Promoting innovation through a new group standard for straight-chained lepidopteran sex pheromones

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Abstract Group standards are a New Zealand regulatory approach to managing a group of hazardous substances of a similar nature, type or having similar circumstances of use, such as paints or cosmetics. Straight-chained lepidopteran sex pheromones (SCLP) can be used for population monitoring or for mating disruption to help reduce reliance on insecticides. To avoid the need for each pheromone substance to be registered separately under Part 5 of the Hazardous Substances and New Organisms Act (1996), Plant & Food Research has developed the Straight-chained Lepidopteran Sex Pheromone Group Standard (HSR100628). This means that new SCLP products for research or sale can be developed, imported or manufactured more efficiently and effectively, promoting innovation in an area with small market size but large beneficial impact on plant protection. Regulatory aspects of pheromones and semiochemicals for research and commercial use are discussed.

Keywords HSR100628, mating disruption, monitoring, pheromone, straight-chained lepidopteran sex pheromone group standard.

INTRODUCTION

Insects use volatile chemicals to communicate with each other in many ways and there are consequently many types of insect pheromones, including aggregation pheromones, trail pheromones and alarm pheromones, of which moth sex pheromones are the largest class (El-Sayed 2012). It has long been recognised that insect sex pheromones offer considerable opportunities to improve pest management, reducing the use and reliance on more hazardous materials, such as many insecticides (Witzgall et al. 2010). The use of sex pheromones is based on two principle modes of action: (i) attraction to point-source lures for population monitoring and control by mass trapping and attract-and-kill, and (ii) air permeation, leading to communication and mating disruption (Witzgall et al. 2010). In New Zealand, there are a number of pheromone lure products available for monitoring both moth pests and beneficial insects and for mating disruption. These products have a proven track record in pest management (Suckling et al. 2008a; Suckling et al. 2012).

This paper discusses the regulation of pheromones, including the first group standard for research and commercialisation of products for population monitoring and control by mass trapping and attract-and-kill, and for mating disruption.
in plant protection. This group standard aims to provide a simpler pathway to market and promote innovation with these substances.

INTERNATIONAL REGULATORY OVERSIGHT OF PHEROMONES FOR RESEARCH AND COMMERCIAL USE

Straight-chained moth pheromones have been recognised by the United States Environmental Protection Agency for many years to be of very low human and environmental hazard (Touhey 1990) and they record that “these compounds do not present any known risks to humans or the environment” (US EPA 2011), leading to fast-track approvals for control using mating disruption (US Federal Register 1994). The US EPA (2011) reports that “Based on low toxicity in animal testing, and expected low exposure to humans, no risk to human health is expected from the use of these pheromones. During more than 10 years of use of lepidopteran pheromones as pesticides, no adverse effects have been reported”. The document goes on to note that “The safety record for lepidopteran pheromones has allowed the Agency to conclude that consumption of food containing residues of the pheromones presents no risk”.

Based upon this, when used at a rate below 150 g of active ingredient/acre/year (=375 g of active ingredient/ha/year) and applied in or onto raw agricultural commodities, these pheromones are exempt from the requirement of a tolerance. Toxicology and environmental data requirements for manufacturing use products are not required, and toxicology and environmental data requirements for end use products are greatly reduced. In addition, these pheromones can be used experimentally without an experimental use permit on areas of up to 250 acres, versus the 10-acre limit imposed on other pesticides (US EPA 2009).

Perhaps due to these reduced information requirements in USA, it is difficult to find recent toxicological data on moth pheromones. Recent re-investigation of the toxicological profile of the pheromone for light brown apple moth was undertaken after the aerial spray of pheromone in California produced a major public controversy. However, the toxicological results confirmed the extremely low hazard profile of these compounds (Anon. 2008), and their aerial or ground application in residential areas is allowed in USA. In certain OECD countries a regulatory approach has been developed that recognises the lower potential risk of arthropod semiochemicals (including pheromones) to human health and the environment than conventional pesticides. This approach allows a substantial reduction in data requirements, particularly for straight-chained lepidopteran sex pheromones (SCLP) as compared with conventional chemical pesticides (OECD 2002). The OECD Working Group on Pesticides has developed a guidance document that aims to harmonise the data requirements for registration. Participating countries may elect to waive data requirements or require additional data (Jones 2001). No mention has been found in either the US EPA or OECD documentation of any regulation of lures, which typically release these natural products at rates similar to insects. Lacey & Sanders (1992) estimated the release of pheromone from female oriental fruit moth Grapholita molesta at $8.5 \times 10^{-9}$ g/h, so it is easy to understand why there has been no risk-based regulation of moth pheromone lures internationally. In New Zealand, if the concentration of a substance in a product is below a certain threshold, products may be classified as non-hazardous. This is the case with lepidopteran lure products available commercially (Suckling et al. 2012).

