application rates of

up to 375 g SCLP/ha/year are generally understood to result in exposure levels that are comparable to natural emissions and safe for nontarget species (R. Maloney, written communication, 1999). This threshold may or may not be applicable for other kinds of semiochemicals; applicants are invited to request waivers of environmental testing, based on information that indicates application rates are comparable to natural emissions.

Compared to conventional pesticides, fewer tests are required for semiochemicals and the number of organisms per test is reduced because of the non-toxic mode of action of semiochemicals and limited exposure of nontarget organisms. Experience to date indicates that SCLPs are not acutely toxic to birds; median lethal concentration (LC_{50}) and median lethal dose (LD_{50}) values greater than 5000 mg/kg and 2000 mg/kg, respectively, have been reported on quail and mallard duck for products submitted for registration (Touhey 1990). Avian dietary toxicity is only of concern for formulations that might be ingested, e.g., granules. Toxicity data for human safety are generally sufficient to assess potential effects on wild mammals, so no wild mammal testing is required. Nontarget terrestrial plant studies (seedling emergence, vegetative vigour) would only be required of a semiochemical if there were reason to suspect possible effects.

Pheromones and other semiochemicals have been characterized as toxic to aquatic invertebrates (*Daphnia*) and fish (United States Federal Register 1994b; Inscoe and Ridgway 1992), although these results may reflect a suffocating effect of the oily surface film formed by high test concentrations of many SCLPs (Touhey 1990). Aquatic invertebrate and fish toxicity data are required for direct application to aquatic sites for all semiochemicals. One species of fish (rainbow trout), an aquatic invertebrate (*Daphnia magna*), and (in Europe) an algal species should be tested. Aquatic testing is not required for fixed-point dispensers applied over land.

For potential effects of nontarget insects, a discussion of available information may be sufficient. There are no widely accepted, simple tests for evaluating effects on nontarget insects because the behavioural effects of semiochemicals are likely to influence reproduction or growth, which require longer term testing and are more difficult to quantify than mortality. Generally, literature is provided by registrants on specificity to target insects. The registrant should also report any adverse effects on nontarget insects noted during efficacy testing, particularly effects on insect predators or parasites of the target organism, species closely related to the target pest, and pollinators. The range of invertebrates likely to be affected by a semiochemical can be established by comparing baited and unbaited traps in environments similar to those of intended use. If no such effects are noted during efficacy testing, and in the absence of any other data indicating potential for adverse effects, no nontarget testing will be indicated.

Environmental fate

Data on the persistence of a semiochemical and its transport from the site of application to another site or medium may be required if ecotoxicity data or public literature indicate a hazard to biota. If the data indicate that significant persistence and transport of these

agents occurs in any part of the environment such that significant exposure to nontarget organisms could be expected, then additional environmental testing will be necessary.

Environmental fate data are used to determine the estimated environmental concentration (EEC) by performing a simple mass-balance analysis of the pesticide, taking into consideration the pesticide application parameters (i.e., rate, frequency, and site of application) following initial tests that measure transport properties (volatility, dispenser-water leaching, vapour pressure, and water solubility). Where persistence testing is required (hydrolysis, aerobic soil metabolism, aerobic aquatic metabolism, soil photolysis, aquatic photolysis, adsorption–desorption, and octanol–water partition coefficient), each of the transformation processes should be expressed as a half-life for the particular environment or as a rate constant for the environmental process, depending on the test. Estimated environmental concentrations can then be calculated for different times using these data and the field application rate of the pesticide. Aquatic use patterns and non-dispenser pesticides will require mass-balance analysis following persistence tests.

2.1.1.D Data for assessment of efficacy

The mode of action of a semiochemical product should be explained in terms of its function in modifying the behaviour of the target pest, and information should be provided to support the claim that the active ingredient is a naturally occurring arthropod semiochemical.

In the European Union and Canada, data from scientifically conducted efficacy trials are required to support pest control claims on the product label and to demonstrate how a product may be used most effectively. Studies should be conducted with the EP proposed for registration, applied in a manner consistent with label instructions regarding timing, rate, method, and site of application. The experimental design should include untreated plots as an indication of population pressure and, if possible, plots receiving a commercial standard treatment with conventional pesticides of known efficacy as a basis for comparison with the semiochemical treatment.

Presubmission consultation is strongly recommended to discuss the adequacy of available information, the need for additional trials, and the performance standard for registration. Sufficient efficacy data are required to confirm the performance. At least one study should evaluate a range of rates to demonstrate the lowest effective rate of application. For products that act through mating disruption and are to be used within an IPM strategy, demonstration that mating success has been reduced (e.g., using caged or tethered female moths) may be sufficient to support registration. Alternatively, data from trap catches and assessment on reductions in pest numbers and damage are required.

In conjunction with the efficacy trials, information on any adverse effects on the crop or site should be reported, including phytotoxicity and effects on nontarget arthropods.

Qualitative information is required on the pest species life cycle, and the nature and extent of damage it causes. Other useful information includes the compatibility of semiochemicals with IPM programs and their contribution to risk reduction.

3.0 Definitions

The following definitions are used for the purpose of these guidelines:

Active ingredient component (AIC)
: an individual chemical compound that contributes to the activity of the active ingredient; more than one component or isomer may be combined to form the active ingredient

Active ingredient (a.i.)
: the ingredient(s) of a control product to which the effects of the control product are attributed, including a synergist and all AICs, but not including a solvent, diluent, emulsifier, or component that by itself is not primarily responsible for the control effect of the control product

Allomone
: a semiochemical produced by individuals of a species that affects the behaviour of individuals of other species to the benefit of the species that produces it

Cooperator
: any individual, corporation, or institution not engaged in pesticide research that has agreed to use or to allow the use of a pest control product for research on a site owned or operated by that individual, corporation, or institution

End-use product (EP)
: a pest control product whose labelling includes directions for direct use or application for its intended pesticidal effect

Kairomone
: a semiochemical produced by individuals of a species which beneficially affects the behaviour of individuals of another species, to the detriment of the emitting species

Pheromone
: a semiochemical produced by individuals of a species which affects the behaviour of other individuals of the same species

Research
: tests, trials, or experiments carried out to generate new data or to confirm results drawn from other studies, as required by the Pest Control Products Regulations, to support registration of a pesticide

Researcher
: any person who is responsible for using or supervising the use of a pesticide for research purposes; in light of the low potential risk to humans and the environment with semiochemicals compared with other types of pesticides, a researcher need not necessarily be affiliated with a research establishment

Research establishment
: any public or private corporation or institution or part thereof, engaged in research on pesticides

Semiochemical
: a message-bearing substance produced by a plant or animal, or a synthetic analogue of that substance, which evokes a behavioural response in individuals of the same or other species; some examples of semiochemicals are allomones, kairomones, pheromones, and synomones; these guidelines pertain only to substances that affect arthropod behaviour

Straight-chained lepidopteran pheromones (SCLP)
: a group of pheromones consisting of unbranched aliphatics having a chain of nine to 18 carbons, containing up to three double bonds, ending in an alcohol, acetate, or aldehyde functional group

Synomone
: a semiochemical produced by individuals of a species that affects the behaviour of individuals of another species, to the benefit of both species

Technical grade of active ingredient (TGAI)
: a manufacturing-use product consisting of an active ingredient that may contain impurities but does not contain added formulants and is produced on a commercial or pilot-plant scale for the manufacture of other pest control products

4.0 Research trials

This section applies to research with type 2 semiochemical EPs described in section 1.0 which are subject to registration.

It should be noted that the sale of treated crops is subject to regulation under the *Food and Drug Act* (FDA). Crops harvested from treated research plots or sites must not be sold for food or feed purposes without written authorization from the PMRA, except when used in research where the semiochemical dispenser does not actually touch the crop plant (i.e., exemption category 4.1(1) in section 4.1). This requirement applies to **any** research where the treated crop is to be sold for food and feed and is independent of the size of the research trial. A waiver may be granted by the PMRA depending on the nature of the product and the use pattern. A scientific rationale must accompany each

application for a waiver (see Appendix I, parts 6 and 7, for more information). Each application and the situation presented will be considered on a case-by-case basis.

