Human Health Risk Assessment of Isomate LBAM Plus

April 2009

Human Health Risk Assessment of Isomate LBAM Plus

Prepared by

Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

April 2009

CONTRIBUTORS AND ACKNOWLEDGEMENT

Author
David Ting, Ph.D.

Primary Reviewers
James Collins, Ph.D.
David Siegel, Ph.D.

Final Reviewers
Anna Fan, Ph.D.
George Alexeeff, Ph.D.

Acknowledgement
A draft of this document has been reviewed by the Department of Pesticide Regulation, California Environmental Protection Agency and the California Department of Public Health.

Human Health Risk Assessment of Isomate LBAM Plus

Executive Summary

This document describes a human health risk assessment on the use of Isomate LBAM Plus conducted by the Office of Environmental Health Hazard Assessment (OEHHA), California Environmental Protection Agency. The Isomate LBAM Plus device, also known as a "twist tie," is a pheromone dispenser. It consists of an aluminum wire and a hollow plastic tube that contains moth pheromones and other additives. It is one of the tools employed by the California Department of Food and Agriculture (CDFA) to control and eradicate the light brown apple moth (LBAM). LBAM is an invasive pest that was first detected in California in early 2007.

In the wild, female moths release a sex pheromone into the air to attract male moths. Male moths detect the pheromone "scent" with a specialized sensory organ and follow it upwind to locate and then mate with the females. The purpose of the pheromone dispenser is to disrupt this communication system and suppress mating and reproduction by preventing male moths from finding females. Pheromones do not kill or harm the moths.

OEHHA evaluated potential health risks associated with exposures to the pheromones and additives in Isomate LBAM Plus. The pheromones belong to a class of chemicals known as Straight Chain Lepidopteran Pheromones (SCLPs). SCLPs share many chemical structure features. The United States Environmental Protection Agency (US EPA) has determined that SCLPs are sufficiently similar toxicologically to be considered as a group. Toxicology data of one member of the SCLPs can be applied to other members. This approach was also used in this evaluation.

OEHHA's evaluation indicates that inhalation is the most relevant route of exposure and the use of Isomate LBAM Plus is not likely to pose a health hazard to humans, including children. The reasons are as follows:

- Low toxicity of SCLPs
- Low application rate of the dispenser
- Low release rate of pheromones from the dispenser
- Low expected human exposure to the pheromones

Furthermore, pheromones in Isomate LBAM Plus have chemical structures similar to the common food items and nutrients known as long-chain fatty acids, and they are expected to be metabolized in a similar fashion in the body. These chemicals are not likely to accumulate in the body or persist in the environment.

Pheromones in Isomate LBAM Plus have been shown to be slight skin irritants in rabbits. While no eye irritation tests have been performed on the pheromones, some SCLPs have

been shown to be slight eye irritants as well, when the chemicals are placed directly into the eye. Therefore, as a precautionary measure, it is advisable to minimize the chance of eye or skin contact with the pheromones.

Under Federal law, the identity and the composition by weight of the additives in a pesticide product such as Isomate LBAM Plus are considered trade secrets. However, scientists from OEHHA had legal access to this information and used it in the assessment. They are prohibited from releasing this information to the public.

OEHHA's evaluation indicates the additives in Isomate LBAM Plus are not likely to pose a health hazard to adults and children. Nevertheless, the additives are potential eye and skin irritants, and as a precautionary measure, it is advisable to minimize the chance of eye or skin contact with the additives.

Introduction

Isomate LBAM Plus (twist tie) is a pheromone dispenser manufactured by the Pacific Biocontrol Corp. It is one of the tools used by the California Department of Food and Agriculture (CDFA) to eradicate the light brown apple moth (LBAM). In the wild, female moths release a sex pheromone into the air to attract male moths. Male moths detect the pheromone "scent" with a special sensory organ and follow it upwind to locate and then mate with the females. The purpose of pheromone dispensers is to disrupt this communication system and suppress mating and reproduction. Pheromone dispensers contain synthetic pheromones that are identical to the natural pheromones produced by the female moths. When properly deployed, pheromone emitted from the dispensers can overwhelm the "scent" given off by the female moths so that male moths cannot locate the females and mate with them. Pheromones do not kill or harm the moths.

Pheromone dispensers have been used successfully to manage and control a variety of pests worldwide for many years (Witzgall et al., 2008). In particular, Isomate LBAM Plus has been effective in reducing LBAM populations in three large-scale mating disruption trials conducted from 2001 to 2004 in southeastern Australia (Mo et al., 2006).

Isomate LBAM Plus consists of an aluminum wire and a hollow polyethylene plastic tube that contains 188 mg (0.00728 fluid ounces) of chemicals (Figure 1) (Pacific Biocontrol Corp., 2009a). The tube serves both as a container and a mechanism for the gradual release of the chemicals. The chemicals migrate by diffusion to the surface of the tube and volatilize into the surrounding air. When in use, Isomate LBAM Plus is hung from tree branches or shrubs at a height of six to ten feet, at a density of approximately 250 per acre. They are designed to continuously release their contents over a period of about 90 days. After that, they are either removed or replaced with fresh ones.

Most of the chemicals inside Isomate LBAM Plus (95% by weight) belong to a group of organic compounds known as Straight Chain Lepidopteran Pheromones (SCLPs). While two of them (E-11-tetradecen-1-yl acetate (63.9 % by weight) and E, E-9,11-tetradecadien-1-yl acetate) (2.6% by weight) target LBAM (Pacific Biocontrol Corp., 2009b), others may affect other moth species. In addition, trace amount of contaminants with chemical structures similar to that of SCLPs sometimes can be found in the dispenser.

Many SCLPs are susceptible to degradation by UV light and oxidants in the air. In order to ensure the SCLPs are effective over a long period of time, an anti-oxidant and a UV-blocker are added to the chemicals in the dispenser and together these two additives constitute approximately 5% of the product by weight (Pacific Biocontrol Corp., 2009a). Under Federal law, the identity and the composition by weight of the chemicals in Isomate LBAM Plus are considered trade secrets.