REGULATORY REQUIREMENTS IN NEW ZEALAND

There are two Acts in New Zealand that regulate the use of pheromones in crops. These are the Agricultural Compounds and Veterinary Medicines Act 1997 (ACVM), which is administered by the New Zealand Food Safety Authority, and the Hazardous Substances and New Organisms Act 1996 (HSNO), which is administered by the Environmental Protection Authority (formerly the Environmental Risk Management Authority, hereafter the Authority). Under the ACVM, ‘repellants’ and ‘attractants’ are exempt from registration. However, pheromones are treated as hazardous substances under HSNO, due to reported toxicity to aquatic algae and risk of skin sensitisation to humans.
The HSNO Act requires that ‘approval’ be sought to import or manufacture a hazardous substance. An approval sets out conditions that enable hazardous substances to be managed safely. This approval may be made under Part 5 of the HSNO Act (which is for a single substance) or under Part 6A (a group standard approval given by the Authority for a group of hazardous substances of a similar nature, type, or having similar circumstances of use). Approval may be sought to work in ‘containment’ (an approval that allows field testing) or for ‘release’ (an approval that allows commercial use). The approval may be for a technical, active ingredient(s), and/or a formulation(s) and/or a product(s). There is allowance for the concentration of the active ingredient in a product to be considered in the application process. At a level below a certain concentration (threshold), a substance may be classified as non-hazardous. Depending upon the risk of the substance, there are different assessment pathways with varying fees, requirements for public notification and statutory time frames.

Until the introduction of this group standard, the usual process for the development of commercial pheromones was to apply for a Part 5 approval. Some mating disruption products have been eligible to apply for a Part 5 approval by the rapid assessment pathway as they met one of the criteria for rapid assessment. These criteria are that the substance is: (i) similar to an already approved substance and (ii) low hazard i.e. ‘the substance has one or more hazardous properties and each hazardous property has the least degree of hazard for that property’. Rapid assessment has a shorter statutory time frame (10 working days) with lower application fees ($575) than a full release application, which may require notification and take up to 30 working days, with fees as high as $17,250. Many commercially available lure products fall below the threshold for hazard and do not require approval based on concentration. For pheromone use for insect pests in horticultural crops, the Authority has issued Part 5 release approvals allowing sale since 2006 and release approvals allowing field trials under containment since 2008.

**BENEFITS OF THE GROUP STANDARD**

The regulatory environment is a key determinant of innovation, and New Zealand has offered international leadership in the management of hazardous substances, through the development of group standards for products of similar risk. As the applicant, Plant & Food Research believed that the SCLP group standard would provide an efficient pathway to market and promote innovation by:

1. the elimination of individual Part 5 application costs, as users do not need to apply to the Authority to use the group standard;
2. the reduction in time delays associated with Part 5 approval applications for both trialling and releasing the product for sale;
3. approval of SCLP for small markets where the provision of toxicological and ecological data can be inhibitory. This would be achieved through the allowance of the use of safety data sheets (SDS) for an appropriate analogue where no SDS is available from the manufacturer or importer. This recognises the similarities in low risks within the SCLP group.
4. ensuring a predictable regulatory outcome, eliminating one of the hurdles in commercial development of a pheromone product.

Before establishing a group standard, the Authority needed to be satisfied that the group standard would be a more efficient and effective way of managing the risks of all the substances in the identified group. In approving the application, the Authority considered this was satisfied through:

1. reduced effort assessing and approving individual applications by the Authority, the Department of Labour or other recognised regulatory bodies;
2. provision of a document with a simplified format and a greater level of guidance than a Part 5 approval.