A two-tiered approach for research trials has been adopted based on risk assessment, thereby allowing flexibility in regulating semiochemical products. The two tiers of regulation are (a) exemption, and (b) research permit. The researcher should determine in which of these two categories the intended research trial fits. Researchers are invited to consult with the PMRA for clarification regarding regulation of research trials conducted with semiochemicals.

It should be noted that certain provinces may require a provincial permit to conduct any research trials, whether conducted under a federal research permit or exemption. **The researcher is responsible for applying to the provincial regulatory officials for such a permit.**

Also note that the research coordinator must ensure the safety of employees and cooperators and seek guidance from appropriate sources regarding use, handling, and disposal procedures. Employees and cooperators should be advised of semiochemical application schedules and be supplied with telephone numbers to access emergency medical information (e.g., product chemistry and antidotal measures).

Whenever possible, research workers should be supplied with a material safety data sheet (MSDS) that includes appropriate precautions regarding accidental exposure. In the absence of such information, research workers should wear chemical-resistant gloves and coveralls during mixing, loading, application, cleanup, and repair.

All field research sites should have appropriate warning signs posted at the most likely point of entry. Posting should be installed immediately before the pesticide application and remain in place until the crop has been harvested, or as long as data are being collected.

4.1 Conditions for an exemption

Under the circumstances regarding small-scale research outlined in this section, persons conducting research are exempt from the requirement of obtaining a research permit under the PCPA and it is not necessary to report the research trial to the PMRA.

Exemptions apply only for the control of arthropod pests on land. Additionally, all of the criteria in one or more of the three exemption categories must be met to qualify for an exemption. The numbers of hectares treated refer to each TGAI, per research establishment, per year. The categories are as follows:

(1) Arthropod pheromones contained in affixed solid matrix dispensers or in retrievable sized polymeric matrix dispensers when applied in either food–feed or non-food–non-feed use areas, providing the treated area does not exceed 100 ha

and the maximum use rate does not exceed 375 g a.i./ha/year. Food or feed from such trials can be sold without written authorization from the PMRA, providing that the pheromone dispenser is not in **direct** contact with the crop.

(2) Arthropod pheromones when applied in non-food–non-feed use areas and providing that the treated area does not exceed 100 ha and the maximum use rate does not exceed 375 g a.i./ha/ year. If research is to be conducted on food–feed crops, a research permit is required if the treated produce will be sold.

(3) Semiochemicals regardless of method of application or application rate. (Note that a research permit will be required if treated produce will be sold.) The following limitations apply:

- **Unregistered** active ingredients: research must involve only the researcher, and the treated area must not exceed 5 ha on land owned or operated solely by the research establishment, i.e., no cooperator participation.

- **Registered** active ingredients (research on new sources, new formulations, or new uses): the treated area must not exceed 10 ha without restrictions on cooperator participation or land ownership.

4.2 Research permit data requirements

A federal research permit is required before starting trials with pheromones or other semiochemicals if any of the following conditions apply:

(1) EPs contain formulant ingredients other than those on the U.S. EPA list 4A of inert ingredients (see Appendix V);
(2) applications are made to an aquatic system;
(3) applications are made aerially;
(4) applications are made directly to food or feed crops and the raw agricultural commodity can be used for human consumption or animal feed, with the exception of semiochemical products described in section 4.1(1); and
(5) all of the criteria within one or more of the three exemption categories listed in section 4.1 have not been met.

The general procedures in Regulatory Directive DIR98-05, *Chemical Pesticides Research Permit Guidelines*, should be followed where applicable, including the following:

2.0 Application for Research Permits;
5.0 Data Submission and Handling;
6.0 Research Records and Data Reporting;
7.0 Labels for Research Uses;
8.0 Review Procedure for Research Permit Applications;

11.0 Provincial Permit;
12.0 Importation of Pesticides for Research Purposes;
13.0 Disposal;
14.0 Sale of Products Under Research;
15.0 Sale and Use of Foods Treated Under Research;
17.0 Advertising;
18.0 Posting of Research Area; and
19.0 Audit.

The applicant must submit the following information in advance of the start of the intended research trial within the time frames indicated in PRO96-01, *Management of Submissions Policy*:

- seven copies each of
  - research permit application form;
  - statement of product specification form for the EP;
  - a description of the dispenser;
  - basic manufacturer's name and address; and
  - proposed experimental label, including application rate and method of application (these may be typewritten);

- two copies each of
  - MSDSs for non-active ingredients and the TGAI, if available; and
  - location and map of the area to be treated (recognizing that the location of pest infestations in forested areas may be difficult to predict at the time the application for a research permit is made, the location and map of the treated forest area should be sent to the PMRA no later than 30 d before the start of the trial);

- for each AIC,
  - common name;
  - chemical name [International Union of Pure and Applied Chemistry (IUPAC) and Chemical Abstracts Service (CAS)];
  - Chemical Abstracts Service (CAS) registry number (if available);
  - structural formula;
  - molecular formula;
  - molecular weight; and
  - manufacturing methods or methods of synthesis, when the proposed product will be used on food and feed for sale; additional information on physical and chemical properties may also be required.

Where a semiochemical product is to be broadcast or sprayed, the applicant is encouraged to submit the following data for the TGAI to determine the risk to aquatic systems:

- freshwater invertebrate (e.g., *Daphnia* sp.) acute toxicity, and

- freshwater fish (e.g., salmon or rainbow trout) acute toxicity.

In the absence of this information, an untreated buffer zone may be required adjacent to aquatic systems.

Notes

(i) Following the review of the data listed in the previous sections, the applicant may be required to submit additional environmental chemistry and fate and environmental toxicology data where the proposed use pattern or the potential for exposure is of concern (e.g., large treatment sites or environmentally sensitive areas).

(ii) Human health safety data may be required if MSDSs indicate any toxicological effects of concern or in situations where the proposed use pattern or the potential for human dietary, occupational, or bystander exposure is of concern.

(iii) The researcher is encouraged to record any effects on nontarget organisms, especially invertebrates, that are observed during a research trial. These records should be submitted with the research data in support of applications for registration of a semiochemical product. (See Appendix II, parts 8 and 9 for suggested procedures for monitoring nontarget effects.)

5.0 Registration

For general registration procedures, applicants should refer to the PMRA *Registration Handbook*. It should be noted that both the TGAI and the EP are subject to registration under the PCPA.

The data requirements for semiochemical TGAIs and EPs are outlined in Appendices I and II, respectively. Data screening tables for pheromones and other semiochemicals are given in Appendix III (tier I) and Appendix IV (tiers II and III).

Potential applicants should consult Regulatory Proposal PRO98-02, *Organizing and Formatting a Complete Submission for Pest Control Products,* for instructions regarding the formatting of data. Note that incomplete or improperly formatted submissions will be returned.

It should be noted that the numbering system of “parts” in the appendices is intended to facilitate data management by the PMRA and form the basis for indices to data submitted by potential applicants. The system follows a standard numbering format pertinent to all applications for the registration of pest control products. If certain parts or data codes (DACOs) are not identified, these data are not required.

To register a second EP containing a TGAI that has already been registered, value (efficacy) and other data may be required depending on the nature of the new EP, the proposed use-pattern, and the potential for exposure to humans and the environment. Similarly, if subsequent to the registration of a TGAI, changes to the composition of the TGAI are proposed (e.g., the addition of other AICs), the need for more data will be assessed on a case-by-case basis.

References

OECD. 2001. *Guidance for registration requirements for pheromones and other semiochemicals used for arthropod pest control*. Part of the Organisation for Economic Co-operation and Development (OECD) Series on Pesticides, Number 12 (ENV/JM/MONO(2001)12).

Bäckman, A.C. 1997. Pheromone release by codling moth females and mating disruption dispensers. *In* Technology Transfer in Mating Disruption, Proceedings of the IOBC WPRS Symposium, Montpellier, 1996. *Edited by* P. Witzgall and H. Arn. IOBC WPRS Bulletin, Vol. 20, No. 1, pp. 175–180.