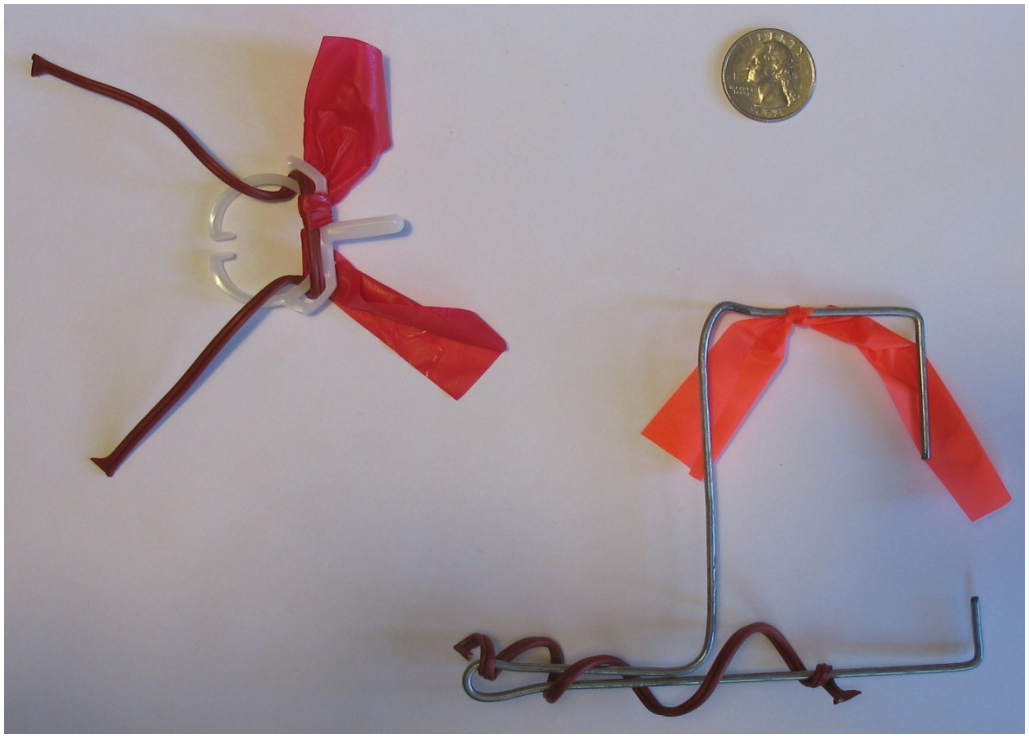


Figure 1. Picture of Isomate LBAM Plus (twist tie). One twist tie is attached to a plastic ring, and the other is attached to a metal hanger. Colored ribbons are for easy identification.

Human Health Risk Assessment

The potential for health effects resulting from exposure to chemicals in the environment depends on the toxicity of the chemicals and on the extent of exposure. In order to observe if health effects can be caused in experimental animals, they are exposed at levels many times higher than those experienced by human. In order to estimate potential health effects, scientists must estimate human exposures and compare them with what has been learned from studies in animals.

In this document, the risk assessment process is described in four steps:

1. Hazard identification - The review of available animal and human toxicity data and the determination of the exposure or treatment levels that would cause the identified health effects.
2. Exposure assessment - The estimation of the extent of human exposure.
3. Dose-response assessment – The determination of the exposure level in humans that is not likely to result in health effects, based on the information gathered from hazard identification.
4. Risk characterization – The estimation of the likelihood that exposed humans will be adversely affected.

These steps are described in the following sections:

(1) Hazard Identification

OEHHA reviewed the available literature on the toxicity of SCLPs. Attention was given to the toxicity data of the SCLPs. Sources of information included data published in the scientific literature, as well as data submitted to the California Department of Pesticide Regulation for registration purposes.

Toxicity evaluation of the SCLPs

The U. S. Environmental Protection Agency (US EPA) defines SCLPs 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. US EPA has 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 food tolerance (i.e., there is no restriction on the concentration that is allowed on produce) (US EPA, 2006). In the present assessment, we used both toxicity data specific to the SCLPs used in the twist ties, and additional applicable data available on other SCLPs.

(a) Acute Toxicity of SCLPs

Overall, SCLPs have been shown to be of very low acute inhalation, oral, and dermal toxicity in mammals. As an initial screen, toxicologists describe acute toxicity by the LD_{50}, the dose that kills half the test animals. When a study uses extremely high dosages (also referred to as "limit doses"), but does not kill any animals, scientists cannot determine the LD_{50}, but can conclude that it is greater than the doses used. This was the case with some acute-toxicity studies of SCLPs. For this reason, LD_{50s} are expressed in terms of "greater than" (>) the limit doses cited in some of the studies discussed below.

Acute inhalation toxicity

According to Health Canada (2002) and US EPA (1994), SCLPs have low acute inhalation toxicity with a median lethal concentration (LC_{50}) generally >5 milligram/liter (mg/L) (Category III-IV, Low - Very Low Toxicity). These US 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 (≤0.05 mg/L) - High Toxicity, Category II (>0.05 through 0.5 mg/L) - Moderate Toxicity, Category III (>0.5 through 2 mg/L) - Low Toxicity, and Category IV (>2 mg/L) - Very Low Toxicity. According to the US EPA acute inhalation toxicity guideline, an exposure duration of 4 hours is recommended for acute inhalation toxicity studies (US EPA, 1998).

Beroza et al. (1975) exposed rats to different pure SCLPs aerosols (1 to 10 micrometer (μm) droplets) for 1 hour and found no deaths or adverse effects for (Z)-7-hexadecen-1-ol acetate, (Z)-7-dodecen-1-ol acetate, and (Z)-7-dodecen-1-ol at levels between 3.8 and 6.7 microgram/liter (mg/L). In a toxicity review, Inscoe and Ridgway (1992) described acute inhalation toxicity of several SCLPs in rats**.** LC_{50s} of (Z+E) 8-dodecenol acetate, (Z)-9-tetradecenal, (Z+E)-11-tetradecenal, and (Z)-11-hexadecenal ranged from >5 mg/L to >75 mg/L. One chemical, (ZZ+ZE)-7, 11-hexadecadienol acetate, was tested at a lower concentration and had an acute inhalation LC_{50s} of >3.3 mg/L. In a US EPA document, (E+Z)-4-tridecenyl acetate was reported to have an acute inhalation LC_{50} >2.5 mg/L in rats (US EPA, 1996).

According to the Material Safety Data Sheet (MSDS) provided by the manufacturer of Isomate LBAM Plus, the pheromone active ingredient within the dispenser has an acute inhalation LC_{50} >5.26 mg/L in rats (Pacific Biocontrol Corp., 2008).

