Consensus Statement on Human Health Aspects of the Aerial Application of Microencapsulated Pheromones to Combat the Light Brown Apple Moth

October 31, 2007

This document represents a scientific consensus of the Department of Pesticide Regulation (DPR) and the Office of Environmental Health Hazard Assessment (OEHHA) on the available health and safety data of the pheromone products associated with the Light Brown Apple Moth (LBAM) eradication program. This is one of the first instances of the aerial application of this material over a highly populated area. Scientists from DPR and OEHHA reviewed the available information and prepared this document with input from the Department of Public Health. This document is not intended to be a detailed human health risk assessment, an epidemiological study of exposed individuals, or an evaluation of occupational exposure. The purpose of this document is to provide information on the toxicity of microencapsulated pheromones, the potential for exposure, and to provide recommendations.

General Information

Pheromones are naturally occurring volatile chemicals and have been loosely described as "pheromone perfumes." Certain insect species produce them, in very small amounts, to influence the behavior of other individuals of the same species. Many lepidopteran species (butterflies and moths) use pheromones to attract mates. These pheromones consist of mixtures of similar chemicals, and the relative amounts of several pheromone chemicals determine which specific moths are attracted.

Synthetically produced pheromones can be used to control insect pests. All the lepidopteran pheromones approved for pest control use are chemicals produced by female moths to attract mates. By releasing a specific pheromone mixture into the air, it is possible to disorient males looking for females. The pheromone alters behavior, not the insects' health or reproductive competence; but it results in many females' failure to mate and lay eggs. Pheromone pesticide products may be applied using slow-release dispensers (often attached to trees) or applied by ground or aerial spray equipment.

Toxicity Information on the Pheromone Active Ingredients in the Products Used to Combat LBAM

The U. S. Environmental Protection Agency (U.S. EPA) defines lepidopteran pheromones chemically as unbranched aliphatic chains (9 to 18 carbon atoms) ending in an alcohol, aldehyde, or acetate functional group and containing up to 3 double bonds in the chain. U.S. EPA has also made two relevant determinations about these chemicals: 1) that they are sufficiently similar toxicologically to be considered as a group, that is, toxicology data on one pheromone is applicable to the other pheromones; and 2) that their toxicity is so minor that they are exempt from the requirement of a tolerance (Federal Register 60, No. 168, pp 45060 to 45062, August 30, 1995). These pheromones are often referred to as Straight Chained Lepidopteran Pheromones (SCLPs).

Active ingredients (A.I.s) are the chemicals in a pesticide product that are effective against the targeted pest. The various products being proposed for use on LBAM contain similar active ingredients in different combinations and ratios. Checkmate OLR-F contains the pheromones (E)-11-tetradecen-1-yl acetate and (Z)-11-tetradecen-l-yl acetate. Checkmate LBAM-F contains the pheromones (E)-11-tetradecen-1-yl acetate and (E, E)-9,11-tetradecen-1-yl acetate. It is the choice of these chemicals and their ratios that results in the specific mating disruption activity for LBAM. Checkmate OLR-F targets the Omnivorous Leaf Roller but also has activity with the LBAM and was used in the first aerial applications in Monterey. Checkmate LBAM-F more specifically targets the LBAM and the California Department of Food and Agriculture (CDFA) has indicated that it will be used in future aerial applications.

DPR and OEHHA scientists have not reviewed toxicity studies on all the specific active ingredients in LBAM pheromone products; however, they have reviewed acute toxicity studies on other lepidopteran pheromones, and according to the USEPA determination, these studies can be considered to apply to any lepidopteran pheromone. These studies show very low acute oral and dermal toxicity. As an initial screen, toxicologists describe acute toxicity by the LD_{50}, the dose that kills half the test animals. The pheromone studies used extremely high dosages, but did not kill any animals. Consequently, scientists cannot determine the LD_{50}, but can conclude that it is larger than the doses used.