Daughtrey, W.C., Smith, J.H., Hinz, J.P., and Biles, R.W. 1990. Subchronic toxicity evaluation of tridecyl acetate in rats. Fundamental and Applied Toxicology, 14: 104–112.

Henson, R.D. 1977. Environmental fate of gossyplure. Environmental Entomology, 6: 821-822.

Howse, P.E., Stevens, I.D.R., and Jones, O.T. 1998. Insect pheromones and their use in pest management. Chapman and Hall, London, 369 pp.

Inscoe, M.N., and Ridgway, R.L. 1992. Non-target effects of lepidopteran sex attractant pheromones. *In* Insect pheromones and other behaviour-modifying chemicals: application and regulation. *Edited by* R.L. Ridgeway, M. Inscoe, and H. Arn. British Crop Protection Council, Monograph 51, pp. 49–59.

Koch, U.T., Lüder, W., Clemenz, S., and Cichon, L.L. 1997. Pheromone measurements by field EAD in apple orchards. *In* Technology Transfer in Mating Disruption, Proceedings of the IOBC WPRS Symposium, Montpellier, 1996. *Edited by* P. Witzgall and H. Arn. IOBC WPRS Bulletin, Vol. 20, No. 1, pp. 181–190.

Nelson, B.K., Brightwell, W.S., and Krieg, E.F., Jr. 1990. Toxicology and Industrial Health, 6: 373–387.

Shaver, T.N. 1983. Environmental fate of (Z)-11-hexadecenal and (Z)-9-tetradecenal, components of a sex pheromone of the tobacco budworm (Lepidoptera: Noctuidae). Environmental Entomology, 12: 1802–1804.

Spittler, T.D., Leichtweis, H.C., and Dennehy, T.J. 1988. Biorational control of crop pest by mating disruption; residue analyses of Z-9-dodecen-1-yl acetate and Z-11-tetradecenyl-1-yl acetate in grapes. *In* Biotechnology for crop protection. *Edited by* P. Hedin, J.J. Menn, and R. Hollingworth. ACS Symposium Series 379, pp. 430–436.

Spittler, T.D., Leichtweis, H.C., and Kirsch, P. 1992. Exposure, fate and potential residues in food of applied lepidopteran pheromones. *In* Insect pheromones and other behaviour-modifying chemicals: application and regulation. *Edited by* R.L. Ridgeway, M. Inscoe, and H. Arn. British Crop Protection Council, Monograph 51, pp. 93–108.

Touhey, J.G. 1990. A review of the current bases for the United States Environmental Protection Agency's policies for the regulation of pheromones and other semiochemicals, together with a review of the available relevant data which may impact the assessment of risk for these classes of chemicals. Part 1: straight chain alcohols, acetate esters and aldehydes. Unpublished report. 474 pp.

United States Federal Register. 1994a. EPA notice: arthropod pheromones in solid matrix dispensers; experimental use permits. Federal Register, 59(3): 3681–3684.

United States Federal Register. 1994b. EPA notice: arthropod pheromones; experimental use permits. Federal Register, 59(3): 34 812 – 34 814.

United States Federal Register. 1995. EPA final rule: lepidopteran pheromones: tolerance exemption. Federal Register, 60(2): 45 060 – 45 062.

List of abbreviations

AIC	active ingredient component
CAS	Chemical Abstracts Service
CR	conditionally required
DACO	data code
EEC	estimated environmental concentration
EP	end-use product
FDA	*Food and Drugs Act*
GLP	good laboratory practice
IPM	integrated pest management
IUPAC	International Union of Pure and Applied Chemistry
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
MRL	maximum residue limit
MSDS	material safety data sheet
NAFTA	North American Free Trade Agreement
OECD	Organisation for Economic Co-operation and Development
PCPA	*Pest Control Products Act*
PMRA	Pest Management Regulatory Agency
R	required
RH	relative humidity
SCLP	straight-chained lepidopteran pheromones
TGAI	technical grade of active ingredient
U.S. EPA	United States Environmental Protection Agency
UV	ultraviolet

Appendix I Data in support of registration of a semiochemical technical grade of the active ingredient

Regulatory Proposal PRO98-02, *Organizing and Formatting a Complete Submission for Pest Control Products,* should be consulted for specific guidance.

Part 0: Index

Part 1: Label
The *Registration Handbook* should be consulted regarding the general labelling requirements for TGAIs.

Part 2: Product Chemistry

Data for the TGAI and each AIC that contributes to its activity are to be provided in accordance with Appendix III. Refer to Regulatory Directive DIR98-04, *Chemistry Requirements for the Registration of a Technical Grade of Active Ingredient or an Integrated System Product*, for detailed requirements; however, when requirements differ between this document and Regulatory Directive DIR98-04, the criteria of this document have priority. The submission format should follow the instructions in Regulatory Proposal PRO98-02, *Organizing and Formatting a Complete Submission for Pest Control Products*.

The descriptive information required by DACOs 2.4–2.9 (see Appendix III) is to be provided for each AIC in the TGAI. Information corresponding to DACOs 2.2 and 2.11 is also required for each AIC if produced by or for the TGAI manufacturer as opposed to being purchased from a commercial supplier. If a commercially available AIC is used in the manufacture of the TGAI, the following are required:

(i) the name and address of the company that produces the AIC or, if that information is not known to the applicant, the name and address of the company that supplies it; and

(ii) all information concerning the composition of each AIC, including a copy of all specifications or other documents describing it.

Product specifications provided in accordance with DACO 2.12 are to include the precise identification of each AIC in the TGAI and impurities present at or above 0.1% w/w in the TGAI if employed for food or feed uses or present at or above 1.0% w/w in the TGAI if employed for non-food – non-feed uses. Impurities may be treated collectively if the semiochemical is a natural extract containing many impurities closely related to the active ingredient. These reporting limits do not apply to impurities of toxicological concern as described in Regulatory Directive DIR98-04. Data supporting the specifications are required from three production batches of representative TGAI.

Parts 4, 5, 6, and 7: Human Health and Safety

Part 4: Toxicology

The purpose of the safety testing is to determine potential risks of semiochemicals to human health. Semiochemicals generally present a very low potential risk to human health because of their mode of action (i.e., behavioural changes of the pest in response to volatile chemical signals), a rapid rate of dissipation, and the quantities used which often reflect concentrations that occur in nature during an outbreak of the pest.

Tier I tests initially required to support the registration of the TGAI are listed here. Applicants may request waivers from testing, where appropriate (e.g., exposure ≤ background levels; TGAI is a member of a well-characterized group such as the SCLPs). Applications for waivers must be supported by sound scientific rationale and will be considered on a case-by-case basis. Surrogate data may be considered for TGAIs that are similar to those already registered, if this can be supported by sound scientific rationale.

Summary of Tier I Tests (see Appendix III)

Data obtained from these studies will be used for the initial toxicological evaluation of the TGAI.

DACO 4.2: Acute studies
- DACO 4.2.1: Acute oral toxicity
- DACO 4.2.2: Acute dermal toxicity
- DACO 4.2.3: Acute inhalation toxicity
- DACO 4.2.4: Primary eye irritation
- DACO 4.2.5: Primary dermal irritation
- DACO 4.2.6: Dermal sensitization

DACO 4.3: Short-term studies
- DACO 4.3.1: 90-d Rodent Study, **OR**
- DACO 4.3.3: 30-d Rodent Study
- [**Note**: Dermal or inhalation exposure may be acceptable if deemed more appropriate.]

DACO 4.5:

Developmental studies
- DACO 4.5.2: Rat developmental study, **OR**
- DACO 4.5.3: Rabbit developmental study

Genotoxicity potential studies
- DACO 4.5.4: Microbial point mutation
- DACO 4.5.5: Mammalian (cell) point mutation
- DACO 4.5.6: An in vitro chromosome aberration assay

DACO 4.8: Additional data
- DACO 4.8: Medical data

Additional tier II and tier III testing may be required if results of tier I studies indicate any toxicological concern and there is potential for exposure of food (for semiochemicals used on or around food) and humans, as summarized in the following.

Summary of Tier II and Tier III Tests (see Appendix IV)
When data from tier I indicate any toxicological effects of concern, data from one or more of the following studies will be required. The need for such data will be assessed on a case-by-case basis.