Using the information in the MSDS of the dispenser and the conclusion of Health Canada and US EPA that SCLPs have low acute inhalation toxicity with a LC_{50} generally >5 mg/L, a no-observed-adverse-effect level (NOAEL) of 5 mg/L or 5,000 milligram/cubic meter (mg/m^3) is assumed for acute inhalation exposure. Assuming complete absorption via the lung, a breathing rate of 0.22 cubic meter/day (m^3/day) or 0.00917 cubic meter/hour (m^3/hr) (US EPA, 1988), and a body weight of 0.2 kilogram (kg) for an adult

rat, an acute inhalation NOAEL of 229 milligram/kilogram body weight – hour (mg/kg-hr) is estimated for the SCLPs.

$$Acute\ inhalation\ \ NOAEL = \frac{5000\,mg/m3 \times 0.00917\,m3/hr}{0.2\,kg} = 229\,mg/kg - hr$$

Acute oral toxicity

In a review of mammalian toxicity of SCLPs, Inscoe and Ridgway (1992) found that these chemicals are of very low oral toxicity in rats. Of the 19 pheromones reviewed, only one has an oral LD_{50} > 3,200 milligrams/kilogram of body weight (mg/kg), others have an oral LD_{50} > 5,000 mg/kg.

For regulatory purposes, the US EPA (1994) used an acute oral toxicity of LD_{50} > 5,000 mg/kg for SCLPs and placed this group of chemicals in Category IV (Very Low Toxicity) for acute oral toxicity. The categories include: Category I (≤50 mg/kg) - High Toxicity, Category II (>50 through 500 mg/kg) - Moderate Toxicity, Category III (>500 through 5000 mg/kg) - Low Toxicity, and Category IV (>5000 mg/kg) - Very Low Toxicity.

An acute oral toxicity study with rats has been conducted for the SCLPs that target LBAM; it showed no mortality and no toxic signs at a dose of 5,000 mg/kg (MB Research Laboratories, 2008a), indicating an oral LD_{50} > 5,000 mg/kg. This study, with a No-Observed-Adverse-Effect Level (NOAEL) of 5,000 mg/kg, is determined to be the critical study for evaluating health effects of acute oral exposure to SCLP's. This study was selected because the SCLPs used were the chemicals that target LBAM and the study provided detailed toxicity information.

Acute eye irritation

SCLPs vary in their potential to cause eye irritation in rabbits. Materials are tested by placing directly into the eye and holding there for a specific period of time. While (Z)-7-hexadecen-1-ol acetate and (Z)-7-dodecen-1-ol acetate are not eye irritants, (Z)-7-dodecen-1-ol was found to cause mild eye irritation at 24 hours and 48 hours after treatment. Nearly complete recovery was noted at 72 hours (Beroza et al., 1975).

In a toxicity review of SCLPs, Inscoe and Ridgway (1992) reported that (E,E)-8,10-dodecadienol, (Z)-7-dodecenol acetate, (Z+E)-8-dodecenol acetate, (E)-4-tridecenol acetate, (ZZ+ZE)-7, 11-hexadecadienol acetate, (EZ+ZZ)-3, 13-octadecadienol acetate, and (E+Z)-11-tetradecenal were not eye irritants. But (Z+E)-9-dodecenol acetate was found to be a slight eye irritant.

In a US EPA document, (E+Z)-4-tridecenyl acetate was reported to be a slight eye irritant. It caused slight iritis and conjunctival irritation in rabbits (US EPA, 1996).

Acute dermal toxicity, skin irritation, and skin sensitization

Beroza et al. (1975) tested several long-chained hydrocarbons on rabbits and reported an acute dermal LD_{50} of 3,700 mg/kg for (Z)-7-dodecen-1-ol. Materials are tested by placing directly onto the bare skin and holding there for a specific period of time. At doses up to 2,025 mg/kg, they did not see any deaths for (Z)-7-hexadecen-1-ol acetate and (Z)-7-dodecen-1-ol. Ataxia, muscular weakness, and hypothermia were noted in the animals treated with (Z)-7-dodecen-1-ol. No untoward behavioral reactions were seen in any of the other animals. However, at the doses indicated, the chemicals caused some local skin reactions such as redness, pustulation, erythema, edema, or scarb. Necropsies revealed no abnormal findings other than these dermal alterations.

US EPA (2006) and Health Canada (2002) classified SCLPs as Category III (Low Toxicity) for acute dermal toxicity, as there were no deaths reported at the limit dose of 2,000 mg/kg. The categories include: Category I (≤200 mg/kg) - High Toxicity, Category II (>200 through 2000 mg/kg) - Moderate Toxicity, Category III (>2000 through 5000 mg/kg) - Low Toxicity, and Category IV (>5000 mg/kg) - Very Low Toxicity.

In a US EPA document, (E+Z)-4-tridecenyl acetate was reported to have an acute dermal LD_{50} of >5,000 mg/kg in rabbits (US EPA, 1996).

According to the MSDS provided by the manufacturer of Isomate LBAM Plus, the pheromone active ingredient within the dispenser has an acute dermal LC_{50} >2000 mg/kg in rats (Pacific Biocontrol Corp., 2008).

For the purpose of this assessment, a NOAEL of 2,000 mg/kg, based on the limit dose, is selected to evaluate health effects associated with acute dermal exposure to the SCLPs. This acute dermal NOAEL is approximately 2.5 fold lower than the acute oral NOAEL. For comparison, estimated acute NOAELs for SCLPs by the oral, inhalation, and dermal routes are provided in Table 1.

An acute skin irritation study in rabbits was conducted for the SCLPs that target LBAM (MB Research Laboratories, 2008b). It showed the SCLPs in the Isomate LBAM Plus, when applied in an undiluted form, can cause slight skin irritation. This result is consistent with animal studies described in Beroza et al. (1975), Inscoe and Ridgway (1992), and the US EPA (1994). They consider SCLPs to be mild to moderate skin irritants in rabbits.

In an acute skin sensitization study, the SCLPs mixture that target LBAM was not determined to be a skin sensitizer in guinea pigs (MB Research Laboratories, 2008c).

Table 1. Comparison of estimated acute toxicity of SCLPs for different exposure routes.

Exposure route	Estimated acute NOAEL	Toxicity information	Toxicity classification
Oral	>5000 mg/kg	Derived from a LD_{50} of >5000 mg/kg with no sign of toxicity in an oral study in rats. The tested chemicals were the SCLPs that targets LBAM	Very Low Toxicity
Inhalation	229 mg/kg-hr	Derived from a LC_{50} of 5 mg/L (LC_{50} range is >5 mg/L to >75 mg/L) in rats. The tested chemicals were SCLPs but they are not for LBAM.	Low to Very Low Toxicity
Dermal	2000 mg/kg	Derived from a limit dose of 2000 mg/kg in rabbits. The tested chemicals were SCLPs but they are not for LBAM.	Low Toxicity
Eye Irritant	N/A		No to Slight Irritant
Dermal Irritant	N/A		Slight Irritant

(b) Sub-chronic toxicity of SCLPs

There are four sub-chronic animal toxicity studies on SCLPs; two are by the inhalation route and two are by the oral route. Some of the characteristics of the studies are summarized in Table 2.