An oral toxicity study in rats produced no mortality and no toxic signs at a dosage of 5,000 mg/kg. Thus, the oral LD_{50} is > 5,000 mg/kg, placing it in Category IV for oral toxicity. (These U.S. EPA-derived toxicity categories are used to select the appropriate signal words to alert users to specific hazards and can also be used to compare the acute toxicity of different chemicals. The categories include Category I- High Toxicity, Category II- Moderate Toxicity, Category III- Low Toxicity, and Category IV- Very Low Toxicity). In a rabbit dermal toxicity study using a single dose of 2,000 mg/kg, there was some diarrhea but no mortality. Thus the dermal LD_{50} is >2,000 mg/kg, placing it in Category III for dermal toxicity. Eye and skin irritation studies indicated the potential for mild to moderate skin and eye irritation (Category III). A study on a chemical similar to one of the active ingredients in the LBAM pheromone does indicate some potential for limited dermal sensitization (Category III), while other studies reviewed by USEPA did not indicate dermal sensitization. The maximum application rates for lepidopteran pheromone products range from 15 to 37.5 grams (about 0.5 to 1.3 ounces) of A.I. per acre per application and a total of 150 grams (about 5 ounces) of A.I. per acre per year. These are very low application rates compared with the dose levels used in the above studies. Chronic toxicity is not addressed in this document because there will not be long-term exposure to the pheromone product.

After reviewing the toxicological data of SCLPs, scientists at the USEPA concluded that "*Based on low toxicity in animal testing, and expected low exposures 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, no adverse effects have been reported. ... The*

safety record for lepidopteran pheromones has allowed the Agency to conclude that consumption of food containing residues of the pheromones presents no risk. ... Adverse effects on non target organisms (mammals, birds, and aquatic organisms) are not expected because these pheromones are released in very small amounts to the environment and act on a select group of insects." This statement refers primarily to the pheromone active ingredients generally used in emitter devices or aerial application over agricultural areas rather than aerial application over populated areas (such as in the present situation).

Toxicity Information on the Product Formulations Used to Combat LBAM

Besides the A.I.s, a product formulation consists of "inert ingredients" that are in the formulation to improve performance, as a manufacturing byproduct, as a diluent, or as a reactant from the manufacturing process. The LBAM pheromone products are available in three formulation types. Each formulation combines the pheromones with materials that release it into the atmosphere slowly, so that the products remain active for a period of time. The dispenser formulation (also referred to as twist-tie) consists of a plastic tube containing the active ingredients. The plastic tube is attached to the target plants, slowly emitting the pheromones. This product has been used extensively in Australia and New Zealand to combat LBAM. Another formulation is a flake (Disrupt Micro-Flake) made up primarily of the A.I.s, a rigid plastic film, and resins. Micro-Tac or Micro-Tac II (adjuvants) may be used with the Micro-Flake to aid in adhesion to foliage. Checkmate OLR-F and Checkmate LBAM-F are microencapsulated forms. Both Micro-Flake and Checkmate products are approved for either ground or aerial application.

Much attention and controversy has centered on the identification and potential toxicity of the individual inert ingredients in the Checkmate OLR-F and LBAM-F products; however, the identity of the inert ingredients has recently been made public. In a recent letter to Assemblymember John Laird from CDFA Secretary A. G. Kawamura, all the ingredients in Checkmate LBAM-F are identified as:

1) Water, the main ingredient.
2) (E)-11tetradecen-l-yl acetate- the pheromone.
3) (E, E)-9,11 tetradecadien-1-yl acetate- the pheromone.
4) Ammonium phosphate- commonly used in "crystal growing" kits for children and as a plant nutrient.
5) 1,2-benzisothiazol-3-one- used as antibacterial and antifungal agents in a variety of products.
6) 2-hydroxy-4-n-octyloxybenzophenone- used in sunscreen and in lots of products made of plastics, including food containers; useful for its UV-blocking properties.
7) Cross linked polyurea polymer- commonly used in manufacturing of plastics such as polyurethane foam production, waterproofing, insulation, and micro encapsulation agent for pesticides.
8) Butylated Hydroxytoluene- common food preservative.

9) Polyvinyl alcohol- polymer commonly used in shampoos and cosmetics, feminine hygiene and incontinence products, children's play putty, glue, lubrication drops for hard contact lens wearers and other products.
10) Tricaprylyl methyl ammonium chloride- commonly used in the manufacture of various pesticides and pharmaceuticals; contributes to product purity.
11) Sodium Phosphate- naturally occurring substance. Sodium phosphate is also an additive in egg products and is a prescribed laxative prior to procedures such as colonoscopy.