DACO 4.3: Short-term studies
- DACO 4.3.2: Dog 6- or 12-month oral study
- DACO 4.3.4: Rat 90-d dermal
- DACO 4.3.5: Rat 21- or 30-d dermal
- DACO 4.3.6: 90-d inhalation study
- DACO 4.3.7: Rat 21- or 30-d inhalation study
- DACO 4.3.8: Other short-term studies

DACO 4.4: Long-term studies
- DACO 4.4.1: Chronic toxicity study
- DACO 4.4.2: Rat oncogenicity study
- DACO 4.4.3: Mouse oncogenicity study
- DACO 4.4.4: Combined chronic–oncogenicity study

DACO 4.5:
- Developmental–reproductive studies
- DACO 4.5.1: Rat reproduction study

- Genotoxicity potential studies
- DACO 4.5.7: in vivo chromosomal aberration assay
- DACO 4.5.8: Other genotoxicity studies

- Metabolism studies
- DACO 4.5.9: Rat pharmacokinetic and metabolite characterization studies

- Neurotoxicity studies
- DACO 4.5.12: Rat acute oral neurotoxicity study
- DACO 4.5.13: Rat 90-d neurotoxicity study

DACO 4.8: Other studies, data, and reports
- DACO 4.8: Special studies (e.g., Immunotoxicity)

All acute studies should be conducted using the TGAI. Protocols for studies should be in general accordance with those stated in the OECD guidelines. When validated methodology for equivalent in vitro studies becomes available, its use will be considered.

Part 5: Occupational and Bystander Exposure
Information is only required for the EP.

Parts 6 and 7: Metabolism and Residue Studies
If semiochemicals are applied directly to food, feed, or tobacco, the same metabolism and residue studies are required as for other agricultural chemicals. For semiochemicals, residue data may not be required if it is determined that detectable residues on the consumable commodity are unlikely to occur or that residue levels are unlikely to exceed natural background levels during outbreaks of the pest and that any residues are not toxic.

The data required for the registration of proposed products when used on terrestrial or greenhouse food are outlined in Appendices IV and V. Proponents should contact the PMRA regarding the data requirements for other use scenarios that would result in direct contact of the semiochemical with food or feed. Guidance is available in Regulatory Directive DIR98-02, *Residue Chemistry Guidelines*, regarding the test substance for studies (i.e., the TGAI or the EP).

Waivers from the requirement to submit residue data may be available if a scientific rationale is accepted, indicating, for example, that there will be no detectable residues in or on the consumable portion of the plant, or that the residues are not of concern, or that the residue levels are not significantly different from background levels that would be experienced during an outbreak of the pest. Additional guidance regarding waiver requests can also be found in Regulatory Directive DIR98-02, *Residue Chemistry Guidelines*.

Parts 8 and 9: Environmental Chemistry and Fate and Environmental Toxicology

Environmental chemistry and fate studies and environmental toxicology studies are required for semiochemicals that will be used outdoors, for example, in the control of agricultural and forestry pests. No such studies are required for semiochemicals to be used in enclosed buildings (i.e., with walls, floor, and ceiling) such as greenhouses, grain storage structures, and residential, commercial, and industrial buildings.

With the exception of aquatic toxicology data, sufficient environmental chemistry and fate and environmental toxicology data have been reviewed for SCLPs to allay concerns regarding their potential environmental impact. Thus, except for aquatic toxicology data, no further data are required in support of applications to register the TGAI of this class of semiochemical. The submission of additional data on SCLPs, however, is encouraged.

For other classes of semiochemicals, the submission of data in addition to the minimum requirements outlined here, if available, is encouraged but not required.

For appropriate methodology in performing environmental chemistry and fate studies, applicants for registration are referred to Trade Memorandum T-1-255, *Guidelines for Determining Environmental Chemistry and Fate of Pesticides*.

Tier I
Tier I data will be used for initial evaluation.

Where a semiochemical product, including an SCLP, is to be broadcast or sprayed, data from the following studies are required for the TGAI to determine the risk to aquatic systems. In the absence of this information, an untreated buffer zone may be required adjacent to aquatic systems.

DACO 9.3: A freshwater invertebrate acute toxicity study, either
DACO 9.3.2: *Daphnia* sp., or
DACO 9.3.4: Other species.

DACO 9.5.2: A freshwater fish acute toxicity study, with one of
DACO 9.5.2.1: Cold water fish (e.g., salmon or rainbow trout) are preferred species,
DACO 9.5.2.2: Warm water fish (e.g., bluegill sunfish), or
DACO 9.5.2.3: Other species.

In addition, for products other than SCLPs, the following data are required for the TGAI.

DACO 9.6: An avian acute oral toxicity study, with one of
DACO 9.6.2.1: Bobwhite Quail
DACO 9.6.2.2: Mallard duck, or
DACO 9.6.2.3: Other species
and an avian dietary toxicity study, with one of
DACO 9.6.2.4: Bobwhite quail,
DACO 9.6.2.5: Mallard duck, or
DACO 9.6.2.6: Other species.

Tier II
Where data from tier I demonstrate hazard to biota, data from one or more of the following studies will be required for each AIC of the TGAI. The need for such data will be assessed on a case-by-case basis and will depend on the properties of the TGAI and the intended use pattern.

DACO 8.2.3.2: Hydrolysis
DACO 8.2.3.3.1: Phototransformation in soil
DACO 8.2.3.3.2: Phototransformation in water
DACO 8.2.3.4.2: Biotransformation in aerobic soil
DACO 8.2.3.5.2: Biotransformation in aerobic water
DACO 8.2.4.2: Adsorption–desorption

Tier III
Where data from tier II demonstrate hazard or risk to the environment or to biota, studies of the effects of the TGAI on one or more of the following groups of organisms will be required. The need for such studies will be assessed on a case-by-case basis.

DACO 9.3: Nontarget freshwater invertebrates
DACO 9.4: Nontarget marine invertebrates
DACO 9.7: Terrestrial animals
DACO 9.8: Nontarget plants

Appendix II Data in support of registration of a semiochemical end-use product (EP)

Regulatory Proposal PRO98-02, *Organizing and Formatting a Complete Submission for Pest Control Products,* should be consulted for specific guidance. Note that if a proposed product contains semiochemicals in combination with other pesticides (e.g., traditional insecticides), these other pesticides must also be registered. The following information should be provided in support of registration for a semiochemical EP:

Part 0: Index

Part 1: Label
The *Registration Handbook* should be consulted regarding the general labelling requirements for EPs.

Part 3: Product Chemistry
Please refer to Regulatory Document DIR98-03, *Chemistry Requirements for the Registration of a Manufacturing Concentrate or an End-Use Product Formulated from Registered Technical Grade of Active Ingredients or Integrated System Products,* for detailed requirements. Storage stability requirements must be met; however, data need not be generated under ambient conditions, rather 1-year stability data may be produced under the recommended storage conditions for the product.

Parts 4, 5, 6, and 7: Human Health and Safety

Part 4: Toxicology
MSDSs must be submitted for all formulant ingredients. In addition, the following acute toxicity studies must be conducted using the EP proposed for registration, if there are formulants other than those on the U.S. EPA list 4A of inert ingredients:

DACO 4.6: Acute Studies
- DACO 4.6.1: Acute Oral Toxicity
- DACO 4.6.2: Acute Dermal Toxicity
- DACO 4.6.3: Acute Inhalation Toxicity
- DACO 4.6.4: Primary Eye Irritation
- DACO 4.6.5: Primary Dermal Irritation
- DACO 4.6.6: Dermal Sensitization

Part 5: Occupational and Bystander Exposure
DACO 5.2: Use Description, Use Scenario (Application and Post-Application).

An estimation of exposure, based on available information (application method, rate, physical–chemical properties), should be provided.

Additional DACO 5 elements will be required if this use description information demonstrates significant exposure potential and if toxicity tests of published data indicate a concern. Solid

matrix dispensers are unlikely to present a significant exposure potential, but some sprayed applications might.