Table 2. Sub-chronic toxicity data for four SCLPs (1-nonanol, 1-decanol, 2-trans,4-trans-decadienal, and 1-dodecanol).

Chemical	Test animals	Route of exposure and doses used	Exposure duration	NOAEL and the reported health effects	Reference
1-nonanol	Pregnant rats	Inhalation, one dose group	19 days	>30 mg/kg-day based on absence of effects at this dose level; no fetal effects	Nelson et al., 1990
1-decanol	Pregnant rats	Inhalation, one dose group	19 days	>17 mg/kg-day based on absence of effects at this dose level; no fetal effects	Nelson et al., 1990
2-trans,4-trans-decadienal	rats	Oral, gavage, one dose group	14 weeks	34 mg/kg-day (LOAEL not described)	WHO Technical Report Series 922, 2004
1-dodecanol	rats	Oral, feed, 0, 100, 500, or 2000 mg/kg-day	37 days	100 mg/kg-day based on small decrease in mean white blood cell counts at 500 mg/kg-day; no reproductive or developmental effects	Hansen (1992) as cited in OECD SIDS, undated

The two 19-day inhalation studies on 1-nonanol and 1-decanol were reported by Nelson et al. (1990). The maximum concentrations of vapor that could be generated were used in these studies; they were 150 mg/m^3 for 1-nonanol and 100 mg/m^3 for 1- decanol. Pregnant rats were exposed for 6-7 hours a day during the gestation period. No treatment-related effects were observed in pregnant females or the fetuses. The sub-chronic inhalation NOAEL calculated for 1-nonanol and 1- decanol are >30 mg/kg-day and >17 mg/kg-day, respectively.

There are also two sub-chronic oral studies on SCLPs. A World Health Organization (WHO) document describes an unpublished 14-week gavage study of 2-trans,4-trans-decadienal in rats. It identified a NOAEL of 33.9 mg/kg-day. Many study details, such as the number of animals per dose group, the dosage, and the adverse health effects observed, were not provided. The reference is given as Damske et al., 1990, an unpublished study, "submitted to WHO by Flavor and Extract Manufacturers Association of the United States."

In a combined sub-chronic and reproductive/developmental toxicity screening study of 1-dodecanol, Hansen (1992 as cited in OECD SIDS) administered the chemical in the diet to male and female rats at 0, 100, 500, or 2000 mg/kg-day for 37 days. After 14 days of exposure, females were placed together with the males. The study found that pregnancy rates were slightly reduced (92% in controls v. 75% in the 2000 mg/kg-day dose group), but this was not statistically significant. No treatment-related effects were observed in the fetuses. The study found minimal maternal and paternal toxicity. The treatment had no effect on body weight, weight gain, food consumption and food efficiency in either sex at all the doses. There was a statistically significant decrease in white blood cell counts in the 500, and 2,000 mg/kg-day dose groups. However, no differences in the differential counts of white blood cell types were seen, making it difficult to assess the toxicological significance of this finding. Based on this observation, a NOAEL of 100 mg/kg-day is determined for 1-dodecanol. This chemical is a permitted food additive in both the United States and the European Union.

In addition to studies using SCLPs, US EPA (2006) has used the results of a 90-day feeding study of a commercial blend of branched acetates (this does not meet US EPA's own definition of SCLPs) with an aliphatic chain length between C10 and C14 to assess the sub-chronic toxicity of SCLPs. At doses of up to 1,000 mg/kg-day, this oral study in rats 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).

Based on the available toxicity database, the two 19-day inhalation studies reported by Nelson et al. (1990) are considered to be appropriate for the evaluation of health effects of sub-chronic inhalation exposure to SCLPs. The NOAELs for 1-nonanol and 1-decanol were >30 mg/kg-day and >17 mg/kg-day, respectively. For this assessment, the lower NOAEL of 1- decanol (>17 mg/kg-day) is chosen as the basis for estimating a sub-chronic inhalation reference dose (RfD) for the SCLPs.

(c) Persistence of SCLPs

SCLPs are not expected to persist in human bodies or in the environment. As shown in Figure 2, SCLPs are structurally similar to long-chain fatty acids, and they are expected to be metabolized in a similar fashion. Long-chain fatty acids are metabolized either by β-oxidation, yielding a series of paired carbon losses, or by complexing with glucuronide and being excreted by the kidneys (OECD, 2002).

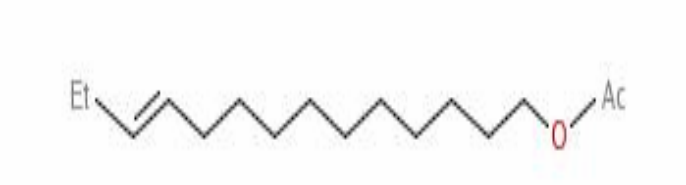
(d) Genotoxicity of SCLPs

DPR has reviewed the gene mutation, chromosome effects, and DNA damage data of a SCLP, (E+Z)-4-tridecen-1-yl acetate, and found it to be negative in all the tests (CDPR, 2002). Kirsch (1988) reported that (Z+E)-8-dodecenol acetate, (E)-4-tridecenol acetate, and (ZZ+ZE)-7, 11-hexadecadienol acetate were not mutagenic. According to US EPA, there is no evidence that SCLPs are mutagenic (US EPA, 2006).

(e) Chronic toxicity of SCLPs

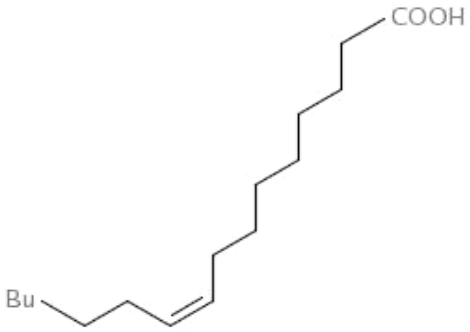
In our literature research, we could not locate any chronic animal toxicity or cancer studies of SCLPs. However, the concern of any health effects associated with long-term exposure to the SCLPs is mitigated by the very low application rates and low acute and sub-chronic toxicities of these chemicals. There is no evidence to indicate the SCLPs are mutagenic. In addition, the SCLPs are structurally similar to some common fatty acids and are likely to be metabolized by the body into by-products that have no known toxicological concern.