**APPLICATION PROCESS**

With these benefits in mind, Plant & Food Research developed a group standard for straight-
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chained lepidopteran sex pheromones. The application for this group standard was formally received by Authority on the 27 June 2011 and publicly notified on the Authority website from 6 July 2011. Various government departments, Crown entities and interested parties, which in the opinion of Authority would be likely to have an interest in the application, were notified of the receipt of the application on the Authority website and provided with an opportunity to comment or make a public submission on the application. There was one submission received in support of the proposal (Northland Regional Council). The submitter highlighted the importance of the use of pheromones in the management of horticultural and agricultural pests. This submission supported work by Jamieson et al. (2004) on the use of pheromones in the management of guava moth Coscinoptycha improbana, a serious pest of macadamias and feijoas in Northland, and by Dymock et al. (2009) who describe the use of pheromones for monitoring and predicting populations of the tropical grass webworm Herpetogramma licarsisalis, a pest of kikuyu (Pennisetum clandestinum) pasture in Northland. Subsequently, minor alterations were made to the definition of the scope of the group standard and a number of conditions were set to ensure consistency with existing group standards for substances with similar hazards and properties. The authority considered that the risks posed by the substances are negligible and that the group standard provides a mechanism for the effective and efficient regulatory approval of SCLP. The proposal to issue the new group standard was considered by the Authority on the 13 December 2011 and notified as approved in the New Zealand Gazette on the 16 February 2012. The Straight-chained Lepidopteran Sex Pheromone Group Standard (HSR100628) came into force on the 16 March 2012.

SCOPE OF THE GROUP STANDARD

The group standard applies to any imported or manufactured substance containing SCLP that is to be used for monitoring or direct behavioural control of insects. SCLPs covered by the group standard are defined in the document as: the group of pheromones consisting of unbranched aliphatics having a chain of eight to 24 carbons, containing up to four double bonds, usually, but not necessarily ending in an alcohol, acetate, ketone or aldehyde functional group. SCLP substances may be a technical pheromone substance, a pheromone-containing formulation or a pheromone-containing product. The group standard may be used for a substance in development or a product at commercialisation.

To be covered by the group standard, the pheromone-containing product must have a solid delivery device that delivers the pheromone substance by gradual emission to give a concentration no greater that 1.1 ng/m³/day for a maximum of 180 days/year. A maximum application rate of 375 g active ingredient/ha/year has been set as this level was considered comparable to naturally occurring emissions of pheromones during an infestation and safe for non-target species or the environment (OECD 2002). The delivery device may be: rubber septa, metered aerosol can, amorphous dollop with a volume of greater than 1 mm³, twist-tie dispenser or a sachet. Where insects other than moths may be controlled by SCLP, the group standard may still be used. One potential example is the Argentine ant that coincidentally uses a SCLP for trail marking, which can disrupt foraging (Suckling et al. 2010).

Certain substances are excluded from coverage by the group standard. These are substances that are: explosive (HSNO class 1), flammable (HSNO class 3.1A, class 4), oxidative (HSNO class 5), of acute toxicity (HSNO 6.1A or 6.1B class), of carcinogenic toxicity (HSNO 6.7A or 6.7B class) or skin corrosive (HSNO 8.2A). To be covered by the group standard, SCLP substances must be manufactured or stored in a place of work and cannot be applied into or onto water or in a wide-dispersive fashion. In most cases, products must not contain any chemical that is not included on the Inventory of Chemicals administered by the Authority (www.epa.govt.nz).

CONDITIONS OF THE GROUP STANDARD

Any new SCLP substance that fits the criteria of the Straight-chained Lepidopteran Sex Pheromone Group Standard is automatically deemed an
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approved substance under HSNO. In order to be compliant, the conditions of the group standard must be met. These conditions detail requirements around: information, site and storage, approved handler and tracking, packaging, equipment, transportation, disposal, exposure limits and notification to the Authority. Requirements differ depending upon the hazard class, concentration and quantities of the SCLP substance(s) being dealt with.