The percentages of these ingredients are still confidential business information. This document does not review the toxicity of these compounds individually, but addresses the formulated product.

While this information is important, DPR noted that inert ingredients other than water are present in very small amounts and exist primarily as the polyurea shell enclosing the pheromones. These particles consist mostly of pheromones. After application of the particles, the pheromones are slowly emitted over a 30- to 90-day period, and the polyurea shell will biodegrade into urea, a low toxicity compound normally found as a result of the breakdown of proteins in the human body.

Another important point is that DPR scientists have reviewed the most relevant data: toxicity studies on the formulated product as a whole. DPR scientists reviewed an acute dermal toxicity study using Checkmate PBW-F, which uses the same microencapsulation as Checkmate OLR-F and LBAM-F. The primary difference is in the selection of pheromones contained within the microencapsulated particles. In the study of Checkmate PBW-F, 2,000 mg/kg was applied to the skin of rabbits and resulted in no mortality, but some diarrhea. The results led to a Category III rating for dermal toxicity. Similarly, an eye irritation study in rabbits, in which 100 mg doses were instilled in the eyes, led to a Category III rating for eye irritation, which means the product was moderately irritating.

Materials that cause eye and skin irritation could reasonably be expected to cause some respiratory irritation if a sufficient amount were inhaled. The animal study results are consistent with the Suterra Checkmate OLR-F and LBAM-F labels that state that the products cause moderate eye and skin irritation. This label designation is for the undiluted product rather than for the significantly diluted water suspension that is actually applied.

The microcapsule particles are very large by inhalation standards (25 micrometers in diameter or larger) and unable to reach the deep lung. As a result, an inhalation toxicity study, which is designed to examine systemic effects resulting from inhalation into the lung, would not be useful and was not conducted. If inhaled, because of the large size, these microcapsules are not likely to reach the pulmonary (air exchange) region of the lung. However, such large particles are likely to be deposited in the nasal passages, pharynx, larynx, and tracheo-bronchial region and are either absorbed or moved to the larynx and swallowed. If a sufficient amount of large particles (regardless of

composition) is inhaled, it is plausible that it could cause irritation of the throat, coughing, sneezing, and excess mucus production in the upper respiratory system.

Taken together, the toxicity data on the pheromones and on microencapsulated products suggest the possibility that exposure to a sufficient amount of airborne Checkmate microcapsule particles could result in some level of eye, skin, or respiratory irritation. However, as the product is diluted and applied over a large area, the degree of exposure as well as the potential for irritation should decrease significantly.

Application and Deposition

The maximum application rates allowed by the label are 20 grams of A.I. per acre per application, corresponding to 83 grams per acre of the Checkmate product. These application rates are very low, both in absolute terms and when compared with the ground or aerial application rates of almost any other pesticide. To put this amount in perspective, a tablespoon of sugar weighs almost 20 grams. The product consists primarily of the polyurea-microencapsulated pheromone suspended in water.

The material applied is a diluted mixture that contains 2.1% A.I. (pheromone). Tank samples collected during the first week of application showed concentrations of the A.I. varied from 0.69% to 3.0%, indicating settling might have occurred in the mixture. Some visual observations also indicated a problem with the product staying well mixed in the application equipment. Changes are being made to the mixing and loading equipment to address this problem in future applications. At the highest proposed application rate, the theoretical concentration of the product hitting the ground should be 0.460 milligrams A.I./square foot. During the first week of application, deposition measurements showed deposition rates below this calculated theoretical maximum. (These data will be available later.) This indicates there were not “pockets” of higher than intended deposition resulting from the tank concentration variations.

Illness Complaints

Before the current LBAM eradication effort, DPR had received few complaints involving pheromones, and has no persuasive cases on file attributed to pheromone exposure in the absence of additional pesticides. DPR evaluated two cases, one in 1982 and one in 1989, as “unlikely” to be related to exposure to pheromone alone or to pheromone with an adjuvant. Another 1982 case provided insufficient information to evaluate. These cases did not involve Checkmate products.