Figure 2. Chemical structure of E-11-tetradecen-1-yl acetate, E, E-9,11-tetradecadien-1-yl acetate, and three fatty acids found in food.

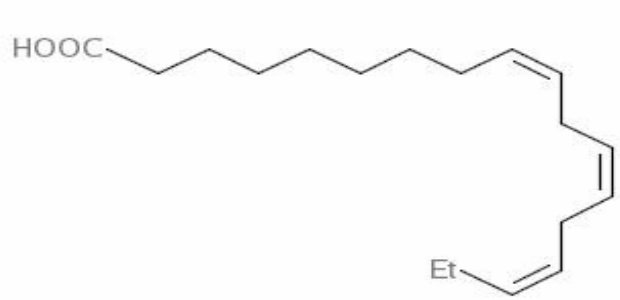


E-11-tetradecen-1-yl acetate [CAS#33189-72-9], is an acetate (ester) with a 14-carbon chain and one carbon-carbon double bond. It is one of the SCLPs in the Isomate LBAM Plus.

E, E-9,11-tetradecadien-1-yl acetate [CAS#30562-09-5], is an acetate (ester) with a 14-carbon chain and two carbon-carbon double bonds. It is one of the SCLPs in the Isomate LBAM Plus.



Palmitoleic acid, or (Z)-9-hexadecenoic acid [CAS# 373-49-9], is a carboxylic acid with a 16-carbon chain and one double bond. It is a common constituent of the glycerides of human adipose tissue. Dietary sources of palmitoleic acid include a variety of animal oils, vegetable oils, and marine oils.



Alpha- Linolenic acid, or (Z,Z,Z)-9,12,15-octadecatrienoic acid [CAS# 463-40-1], is a carboxylic acid with an 18-carbon chain and three double bonds. It is found in many common vegetable oils such as rapeseed (canola), soybeans, walnuts, flaxseed (Linseed), perilla, chia and hemp.

Lauric acid, or dodecanoic acid [CAS# 143-07-7], is a carboxylic acid with a 12-carbon chain. It is the main acid in coconut oil and in palm kernel oil. It is also found in human milk, cow's milk, and goat's milk.

(2) Exposure Evaluation

This section describes how OEHHA estimated exposure to the chemicals in Isomate LBAM Plus. When the Isomate LBAM Plus is used as designed, inhalation and dermal exposures are the most relevant exposure pathways. The potential for oral exposure is considered to be very low. Nevertheless, this evaluation includes a one-time accidental exposure scenario where a child chews on a pheromone dispenser and ingests the chemicals inside.

(a) Inhalation exposure

The Isomate LBAM Plus is designed to be hung on tree branches or shrubs, approximately six to ten feet off the ground. It is effective for about 90 days. During that time, the SCLPs in the plastic tube diffuse to the surface of the tube and volatilize into the surrounding air.

(i) Estimation of concentration of SCLPs in air

Direct measurement and modeling are the two approaches that can be used to determine concentrations of chemicals in air. Due to the low release rate of SCLPs from the Isomate LBAM Plus, it is difficult to measure the chemicals in the field. Even if such measurements were performed, the data only represent air concentrations achievable under a specific set of conditions. There is indication that the release rate of the pheromone varies with environmental factors, such as temperature and wind velocity, as well as days in the field (Bradley et al., 1995; Knight et al., 1995; Van der Kraan and Ebbers, 1990). Measurement data collected under a particular situation may not be appropriately extrapolated to other situations.

We chose the modeling approach to determine concentrations of chemicals in the air. First, we estimated the volume of air that is to be filled with chemicals released from a single dispenser. In order for the pheromone dispensers to be effective, the manufacturer of Isomate LBAM Plus, Pacific Biocontrol Corp., recommends an application rate of 200-300 dispensers per acre. According to CDFA, the target application rate of the pheromone dispenser would be 250 dispensers per 4,046.9 m^2 (or 250 per acre). Using a square-shaped grid, this is equivalent to approximately one dispenser per 16.2 m^2. This means the average distance between two pheromone dispensers would be approximately 4 meters (m) (13 feet). Isomate LBAM Plus is designed to be attached to tree branches or shrubs at a height of 1.8 to 3 m (6 to 10 ft). In the modeling, it is assumed that a pheromone dispenser is hung at a height of 1.8 m and the chemical vapor it releases fills the air from the ground level to a height of up to 4 m (13 ft). Using these dimensions (4 m x 4 m x 4 m), the volume of air that is to be filled with chemicals released from a single dispenser is calculated to be 64 m^3 (Figure 3).

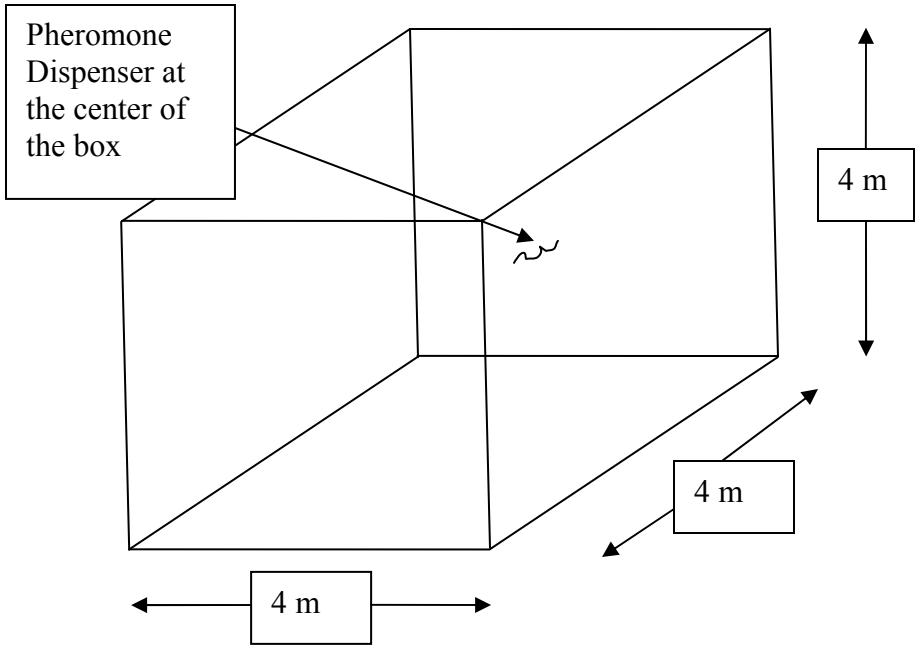


Figure 3. A diagram to show the dimensions used in estimating the concentrations of chemicals that would be in the air.