SUBSTANCES NOT WITHIN THE SCOPE OF THE GROUP STANDARD
Pheromones and other semiochemicals that are not within the scope of the Straight-chained Lepidopteran Sex Pheromone Group Standard may be approved under a Part 5 approval or another group standard. An example is Lurem-TR, an attractant for monitoring thrips (HSR100566). After advice from the Authority, lures for the burnt pine longhorn beetle, *Arhopalus ferus*, which contained the essential oil alpha-pinene (Brockerhoff et al. 2006) were released for use under the Food Additives and Fragrance Materials (Flammable) Group Standard 2006 and the Denatured Ethanol Group Standard 2006. These examples illustrate the complexity of this area.

Many other pheromones and semiochemicals are not covered by a group standard but have potential for improving pest management or biosecurity, including parasitoid pheromones for use in biological control (Suckling et al. 2010), mealybug (*Pseudococcus* spp.) pheromones (El-Sayed et al. 2010), apple leaf curling midge (*Dasinuera mali*) pheromones (Suckling et al. 2007), grass grub (*Costelytra zealandica*) pheromone (Unelius et al. 2008) and exotic fruit fly attractants (Suckling et al. 2008b). Some of these may not need approval due to the small quantities involved in lures, but have not been assessed as yet.

Non-pheromone semiochemicals can include natural substances such as fruit, foliage or flower odours to attract insects in traps. Some of these substances can cause skin irritation or other symptoms if applied in sufficient quantity, but in reality the small amounts used in traps seem unlikely to cause such adverse effects. No other jurisdictions are known to regulate natural odours, since common sense indicates that plants produce vast quantities of them and these sources are not considered hazardous or regulated. An example of such a substance is cis-jasmone, a floral volatile identified from honeysuckle that attracts New Zealand flower thrips (*Thrips obscuratus*) (El-Sayed et al. 2009). These natural substances are likely to be of broadly similar hazard profile and use pattern to SCLP pheromones, and their successful commercial use could be expected to have similar beneficial effects on insecticide risk reduction.

Release of ‘natural’ scents indoors represents a major growth industry, but their release in nature from man-made formulations ironically remains problematical at the regulatory level.

It is unlikely that these other pheromones and semiochemicals when used for pest management would normally be covered by the Food Additives and Fragrance Materials Group Standard, as compliance with conditions of this group standard could prove difficult. Although perfumes are included in the scope of the Cosmetic Products Group Standard, these must be for a cosmetic product. At this stage commercialisation could proceed only after acquiring a Part 5 approval. However, a lack of toxicological data may also be limiting for some these substances, as could the cost of Part 5 for niche market applications.

FIELD TRIALLING PHEROMONES AND SEMIOCHEMICALS
While approval under a group standard is suitable for products at a commercial stage, conducting field trials under this type of approval may not be feasible. Examples include trials with multiple substances (some of which may not be covered by the group standard) or for substances where data are lacking. This means a Part 5 approval for work ‘in containment’ must be used. The Authority also has the ability to issue ‘generic’ containment approvals that allow field testing of a group of similar substances, for example ‘plant protection compounds’. Plant & Food Research has been conducting field trials on pheromones under this type of approval. Under this approval the Authority requires advance notification for
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all active ingredients. Given the low risk to users and the environment from the quantities being trialled, and the potential benefits from hazardous substance risk reduction, conditions set in this approval seem onerous but it is hoped that the new group standard will facilitate reduced requirements for SCLP. Adopting an approach similar to that of the USA for experimental research would facilitate field testing and development of pheromones and semiochemicals and aid their commercialisation. This situation contrasts with Australia, where problems in the commercial development of semiochemicals have been highlighted (Gregg 2010).

CONCLUSIONS
This group standard promotes innovation by allowing new SCLP substances for research or sale to be developed, imported or manufactured more efficiently and effectively by: (i) reducing individual Part 5 application costs; (ii) reducing time delays in both trialling and releasing the product for sale; (iii) reducing effort in assessment and approval of individual applications; (iv) provision of a document that achieves better management of risk; and (v) ensuring predictable regulatory outcomes. Most other pheromones and semiochemicals still require individual Part 5 approvals for research or commercialisation. With the rising demand for pesticide risk reduction along with a more efficient and effective regulatory approach, the prospect for use of pheromone products in New Zealand looks set to grow, but further reductions in the regulatory burden appear warranted.

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