Parts 6 and 7: Metabolism and Residue Studies
If semiochemicals are applied directly to food, feed, or tobacco and residue data are required, the semiochemical metabolites in the plant must be investigated using either the TGAI or the EP. For additional information see the metabolism and residue requirements for TGAIs in Appendix I, parts 6 and 7.

Parts 8 and 9: Environmental Chemistry and Fate and Environmental Toxicology

Tier I
DACO 9.2.9: Field studies

To determine whether semiochemicals adversely affect nontarget arthropods, field studies are required for EPs intended for use outdoors that contain semiochemicals other than the SCLPs. The data from these studies are not required for EPs containing SCLPs only, as sufficient data have been reviewed for these compounds to allay concerns regarding their potential impact on nontarget arthropods. Field data should be acquired from areas that have not received conventional pesticide treatments. For example, nontarget invertebrates affected by the semiochemical can be identified by comparing semiochemical-baited and unbaited traps placed in environments similar to those of intended use. As the semiochemicals may affect other species beyond the flight period of the intended target, these traps should be monitored until data indicate that the semiochemical is no longer active. Nontarget species attracted in large numbers should be identified and recorded. Species investigated should include:

- beneficial arthropods, including wasps and bees;
- parasites and predators of the pest species; and
- organisms that are closely related taxonomically to the pest species (i.e., in the same family or genus).

Tier II
Where data from studies on the TGAI submitted under tier I, parts 8 and 9, demonstrate any hazard to biota, some or all of the following data will be required on a case-by-case basis:

DACO 8.2.4.6: Special studies using the EP

(a) Leaching by water, from dispensers containing the EP, of any of the AICs;

(b) Volatilization under conditions typical of the proposed use (rate and duration are of particular interest), supported by relevant data from vapour pressure studies. For example, release rate characteristics (µg/dispenser/h) of the EP could be researched at 20°C, 50% relative humidity (RH), and wind speed 5 km/h.

Part 10: Value (including Efficacy)

Consistent with the requirements of the PCPA and Pest Control Products Regulations, information is required to demonstrate the value of the proposed product. The purpose of the value assessment is to allow for a balanced decision by considering the benefits from use of the product in addition to any identified risks to human health or the environment. The components of value include efficacy (including adverse effects to the crop and site), economics, and sustainability.

The following information is required to allow for an assessment of value:

DACO 10.1: Value summaries

An overall summary should be provided of the elements submitted in part 10.

DACO 10.2: Efficacy studies

DACO 10.2.1: Mode of action

Unlike conventional chemical pesticides, semiochemicals are typically non-lethal to the target pest. The proponent should describe the function of the semiochemical in modifying the behaviour of the target pest and provide information to support the claim that the active ingredient is a semiochemical. This could include copies of references from refereed journals indicating attraction (or other behavioural modification) of the pest to a semiochemical source as the proposed product in the laboratory or field, or electroantennogram studies. The proponent should also provide a description of the mode of action of the semiochemical in the EP (e.g., controls the pest population through mating disruption, acts as an attractant in a pesticidal bait).

DACO 10.2.2: Description of pest problem in Canada

Information should be provided on the biology and life cycle of the pest and the nature and extent of the damage caused by the pest. This information is useful in the interpretation of results from efficacy trials. Information should also be provided on the crops and sites affected by the pest and the geographic distribution of the pest problem in Canada. References should be provided.

DACO 10.2.3: Efficacy trials

Data from scientifically conducted efficacy trials are required to demonstrate that the product is effective for its intended purpose when used in accordance with label directions. Information of a testimonial nature without supporting scientific documentation is not acceptable. The proponent should submit study reports for the individual efficacy trials and a summary assessment of all efficacy results.

As a general guide, proponents should consult Regulatory Directive DIR93-07a, *Guidelines for Efficacy Assessment of Chemical Pesticides*, for guidance regarding the principles of efficacy testing and reporting of data. Although Regulatory Directive DIR93-07a pertains to efficacy assessment of chemical pesticides, the general principles of efficacy testing and reporting are also

applicable to semiochemical products. Efficacy data should be generated and reported in accordance with the principles outlined as follows:

- Studies should be conducted with the EP proposed for registration. Data from studies conducted with similar, but not identical, formulations will be considered provided that an adequate scientific rationale is provided to support equivalence in efficacy to the product proposed for registration.

- Data are required for each of the target pests on the label.

- The EP should be applied in a manner consistent with the proposed label instructions with regards to the rates, timing, and methods of application.

- Study reports should clearly state the objective of the trial, experimental design, evaluation methods, results, and conclusions.

- The experimental design of efficacy studies should include untreated check plots as an indication of population pressure. Where possible, plots receiving a commercial standard treatment of known efficacy should be included as a basis for comparison with the semiochemical treatment.

- The criteria for performance assessment should be clearly outlined in the study report. For semiochemicals that act through mating disruption, data should be provided on the effectiveness of the treatment at disrupting the pest from locating a semiochemical source (e.g., through trap catches) and on reductions in pest numbers and damage.

- At least one of the studies should evaluate a range of rates to demonstrate the lowest effective rate of application.

- For outdoor uses (e.g., agricultural crop protection, forestry), studies should be conducted over more than one season in areas that are representative of the major geographical regions where the product is intended to be used to account for variations in pest population pressures, climate, insect resistance, cultural practices, etc. Studies conducted in adjacent regions of the U.S. are acceptable if climatic and production practices are similar to those found in Canada.

- For indoor uses (e.g., greenhouses), studies from outside of Canada may be considered, provided that the test conditions are similar to those found in Canada.

- As a general rule, a minimum of **three** studies or trials are required for each proposed pest–site combination proposed for registration. Fewer trials may be adequate for some uses if supported by an adequate scientific rationale (e.g., use of bridging data).

DACO 10.3: Adverse effects
Information should be provided on any adverse effects on the crop and site (e.g., phytotoxicity) resulting from use of the EP. This type of information can be generated in conjunction with the efficacy trials.

DACO 10.4: Economic considerations
Although it is anticipated that an assessment of economic benefits will not be required for most semiochemical products, if such an assessment is requested by the PMRA, proponents are referred to Regulatory Directive DIR93-17, *Assessment of the Economic Benefits of Pesticides*, for guidance regarding the type of information to be submitted for review.

DACO 10.5: Sustainability
In addition to efficacy and economics, information on the contribution of the product to sustainable pest management is also required in the assessment of value. Sustainability considerations may be important for semiochemical products that may not provide the same level of pest reduction achieved with chemical pesticides but are of value because of compatibility with IPM, contribution to risk reduction, reduced reliance on pesticides, or other sustainability considerations. In most cases, qualitative information would be adequate in lieu of specific studies; however, specific studies should be submitted if available.

DACO 10.5.1: Survey of alternatives
The proponent should provide a list of currently available control options (chemical and non-chemical) for the target pest and a brief description of their effectiveness in comparison with the proposed EP.

DACO 10.5.2: Compatibility with current management practices including IPM
Information should be provided on the compatibility of the proposed EP with established or developing pest management strategies for the crop. This should include any positive features of the semiochemical (e.g., low toxicity to pest predators or parasites) or negative features (e.g., flair-up of secondary pest species that were previously held in check by broad-spectrum chemicals used for control of the target pest) which could impact on pest management strategies. Documented studies to support these claims should be provided, if available.

DACO 10.5.3: Resistance management
Resistance to chemical pesticides is a problem in the control of many pests. Semiochemicals have a different mode of action from that of chemical pesticides. The proponent should indicate whether resistance to conventional chemical pesticides is a problem with the target pest and explain how the EP may fit in with strategies to manage resistance.

DACO 10.5.4: Contribution to risk reduction
The proponent should discuss how the proposed EP may contribute to risk reduction (e.g., may provide an alternative to highly toxic, broad-spectrum chemical pesticides; reduced reliance on chemicals; reduced pesticide residues on food).