According to the information provided in the MSDS of Isomate LBAM Plus, the maximum emission rate is estimated to be 35 μg per hr per dispenser (Pacific Biocontrol Corp. (2008). The manufacturer states that 95 % (by weight) of the chemicals inside the plastic tube is pheromone and the remaining 5 % is made up of an anti-oxidant and a UV-blocker (Pacific Biocontrol Corp., 2009a). The UV-blocker is not volatile and is likely to remain inside the dispenser. A study with codling moth mating disruption dispensers showed that as pheromones volatilize out of a dispenser, the relative concentration of nonvolatile chemicals such as the UV-blocker increases. In a field-aged dispenser, it can contain up to 75% non-volatile materials (Millar and McElfresh, 1994).

For the purpose of this risk assessment, it is assumed that a dispenser releases 35 μg of material into a volume of 64 m^3 once an hour, and this volume of air is completely replaced with fresh air once an hour and there is no dilution or loss of material before then. This is equivalent to assuming the air-change rate (ventilation rate) is once an hour (1 hr^{-1}). It is a health-protective assumption as indicated by the air-exchange rates measured in different types of buildings in different geographical areas. In general, the air-exchange rate depends on the climate, the type of building and its operation as well as the lifestyle of the occupants. Monitoring data show that for residential houses in Australia, with a mild-to-warm climate, air exchange was on the high end, with an average of 26.3 hr^{-1}. In Canada and Sweden, with much cooler climates, the air exchange rate was reported to be lower, about 4.4 and 3.7 hr^{-1}, respectively. Data also show that air-exchange rate in office buildings is usually much lower, about 0.9 hr^{-1} in the USA

and about 0.8 hr^{-1} in Brisbane (Pluschke, 2004). Since the pheromone dispenser is only used in an outdoor environment, the assumption that the air-exchange rate is lower than those measured in residential houses is likely to over-estimate the actual air concentrations of Isomate LBAM Plus chemicals.

For this evaluation, it is also assumed that 95% of the emission material is the SCLPs and the remaining 5% is the anti-oxidant.

$$\text{Estimated concentration of SCLPs in air for acute exposure} = \frac{35\,\mu\text{g} \times 0.95}{64\,\text{m}^3} = 0.52\,\mu\text{g}/\text{m}^3$$

These calculations represent "high-end air concentration estimates." They are likely to over-estimate the actual air concentrations; they assume that the volatilized material is confined to a relatively small volume, no material is lost due to absorption, and there is no dilution due to diffusion or mass air movement within one hour. The "high-end air concentration estimates" are used in the evaluation of health hazards associated with acute inhalation exposure.

The dispensers are designed to continuously release the SCLPs for about 90 days and if LBAM infestation is not abated after that time, they are replaced with fresh ones. This means it is possible to have sub-chronic inhalation exposure to the SCLPs and the anti-oxidant. While it is appropriate to assume a "worst case" for acute exposures, it is not reasonable to assume the "high-end air concentration estimates" are maintained for weeks and months. For this reason, a dilution factor of 10 is applied to the "high-end air concentration estimates" for the evaluation of health effects associated with longer exposures. This is equivalent to assuming the air-exchange rate is ten times an hour (10 hr^{-1}). It is a conservative assumption as monitoring data show that air-exchange rate in a residential house in a mild-to-warm climate can be as high as 26.3 hr^{-1} and air-exchange rate in office buildings is usually much lower, about 0.9 hr^{-1} in the USA and about 0.8 hr^{-1} in Brisbane (Pluschke, 2004).

Using this assumption, the estimated air concentration for sub-chronic exposure would be 10 times lower than that estimated for acute exposure. The estimated air concentration for evaluating sub-chronic exposure to SCLPs is 0.052 $\mu g/m^3$.

(ii) Estimation of acute inhalation dose

For the purpose of this assessment, the following assumptions are made in the construction of acute inhalation exposure scenarios:

- Individuals are exposed to relatively high concentrations of chemicals in the air,
- Individuals have high activity levels and thus high breathing rates, and
- Individuals are exposed for a short period of time (one hour).

Using the following equations, estimated acute inhalation doses for an adult and a child are calculated:

$$\text{Acute inhalation dose of an adult } (\mu g/kg) = C_A \times \frac{BR}{BW \times ET}$$

where:

C_A = concentration in air, $\mu g/m^3$

BR = estimated high-end hourly breathing rate for an adult, 3.2 m^3/hr (US EPA, 1997)

BW = default body weight of an adult, 70 kg

ET = exposure duration, 1 hr

$$\text{Acute inhalation dose of a child } (\mu g/kg) = C_A \times \frac{BR}{BW \times ET}$$

where:

C_A = concentration in air, $\mu g/m^3$

BR = estimated high-end hourly breathing rate for a child, 1.9 m^3/hr (US EPA, 1997)

BW = estimated body weight of a child, 18 kg (from Table 10.4 of OEHHA, 2000)

ET = exposure duration, 1 hr

Using these two equations, acute inhalation doses of SCLPs estimated for an adult and a child are 0.024 and 0.055 µg/kg-hr, respectively.

(iii) Estimations of sub-chronic inhalation dose

For the purpose of this assessment, the following assumptions are made in the construction of sub-chronic inhalation exposure scenarios:

- Concentrations of chemicals in air for estimating sub-chronic exposures are ten-fold lower than those used in modeling acute exposures
- Individuals have average activity levels and thus average breathing rates, and
- Individuals are exposed continuously for weeks or months.

Using the following equations, estimated sub-chronic inhalation doses for an adult and a child are calculated:

$$\text{Sub-chronic inhalation dose of an adult } (\mu g/kg\text{-day}) = C_A \times \frac{BR}{BW}$$

where:

C_A = concentration in air, $\mu g/m^3$

BR/BW = estimated average daily breathing rate per body weight for an adult, 0.232 m^3/kg-day (from Table 3.22 in OEHHA, 2000)

$$\text{Sub-chronic inhalation dose of a child}\,(\mu g/kg\text{-day}) = C_A \times \frac{BR}{BW}$$

where:

C_A = concentration in air, $\mu g/m^3$

BR/BW = estimated average daily breathing rate per body weight for a child, 0.452 m^3/kg-day (from Table 3.22 in OEHHA, 2000)

Using these two equations, sub-chronic inhalation doses of SCLPs estimated for an adult and a child are 0.012 and 0.0235 µg/kg-day, respectively.