California law requires physicians to report known or suspected pesticide-related illnesses to their local health department within 24 hours after seeing a patient. The health department forwards these reports to the State. Only one pesticide illness report (PIR) was received from the Monterey County Health Department during or soon after the Checkmate spraying September 9-12, 2007. A 57-year old man was diagnosed with pharyngeal irritation after visiting a doctor on September 16. The exposure date was listed as September 16, which was after the Checkmate spraying had been completed.

However, additional data clarified that the exposure occurred on September 11. DPR's surveillance system, like others, under detects pesticide illnesses for various reasons, including that pesticide illnesses may mimic other illnesses and that physicians and patients may not ascribe symptoms to pesticide exposure.

The California Environmental Protection Agency (Cal/EPA) received a compilation of e-mails from area citizens with complaints of adverse reactions to the aerial spraying of Checkmate from September 9 to 12, 2007. Although it is likely that we do not have complete reporting of all health complaints attributed to spraying, certain patterns do emerge from the information we have. Upper respiratory symptoms, including cough, sore throat, runny nose, and congestion were the predominant complaints. Also frequently reported were headaches, itchy eyes, nose, and throat; shortness of breath; muscle aches; diarrhea; and fatigue.

Most reported symptoms are consistent with inhalation of a nonspecific irritant material, but because they are also consistent with other possible causes, it is not possible to confirm the symptoms are or are not due to the application of Checkmate. For example, some of the symptoms are consistent with infectious or allergic conditions or other health effects not caused by exposure to Checkmate.

Based on the available toxicological information on the Checkmate product, some of the reported health effects such as eye, skin, or respiratory irritation could be consistent with inhalation of a sufficient amount of the applied material. But because the measurements confirm the application rate was extremely low, it is likely that exposure occurred at levels below those that would be expected to result in health effects. However, because not all health effects can be predicted and because the general population includes susceptible populations, such as children, the elderly, and those with chronic diseases, we cannot provide a definitive cause for their symptoms. A well designed formalized study and tracking program that looks at several factors including, but not limited to both long- and short-term health outcomes, exposed and unexposed persons, the potential effects of stress and outreach methods on illness complaints would be needed to begin to properly address the question of causality.

Conclusions

- The toxicity data on the pheromone active ingredients as well as on microencapsulated pheromone product formulations suggest that exposure to a high dose of airborne Checkmate microcapsule particles could cause eye, skin, or respiratory irritation.

- The application rates were extremely low. Measured deposition rates fell below the proposed rate of 20 grams A.I. per acre.

- Public concern has centered on the previously undisclosed inert ingredients, which have now been disclosed. The bulk of the inerts is water, as the microencapsulated polyurea particles consist primarily of the pheromone active ingredients. The

polyurea shell exists only as a component of the particles, and makes up only a small percentage of the particle weight.

- The toxicological information on the Checkmate product indicates that exposure to high levels of the applied material would be consistent with many of the reported symptoms. However, because the application rate was extremely low, it is likely that exposure occurred at levels below those that would be expected to result in health effects.

Recommendations to CDFA

(Note: Some of these recommendations may already have been implemented.)

- In describing the long history of safe use of lepidopteran pheromone products, care should be taken to indicate clearly that most of this use involved pheromone dispensers (for example, twist ties) and aerial application over agricultural areas.

- The outreach program should better explain the rationale behind the choice of specific eradication methods.

- A credible and trusted mechanism for collecting symptom complaints from people in the eradication zone should be established.

- The eradication program should have a public notification and education component that encourages residents to consult doctors about symptoms that they attribute to pesticide exposure and to remind their doctors that California law requires doctors to report pesticide illnesses. These official records can be used in follow-up investigations by local and State health and agricultural staff to identify adverse health reactions from particular pesticide formulations or application techniques.

- Prior to spraying, the State should work with local health officers to ensure that physicians and other health care providers are given information on the application; what, if any, symptoms are likely to be seen; and how to report, among others. In general, the physicians and health care providers should be informed of the illness reporting requirements and should receive training on pesticide poisoning recognition and management.

- Air sampling should be considered to investigate the contribution of the aerially released microcapsule particles to the overall ambient air particulate load.

- A formalized plan to address the above recommendations should be in place prior to spraying.

- A well designed formalized study and tracking program that looks at a number of factors including, but not limited to both long- and short-term health outcomes, exposed and unexposed persons, the potential effects of stress and outreach methods

on illness complaints would be needed to begin to properly address the question of causality.