Appendix III Pest Management Regulatory Agency (PMRA) data requirements for pheromones and other semiochemicals: Tier I

Data code (DACO)	Title	Data required for SCLPs[1]	Data required for non-SCLPs[1]	Conditions
0	**Index**	**R**	**R**	
1	**Label**	**R**	**R**	
2	**Chemistry for registration of a technical grade of active ingredient (TGAI)**			
2.1	**Name and office address of applicant**	R	R	
2.2	**Name and office address of manufacturer and name and address of manufacturing plant**	R	R	
2.3	**Product trade name**	R	R	
2.3.1	Other names	R	R	
2.4	**Common name**	R	R	
2.5	**Chemical name**	R	R	Provide IUPAC and CAS
2.6	**Chemical abstracts registry number**	R	R	
2.7	**Structural formula**	R	R	
2.8	**Molecular formula**	R	R	
2.9	**Molecular weight**	R	R	
2.11	**Manufacturing methods**			
2.11.1	Manufacturing summary	R	R	
2.11.2	Description of starting materials	R	R	
2.11.3	Detailed process description	R	R	
2.11.4	Discussion of formation of impurities	R	R	
2.12	**Specifications**			
2.12.1	Establishing certified limits	R	R	A justification must be provided if standard limits are not met
2.12.2	Statement of product specification form	R	R	
2.13	**Preliminary analysis**			
2.13.1	Methodology–validation	R	R	
2.13.2	Confirmation of identify	R	R	Where the starting materials and manufacturing process are such that impurities and by-products which are particularly undesirable could be present in the TGAI, the content of each such component must be determined and reported, even if below 1 g/kg (0.1% w/w), where possible
2.13.3	Batch data	R	R	
2.13.4	Impurities of toxicological concern	CR	CR	Required if a review of the starting materials and manufacturing process indicates that a potential for presence of such impurities exists
2.14	**Chemical and physical properties for each AIC**			
2.14.4	Melting point or range	CR	CR	Required if solid at room temperature
2.14.5	Boiling point or range	CR	CR	Required if liquid at room temperature
2.14.7	Water solubility (mg/L)	R	R	

Data code (DACO)	Title	Data required for SCLPs[1]	Data required for non-SCLPs[1]	Conditions
2.14.8	Solvent solubility (mg/L)	R	R	
2.14.9	Vapour pressure	R	R	
2.14.10	Dissociation constant	CR	CR	Required when the test substance contains an acid or base functionality and either when used on food crops and residue data are required or possibly when tier I environmental toxicity tests demonstrate hazard to biota
2.14.11	Octanol–water partition coefficient	CR	CR	Required if the chemical is organic, unless it hydrolyses in water or is soluble in water in all proportions
2.14.13	UV–visible absorption spectra	CR	R	Required if used on food crops and residue data are required; if tier I environmental toxicity tests demonstrate hazard to biota, these data will be required on a case-by-case basis
	Properties for the TGAI			
2.14.1	Colour	R	R	
2.14.2	Physical state	R	R	
2.14.3	Odour	R	R	
2.14.6	Density or specific gravity	R	R	
2.14.14	Stability (temperature, metals)	R	R	
2.15	Other studies, data, and reports			
3	**Specifications and analytical methodology required for registration of an EP**			
3.1	**Product identification**			
3.1.1	Name and office address of applicant	R	R	
3.1.2	Name and address of formulating plant	R	R	
3.1.3	Trade name	R	R	
3.1.4	Other names	R	R	
3.2	**Formulation process**			
3.2.1	Description of starting materials	R	R	
3.2.2	Description of the formulation process	R	R	
3.2.3	Discussion of the formation of impurities and impurities of toxicological concern	CR	CR	Required if the formulants or formulation process may potentially introduce or enhance the presence of impurities of toxicological concern
3.3	**Specifications**			
3.3.1	Establishing certified limits	R	R	A justification must be provided if standard limits are not met
3.3.2	Statement of product specification form	R	R	
3.4	**Product analysis**			
3.4.1	Enforcement analytical method	R	R	
3.4.2	Impurities of toxicological concern	CR	CR	Required if the formulants or formulation process may potentially introduce or enhance the presence of impurities of toxicological concern
3.5	**Chemical and physical properties**			
3.5.1	Colour	R	R	

Data code (DACO)	Title	Data required for SCLPs[1]	Data required for non-SCLPs[1]	Conditions
3.5.2	Physical state	R	R	
3.5.3	Odour	R	R	
3.5.4	Formulation type	R	R	
3.5.5	Container material and description	R	R	
3.5.6	Density or specific gravity	R	R	
3.5.7	pH	R	R	
3.5.9	Viscosity	CR	CR	Required if a liquid
3.5.10	Storage stability data	R	R	
3.6	Other studies, data, and reports			
4	**Toxicology**			
4.1	Summaries - toxicology profile			
4.2	**Acute studies - TGAI**			
4.2.1	Acute oral	R	R	Data may be waived for TGAI if substance is a member of a well-characterized group (e.g., SCLPs) and the acute toxicity of that group is described
4.2.2	Acute dermal	R	R	
4.2.3	Acute inhalation	R	R	
4.2.4	Primary eye irritation	R	R	
4.2.5	Primary dermal irritation	R	R	
4.2.6	Dermal sensitization	R	R	
4.3	**Short-term studies**			
4.3.1	90-d rodent study	CR	CR	One of 4.3.1 or 4.3.3 is required if there is a significant exposure potential (e.g., above background levels) or if a tolerance–MRL will be set; data may be required if the substance is not a member of a well-characterized group (e.g., SCLPs) and the repeated-dose toxicity of that group is not described
4.3.3	30-d rodent study	CR	CR	
4.5	**Special studies TGAI**			
4.5.2	Rat developmental study	CR	CR	One of 4.5.2 or 4.5.3 is required if there is a significant exposure potential (e.g., above background levels) or if a tolerance–MRL will be set; data may be required if the substance is not a member of a well-known group of substances for which the teratogenicity – developmental toxicity is described
4.5.3	Rabbit developmental study	CR	CR	
4.5.4	Genotoxicity: microbial point mutation	R	R	Data may be waived if the substance is a member of a well-characterized group (e.g., SCLPs) and the mutagenicity of that group is described
4.5.5	Genotoxicity: mammalian (cell) point mutation	R	R	
4.5.6	Genotoxicity: in vitro chromosomal aberrations	R	R	

Data code (DACO)	Title	Data required for SCLPs[1]	Data required for non-SCLPs[1]	Conditions
4.6	**Acute studies (EP)**			
4.6.1	Acute oral	R	R	Data may be waived for the EP if formulants are listed on the U.S. EPA list 4A of inert ingredients
4.6.2	Acute dermal	R	R	
4.6.3	Acute inhalation	R	R	
4.6.4	Primary eye irritation	R	R	
4.6.5	Primary dermal irritation	R	R	
4.6.6	Dermal sensitization	R	R	
4.8	Other studies, data, and reports	R	R	Medical data are required, if available, for both the TGAI and the EP
5	**Exposure (occupational and bystander) (EP)**			
5.1	Summaries	R	R	
5.2	Use description–scenario (application and post-application)	R	R	Estimation of exposure based on available information (application method, rate, physical–chemical properties)
5.14	Other studies, data, and reports			
6	**Metabolism–toxicokinetics studies for direct application of semiochemicals to greenhouse or terrestrial food or feed crops (contact the PMRA for requirements pertaining to other use–site categories) (TGAI or EP)**			
6.1	Summaries	CR	CR	Trigger: required if a tolerance–MRL is required (i.e., if the semiochemical is for use on food – feed crops and if a toxicity concern is raised by toxicity data)
6.2	Livestock	CR	CR	
6.3	Plants	CR	CR	
6.4	Other studies, data, and reports			
7	**Food, feed, and tobacco residue studies for direct application of semiochemicals to greenhouse or terrestrial food or feed crops (contact the PMRA for requirements pertaining to other use–site categories)**			
7.1	Summaries	CR	CR	
7.2	Analytical methodology (food crops and tobacco)			
7.2.1	Supervised residue trial analytical methodology	CR	CR	
7.3	Freezer storage stability tests	CR	CR	Depends on length of storage
7.4	Crop residue data			
7.4.1	Supervised residue trial study	CR	CR	Trigger: required if a tolerance–MRL is required (i.e., if the semiochemical is for use on food – feed crops and if a toxicity concern is raised by toxicity data)
7.4.2	Temporal residue trial study	CR	CR	Trigger: required if a tolerance–MRL is required (i.e., if the semiochemical is for use on food – feed crops and if a toxicity concern is raised by toxicity data)
7.4.3	Confined crop rotation trial study	CR	CR	
7.4.4	Field crop rotation trial study	CR	CR	
7.4.5	Processed food–feed	CR	CR	
7.4.6	Residue data for crops used as livestock feed	CR	CR	
7.5	Livestock, poultry, egg, and milk residue data (from feeding of treated crops)	CR	CR	
7.6	Livestock, poultry, egg, and milk residue data (external application)	CR	CR	
7.7	Tobacco residue data	CR	CR	
7.8	Other studies, data, and reports	CR	CR	