(b) Dermal exposure

Dermal exposure occurs when individuals handle the pheromone dispensers with bare hands. Since both the anti-oxidant and the SCLPs are relatively volatile, they are not likely to stay for long on the surface of the dispenser. At any point in time, only a small quantity of material would be available for dermal exposure. According to information provided in the MSDS, the maximum emission rate of the material is 35 µg per hr per dispenser. We assume this amount of material is available for dermal exposure and 95% of the material is the SCLPs and 5% is the anti-oxidant. It is assumed that the UV-blocker stays inside the pheromone dispenser and is not available for dermal exposure. Assuming a default dermal absorption factor of 10% for the SCLPs (US EPA, 2004), the estimated acute dermal doses for an adult (who weighs 70 kg) and a child (who weighs 18 kg) that has come into contact with a single pheromone dispenser are calculated as follows:

$$\text{Estimated acute dermal exposure for an adult} = \frac{35\ \mu g \times 0.95 \times 0.1}{70\ \text{kg}} = 0.048\ \mu g/\text{kg}$$

$$\text{Estimated acute dermal exposure for a child} = \frac{35\ \mu g \times 0.95 \times 0.1}{18\ kg} = 0.18\ \mu g/kg$$

(c) Oral exposure

When Isomate LBAM Plus is used the way it was designed to be, the potential for oral exposure to the chemicals inside is very low. Nevertheless, in the unlikely event that a child gets hold of a dispenser and chews on it, it is conservatively assumed that up to 25% of the chemical inside the dispenser can be ingested. According to the manufacturer, each dispenser contains 188 mg of chemical and 95% is SCLPs and 5% are

the two additives. Assuming a child's body weight of 18 kg, the estimated acute oral doses are calculated as follows:

$$\text{Estimated acute oral dose of the SCLPs} = \frac{188\,mg \times 0.95 \times 0.25}{18\,kg} = 2.5\,mg/kg$$

(3) Dose-Response Evaluation

In this section, critical threshold exposure levels (NOAELs) of the SCLPs identified in the hazard identification section are used to derive reference doses (RfDs). A reference dose is defined as an exposure level that is not likely to cause adverse health effects in humans. For NOAELs derived from animal toxicity studies, an overall uncertainty factor (UF) of 100 is used to convert the NOAELs to the corresponding RfDs; a factor of 10 is used for inter-species variability, and another factor of 10 for intra-species variability. Using this approach and the acute NOAEL determined, acute RfDs are developed and presented in Table 3.

Table 3. A summary table of the acute RfDs developed for SCLPs.

Exposure route	Acute NOAEL (mg/kg)	UF	Acute RfD
Inhalation	229	100	2.29 mg/kg-hr
Dermal	2000	100	20 mg/kg
Oral	5000	100	50 mg/kg

As described in the hazard identification section, a sub-chronic inhalation NOAEL of >17 mg/kg-day was determined for the SCLPs. Applying an overall UF of 300, a factor of 10 for inter-species variability, a factor of 10 for intra-species variability, and a factor of 3 for an exposure period of the animal study of less than 90 days, a sub-chronic inhalation RfD of 57 μg/kg-day can be calculated.

(4) Risk Characterization

The risk characterization process integrates the information obtained in hazard identification, exposure evaluation, and dose-response evaluation in order to determine the likelihood that exposed humans will be adversely affected by the chemical exposure. In this assessment, a hazard index (HI) approach is used to estimate this likelihood. A HI is a ratio calculated by dividing an estimated human exposure with an appropriate RfD. The lower the HI, the lower is the health risk. Underlying this approach is the recognition that there is a threshold in non-tumor adverse health effects to a chemical

exposure. No adverse health effect is expected when the estimated exposure is below the threshold.

HIs estimated for an adult and a child resulted from acute exposures to SCLPs are summarized in Table 4.

Table 4. A summary table of the hazard indices (HIs) estimated for an adult and a child resulted from acute exposures to SCLPs.

Route	Estimated dose	Acute RfD	HI	Potential Health Risk to Adult or Child
Inhalation exposure (adult)	0.024 μg/kg-hr	2,290 μg/kg-hr	0.00001 (1.0×10^{-5})	Very low to none
Inhalation exposure (child)	0.055 μg/kg-hr	2,290 μg/kg-hr	0.000024 (2.4×10^{-5})	Very low to none
Dermal exposure (adult)	0.048 μg/kg	20,000 μg/kg	0.0000024 (2.4×10^{-6})	Very low to none
Dermal exposure (child)	0.18 μg/kg	20,000 μg/kg	0.000009 (9×10^{-6})	Very low to none
Accidental oral exposure (child)	2.5 mg/kg	50 mg/kg	0.05	Very low

Using the sub-chronic inhalation dose estimates calculated and a RfD of 57 μg/kg-day for the SCLPs, the estimated HIs for an adult and a child resulting from sub-chronic inhalation exposure are 0.00021 (2.1×10^{-4}) and 0.00041 (4.1×10^{-4}), respectively.

Based on this risk assessment on using the pheromone dispenser, the potential health risks to an adult or a child exposed to the SCLPs through inhalation and dermal routes are very low. If the device is used in the way it is designed, there should be no oral exposure to the SCLPs inside the sealed device. In the unlikely event that a child gets hold of a pheromone dispenser and chews on it, the HI for this incident is estimated to be 0.05. No adverse health effect is expected when a HI is below one. Though no chronic toxicity or cancer studies of the SCLPs in experimental animals have been located, the concern of any health effects associated with long-term exposure to the SCLPs is mitigated by the very low HIs determined for sub-chronic inhalation exposures. There is no evidence to indicate the SCLPs are carcinogenic. In addition, the SCLPs are structurally similar to some common fatty acids and are likely to be metabolized by the body into by-products that have no known toxicological concern.

One source of uncertainty is related to the modeling of air concentrations of the SCLPs. Using a simple dilution model, it is estimated that the SCLPs' concentration in air for

short-term and long-term exposures are 0.52 μg/m^3, and 0.052 μg/m^3, respectively. Suckling et al. (1999) using a similar type of pheromone dispenser that targets LBAM estimated that pheromone concentrations in air ranged from 0.004 to 0.09 μg/m^3, at an application rate of approximately 400 dispensers per acre. The estimated SCLPs concentrations in air are near the high-end of the range of air concentrations predicted by Suckling et al. (1999).

As discussed in the hazard identification section, the pheromones in Isomate LBAM Plus in an undiluted form were shown to be slight skin irritants. While no eye irritation tests have been performed on these chemicals, some SCLPs have been shown to be slight eye irritants as well. For these reasons, the SCLPs in the Isomate LBAM Plus in undiluted form should be considered as potential skin and eye irritants. As a precautionary measure, it is advisable to minimize the chance of eye or skin contact with the pheromones.