Data code (DACO)	Title	Data required for SCLPs[1]	Data required for non-SCLPs[1]	Conditions
9	**Environmental toxicology**			
9.1	Summary	R	R	
9.2	**Non-target terrestrial invertebrates**			
9.2.9	Field studies (EP) (i.e., beneficial arthropods including bees and wasps, parasites and predators of the pest species, and taxonomically related organisms of the pest)	—	CR	Information–discussion to address whether behaviour or reproduction would be affected is required if exposure is likely to exceed natural background levels (e.g., >375 g a.i./ha/year for SCLPs)
9.3	**Nontarget freshwater invertebrates (TGAI)**	—	CR	Trigger: required if applied by air or directly to water or at rate exceeding natural background levels (e.g., >375 g a.i./ha/year for SCLPs); not required for product in affixed dispensers on land
9.3.2	*Daphnia* sp. acute	CR	CR	See 9.3; one of 9.3.2 or 9.3.4 is required
9.3.4	Laboratory studies with other species	CR	CR	
9.5	**Fish (TGAI)**			
9.5.2	**Acute studies**			
9.5.2.1	Cold water fish (e.g., salmon or rainbow trout)	CR	CR	See 9.3; one of 9.5.2.1, 9.5.2.2, or 9.5.2.3 is required; 9.5.2.1 is preferred
9.5.2.2	Warm water fish (e.g., bluegill sunfish)	CR	CR	
9.5.2.3	Other freshwater fish species	CR	CR	
9.6	**Wild birds (TGAI)**			
9.6.2	**Acute studies**			
9.6.2.1	Oral (LD_{50}) bobwhite quail	—	CR	One of 9.6.2.1, 9.6.2.2, or 9.6.2.3 is required
9.6.2.2	Oral (LD_{50}) mallard duck	—	CR	
9.6.2.3	Oral (LD_{50}) other species	—	CR	
9.6.2.4	Dietary (LC_{50}) bobwhite quail	—	CR	One of 9.6.2.4, 9.6.2.5, or 9.6.2.6 is required
9.6.2.5	Dietary (LC_{50}) oral mallard duck	—	CR	
9.6.2.6	Dietary (LC_{50}) oral other species	—	CR	
9.9	Other studies, data, and reports			
10	**Value (applicable to each pest–site or host combination) (EP)**			
10.1	Value summaries	R	R	
10.2	**Efficacy studies**			
10.2.1	Mode of action - TGAI	R	R	
10.2.2	Description of pest problem	R	R	
10.2.3	**Efficacy trials (EP)**			
10.2.3.1	Small-scale trials laboratory, greenhouse	CR	CR	May be submitted in support of 10.2.1
10.2.3.2	Field trials – operational use trials	R	R	
10.3	**Adverse effects on use site (EP)**			
10.3.1	Adverse effects to crop (phytotoxicity), host animals, note of application	R	R	
10.4	Economics	—	CR	Required if health or environmental concerns have been identified that cannot be easily mitigated by use restrictions or limitations

Data code (DACO)	Title	Data required for SCLPs[1]	Data required for non-SCLPs[1]	Conditions
10.5	**Sustainability**			
10.5.1	Survey of alternatives (chemical and non-chemical)	R	R	
10.5.2	Compatibility with current management practices including IPM	R	R	
10.5.3	Resistance management	R	R	
10.5.4	Contribution to risk reduction	R	R	
10.6	Other studies, data, and reports			
12	**Summaries**			
12.5	Foreign reviews			Please code 12.5.X and include at end of applicable part (e.g., a foreign review of value would be coded 12.5.10 and submitted under part 10.6)
12.7	Comprehensive summaries	R	R	Required for new active ingredients and major new uses of registered active ingredients

[1]CR, conditionally required; R, required.

Appendix IV Pest Management Regulatory Agency (PMRA) data requirements for pheromones and other semiochemicals: Tier II and Tier III

Data code (DACO)	Title	Data required for SCLPs[1]	Data required for non-SCLPs[1]	Tier	Conditions
0	**Index**	**R**	**R**		
1	**Label**	**R**	**R**		
2	**Chemistry for registration of a technical grade of active ingredient (TGAI)**				
2.13	**Preliminary analysis**				
2.13.4	Impurities of toxicological concern	CR	CR	II	Required if a review of the starting materials and manufacturing process indicates that a potential for the presence of such impurities exists
3	**Specifications and analytical methodology required for registration of an EP**				
3.2	**Formulation process**				
3.2.3	Discussion of the formation of impurities of toxicological concern	CR	CR	II	Required if the formulants – formulation process may potentially introduce or enhance the presence of impurities of toxicological concern
3.4	**Product analysis**				
3.4.2	Impurities of toxicological concern	CR	CR	II	Required if the formulants – formulation process may potentially introduce or enhance the presence of impurities of toxicological concern
4	**Toxicology**				
4.3	**Short-term studies (TGAI)**				
4.3.2	Short-term oral (6–12 month) (non-rodent, e.g., dog)	CR	CR	II	Trigger: required if tier I toxicity tests indicate a need
4.3.4	Short-term dermal (90 d)	CR	CR	II	
4.3.5	Short-term dermal (21 d, 30 d)	CR	CR	II	
4.3.6	Short-term inhalation (90 d)	CR	CR	II	
4.3.7	Short-term inhalation (21 d, 30 d)	CR	CR	II	
4.3.8	Other short-term studies	CR	CR	II	
4.4	**Long-term studies (TGAI)**				
4.4.1	Chronic toxicity study	CR	CR	II, III	Trigger: required if adverse effects in mutagenicity and short-term studies; waived if long-term exposure above background levels can be excluded
4.4.2	Oncogenicity (rodent species 1)	CR	CR	II, III	
4.4.3	Oncogenicity (rodent species 2)	CR	CR	II, III	
4.4.4	Combined chronic–oncogenicity (rodent)	CR	CR	II, III	
4.5	**Special studies TGAI**				
4.5.1	Rat reproduction study	CR	CR	II, III	Trigger: required if tier I and tier II toxicity studies indicate a need
4.5.7	Genotoxicity: in vivo chromosomal aberrations	CR	CR	II, III	
4.5.8	Other genotoxicity studies	CR	CR	II, III	

Data code (DACO)	Title	Data required for SCLPs[1]	Data required for non-SCLPs[1]	Tier	Conditions
4.5.9	Rat pharmacokinetic–metabolite characterization studies	CR	CR	II, III	
4.5.12	Acute neurotoxicity - rat	CR	CR	II, III	
4.5.13	Rat 90-d neurotoxicity study	CR	CR	II, III	
4.8	**Other studies, data, and reports**				
4.8	Special studies (e.g., immunotoxicity)	CR	CR	II, III	Trigger: required if tier I and tier II toxicity studies indicate a need
5	**Exposure (occupational and bystander)**				
5.4	Mixer–loader–applicator – passive dosimetry data	CR	CR	II	Trigger: required if tier I toxicity tests indicate a need and product use involves human exposure
5.5	Mixer–loader–applicator – biological monitoring data	CR	CR	II, III	Trigger: required if tier I toxicity tests indicate a need and product use involves human exposure
5.6	Post-application – passive dosimetry data	CR	CR	II	
5.7	Post-application – biological monitoring data	CR	CR	II, III	
5.8	Dermal absorption	CR	CR	II, III	
5.9	Dislodgeable residues (foliar, soil, and surface)	CR	CR	II	
5.1	Ambient air samples (indoor–outdoor)	CR	CR	II	
5.11	Glove–clothing penetration data	CR	CR	II, III	
5.12	Epidemiology	CR	CR	II, III	
5.13	Package integrity study	CR	CR	II, III	
8	**Environmental chemistry and fate**				
8.1	**Summary**				
8.2	**Laboratory studies of physicochemical properties**				
8.2.3	**Laboratory studies of transformation (TGAI)**				Analysis must be conducted for each AIC; where data from tier I (TGAI) demonstrate hazard to biota, these data will be required on a case-by-case basis
8.2.3.2	Hydrolysis	—	CR	II	See 8.2.3
8.2.3.3	**Phototransformation (TGAI)**				
8.2.3.3.1	Soil	—	CR	II	See 8.2.3
8.2.3.3.2	Water	—	CR	II	See 8.2.3
8.2.3.4	**Biotransformation in soil (TGAI)**				
8.2.3.4.2	Aerobic soil 20°–30°C	—	CR	II	See 8.2.3
8.2.3.5	**Biotransformation in aquatic systems (TGAI)**				
8.2.3.5.2	Aerobic water 20°–30°C	—	CR	II	See 8.2.3
8.2.4	**Laboratory studies of mobility**				
8.2.4.2	Adsorption–desorption (TGAI)	—	CR	II	See 8.2.3

Data code (DACO)	Title	Data required for SCLPs[1]	Data required for non-SCLPs[1]	Tier	Conditions
8.2.4.6	Special studies: (a) leaching by water from dispenser (EP)	—	CR	II	See 8.2.3
	(b) volatization under conditions typical of use (EP)	—	CR	II	Where data from tier I (TGAI) demonstrate hazard to biota, these data will be required on a case-by-case basis
9	**Environmental toxicology**				
9.3	**Nontarget freshwater invertebrates (TGAI)**				Where broadcast or sprayed, these data are required for each TGAI to determine the risk to aquatic systems; in the absence of this information, an untreated buffer zone may be required adjacent to aquatic systems
9.3.3	*Daphnia* sp. chronic (life cycle)	—	CR	III	Where data from tier II demonstrate hazard to biota, these data will be required on a case-by-case basis
9.3.5	Laboratory studies with EP	—	CR	III	See 9.3.3
9.3.6	Field studies (EP)	—	CR	III	
9.4	**Nontarget marine invertebrates (TGAI)**				Where data from tier II (TGAI) demonstrate hazard to biota, these data will be required on a case-by-case basis
9.4.2	Acute (crustacean)	—	CR	III	See 9.4
9.4.3	Mollusk embryo larvae	—	CR	III	
9.4.4	Mollusk shell deposition	—	CR	III	
9.4.5	Chronic (mollusk or crustacean)	—	CR	III	
9.4.6	Laboratory studies with EP	—	CR	III	
9.4.7	Field studies (EP)	—	CR	III	
9.4.8	Bioconcentration–depuration (bivalve or crustacean)	—	CR	III	
9.7	**Wild mammals (TGAI)**				
9.7.2	Field studies (EP) (i.e., terrestrial animals)	—	CR	III	Where data from tier II (TGAI) demonstrate hazard to biota, these data will be required on a case-by-case basis
9.8	**Nontarget plants (TGAI)**				Where data from tier II (TGAI) demonstrate hazard to biota, these data will be required on a case-by-case basis
9.8.2	Freshwater algae	—	CR	III	See 9.8
9.8.3	Marine algae	—	CR	III	
9.8.4	Terrestrial vascular plants	—	CR	III	
9.8.5	Aquatic vascular plants	—	CR	III	
9.8.6	Laboratory studies with EP	—	CR	III	
9.8.7	Field studies (EP)	—	CR	III	

[1]CR, conditionally required; R, required.

Appendix V U.S. EPA List 4A, Minimum risk inerts (current)

Acetic acid
Agar
Alfalfa
Alfalfa meal
Almond hulls
Almond shells
Alpha cellulose
Apple pomace
Attapulgite-type clay
Beef fat
Beeswax
Beet powder
Bentonite
Bone meal
Bran
Bread crumbs
Calcareous shale
Calcite
Calcium carbonate
Canary seed
Cane syrup
Carbon dioxide
Cardboard
Carrageenan
Carrots
Casein
Cheese
Chlorophyll
Cinnamon
Citric acid
Citrus meal
Citrus pectin
Citrus pulp
Clam shells
Cloves
Cocoa
Cocoa shells
Cocoa shell flour
Cod liver oil
Coffee grounds
Cookies
Cork
Corn
Corn cobs
Corn flour
Corn meal
Corn oil
Cornstarch
Corn syrup
Cotton
Cottonseed meal
Cottonseed oil
Cracked oats
Cracked wheat
Dextran
Dextrose
Dolomite
Douglas-fir bark, ground
Eggs
Egg shells
Edible fish meal
Edible fish oil
Flour
Fuller's earth
Gelatin
Glue, as depolymerized animal collagen
Glycerin
Granite
Grape pomace
Graphite
Ground oats
Guar gum
Gum arabic
Gum tragacanth
Gypsum
Hearts of corn flour
Hydrogenated vegetable oils
Honey
Invert sugar
Invert syrup
Kaolinite-type clay
Lactose
Lanolin
Lard
Latex
Lecithin
Lime
Limestone
Linseed oil
Malt flavour
Meat meal
Meal scraps
Medicated feed
Mica
Milk
Millet seed
Mineral oil, USP
Molasses
Montmorillonite-type clay
Nitrogen
Nutria meat
Nylon
Oatmeal
Oats
Olive oil
Onions
Orange pulp
Oyster shells
Paper
Paprika
Paraffin wax
Peanut butter
Peanut oil
Peanuts
Peanut shells
Peat moss
Pecan shell flour
Pectin
Polyethylene film
Polyethylene pellets
Potatoes
Pumice
Raisins
Red cedar chips
Red dog flour
Rice
Rice hulls
Rubber
Rye flour
Safflower oil

Sawdust	Soy flour	Walnut flour
Seaweed, edible	Soy protein	Walnut shells
Shale	Sucrose	Water
Soapstone	Sugarbeet meal	Wheat
Sodium bicarbonate	Sunflower seeds	Wheat germ oil
Sodium chloride	Tallow	Whey
Sorbitol	Vanillin	Wintergreen oil
Soybean hulls	Vermiculite	Wool
Soybean meal	Vitamin C	Xanthan gum
Soybean oil	Vitamin E	Yeast

Note: Substances commonly consumed as foods also are assigned to this list.

Appendix VI List of relevant publications

Regulatory Authority

Pest Control Products Act (PCPA)
Pest Control Products Regulations
Food and Drugs Act (FDA)

Submission Formatting

Regulatory Proposal PRO98-02, *Organizing and Formatting a Complete Submission for Pest Control Products*

Guidelines for General Guidance and Background

Registration Handbook for Pest Control Products Under the Pest Control Products Act and Regulations

DIR93-07a	*Guidelines for Efficacy Assessment of Chemical Pesticides*
DIR93-17	*Assessment of the Economic Benefits of Pesticides*
T-1-255	*Guidelines for Determining Environmental Chemistry and Fate of Pesticides*
PRO96-01	*Management of Submissions Policy*
DIR98-01	*Good Laboratory Practice*
DIR98-02	*Residue Chemistry Guidelines*
DIR98-03	*Chemistry Requirements for the Registration of a Manufacturing Concentrate or an End-Use Product Formulated from Registered Technical Grade of Active Ingredients or Integrated System Products*
DIR98-04	*Chemistry Requirements for the Registration of a Technical Grade of Active Ingredient or an Integrated System Product*
DIR98-05	*Chemical Pesticides Research Permit Guidelines*

Updated Procedures for Joint Review of Microbials and Semiochemicals (North American Free Trade Agreement (NAFTA) Technical Working Group on Pesticides)

Note: The above documents may be revised in the future. When a revised or final document is issued, the title may be slightly modified and there will be a new reference number. The applicant should contact the PMRA or refer to the PMRA web site, accessed through the Health Canada site at http://www.hc-sc.gc.ca/, to determine whether any of the listed references have been superseded by more recent or final versions.