Health risk assessments of the anti-oxidant and UV-blocker in Isomate LBAM Plus indicate that these two chemicals are not likely to pose a health risk. However, they have very low potentials for eye and skin irritation and it is advisable to minimize the chance of getting the content of the pheromone dispenser into the eye or onto the skin.

(5) SUMMARY

This assessment is based on a number of factors, including the generally low toxicity and high volatility of pheromones, the low application rate, and the low human exposure expected from pheromones used in these devices. The conclusion of this assessment is that pheromones in solid matrix dispensers will not cause adverse effects in humans, which is consistent with a determination from the U.S. EPA.

References

Beroza M, Inscoe MN, Schwartz PH, Keplinger ML Jr., Mastri CW (1975). Acute toxicity studies with insect attractants. Toxicol Appl Pharmacol, 31: 421-429.

Bradley SJ, Suckling DM, McNaughton KG, Wearing CH, Karg G (1995). A temperature-dependent model for predicting release rate of pheromone from a polyethylene tubing dispenser. J Chem Ecol 21(6): 745-760.

CDPR (2002). Summary of toxicology data: (E)-4-tridecen-1-yl acetate and (Z)- 4-tridecen-1-yl acetate. California Environmental Protection Agency, Department of Pesticide Regulation, Medical Toxicology Branch. April 8, 2002.

Daughtrey WC, Smith JH, Hinz JP, Biles RW (1990). Subchronic toxicity evaluation of tridecyl acetate in rats. Fundam Appl Toxicol 14(1): 104-112.

Federal Register (2006). Lepidopteran pheromones; Exemption from the requirement of a tolerance. US EPA, 40 CFR Part 180. Federal Register: August 9, 2006 (Volume 71, Number 153).

Hansen (1992 as cited in OECD SIDS) Screening Information Data Sets. 1-Dodecanol. UNEP publications date?

Health Canada (1999). Regulatory decision document. PRDD99-04. 3M sprayable pheromone for mating disruption of blackheaded fireworm Z-11-tetradecenyl acetate. Pest Management Regulatory Agency. Health Canada, Ottawa, Ontario. September 3, 1999.

Health Canada (2008). CM/LR TT Pheromone Technical. Registration decision. Pest Management Regulatory Agency, Health Canada, Ottawa, Ontario. April 9, 2008.

Hodosh RJ, Keough EM, Luthra Y (1985). Toxicological evaluation and registration requirements for biorational pesticides. In: Handbook of Natural Pesticides: Methods. Vol. 1. Theory, Practice, and Detection. N.B. Mandava (Ed.) Boca Raton, FL: CRC Press. Pp. 231-272.

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

Kirsch P (1988). Pheromones: their potential role in control of agricultural insect pests. American J Alternative Agriculture 3: 83-97.

Knight AL, Howell JF, McDonough LM, Weiss M (1995). Mating disruption of codling

moth (Lepidoptera: Tortricidae) with polyethylene tube dispensers: determining emission rates and the distribution of fruit injuries. J Agric Entomol 12(2-3): 85-100.

Mo J, Glover M, Munro S, and Beattie GAC (2006). Evaluation of mating disruption for control of lightbrown apple moth (Lepidoptera: Tortricidae) in citrus. J Econ Entomol 99 (2): 421-426.

Nelson BK, Brightwell WS, Krieg EF Jr. (1990). Developmental toxicology of industrial alcohols: a summary of 13 alcohols administered by inhalation in rats. Toxicol Indust Health, 6 (314): 373-387.

OECD (2002). OECD series on pesticides, Number 12. Guidance for registration requirements for pheromones and other semiochemicals used for arthropod pest control. Organisation for Economic Co-operation and Development. ENV/JM/MONO(2001)12 February 26, 2002.

Pacific Biocontrol Corp. (2008). Material safety data sheet. Isomate®-LBAM plus. Revision date: February 2008.

Pacific Biocontrol Corp. (2009a). LBAM information. Webpage: http://www.pacificbiocontrol.com/Pacific_Biocontrol_Corporation/Light_Brown_Apple_Moth_files/What%20is%20Isomate-LBAM.pdf. Accessed on February 3, 2009

Pacific Biocontrol Corp. (2009b). Label of Isomate LBAM Plus. Webpage: www.cdfa.ca.gov/phpps/pdep/**lbam**/pdfs/FactSheets/Label-**LBAM**Plus.CASect18_q&a.pdf. Accessed on February 3, 2009.

Pluschke P. edit (2004). The Handbook of Environmental Chemistry. Volume 4. Indoor Air Pollution. Part F. Jan. 2004. Publisher: Springer-Verlag, N.Y. Page 132.

Suckling DM, Karg G, Green S, and Gibb AR (1999). The effect of atmospheric pheromone concentrations on behavior of lightbrown apple moth in an apple orchard. J Chem Ecology 25 (9): 2011-2025.

Van der Kraan C, Ebbers A (1990). Release rates of tetradecen-1-ol acetates from polymeric formulations in relation to temperature and air velocity. J Chem Ecol 16 (4): 1573-1561.

US EPA (1994). Federal Register Vol. 59, No. 17. Environmental Protection Agency. [OPP-50573; FRL-4755-1] Arthropod pheromones in solid matrix dispensers; experimental use permits. 59FR3681.

US EPA (1996). Reregistration Eligibility Decision (RED). Tridecenyl acetates. United States Environmental Protection Agency. Prevention, Pesticides and Toxic Substances. EPA 738-R-96-021. October 1996.

US EPA (1997). Memorandum. From Freshten Toghrol, Biopesticides and Pollution Prevention Division, to Rita Kumar, Biopesticides and Pollution Prevention Division. US EPA. Feb. 28, 1997.

US EPA (1998). Health Effects Test Guidelines. OPPTS 870.1300. Acute Inhalation Toxicity. United States Environmental Protection Agency. Prevention, Pesticides and Toxic Substances. EPA 712-C-98-193. August 1998.

US EPA (2004). EPA notice: arthropod pheromones in solid matrix dispensers; experimental use permits. Federal Register, 59 (3): 3681-3684.

US EPA (2004b). Risk assessment Guidance for Superfund. Volume 1: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment). Final. EPA/540/R/99/005. July 2004.

US EPA (2006). Lepidopteran pheromones; exemption from the requirement of a tolerance. Federal Register: August 9, 2006 (Volume 71, Number 153).

Witzgall P, Stelinski L, Gut L, and Thomson D. 2008. Codlingmoth management and chemical ecology. Ann Rev Entomol 53: 503-22.