Human Health Risk Assessment of Isomate®-EGVM

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Prepared by

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Executive Summary

This document describes a human health risk assessment on the use of Isomate®-EGVM conducted by the Office of Environmental Health Hazard Assessment (OEHHA), California Environmental Protection Agency. The Isomate®-EGVM device, also known as a "twist tie," is a pheromone dispenser. It consists of an aluminum wire and a hollow plastic tube sealed at both ends that contains a moth pheromone and two additives. It is one of the tools employed by the California Department of Food and Agriculture (CDFA) to control and eradicate the European Grape Vine Moth (EGVM) (*Lobesia botrana*). EGVM was first detected in California in September 2009 and has been determined to be an invasive pest.

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 pheromone and additives in Isomate®-EGVM. The pheromone belongs 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. The pheromones can be easily and rapidly broken down by UV light and oxidation. The pheromone dispenser contains two additives: butylated hydroxytoluene (BHT), an anti-oxidant, and bumetrizole, a UV blocker. They are used to protect the longevity of the pheromone.

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

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

Furthermore, the pheromone in Isomate®-EGVM has a chemical structure similar to many 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.

In highly concentrated forms, the pheromone and the additives in Isomate®-EGVM have been shown to be slightly irritating to the skin and eye in laboratory animals. As a precautionary measure, it is advisable to minimize the chance of eye or skin contact with the contents of the twist tie device.

Introduction

Isomate®-EGVM (twist tie) is a pheromone dispenser manufactured by the Pacific Biocontrol Corporation. It is one of the tools used by the California Department of Food and Agriculture (CDFA) to eradicate the European Grape Vine Moth (EGVM) (*Lobesia botrana)*. In the wild, female moths release sex pheromones 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 light brown apple moth (LBAM or *Epiphyas postvittana*) populations in three large-scale mating disruption trials conducted from 2001 to 2004 in southeastern Australia (Mo et al., 2006).

Isomate®-EGVM consists of an aluminum wire and a hollow plastic tube that contains 253 mg of the pheromone and two additives (Figure 1) (Pacific Biocontrol Corp., 2010a and 2010b). 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 used in vineyards, Isomate®-EGVM twist-ties are hung from grape vines at the trellis height of four to five feet. When used in olive trees, they are hung from tree branches at a height of six to ten feet. The manufacturer recommends a maximum application rate of 200-250 dispensers per acre. However, the application rate used by the CDFA can be as low as 50 dispensers per acre because only about 20% of the land is covered by vegetation in urban areas. The other 80% consists of roads, houses, commercial buildings, and open land that cannot be treated. The pheromone dispensers are designed to continuously release their contents for about 120-180 days (Pacific Biocontrol Corp., 2010b). After that, they are either removed or replaced with fresh ones.

Most of the chemicals inside Isomate®-EGVM belong to a group of organic compounds known as the Straight Chain Lepidopteran Pheromones (SCLPs). One of them, (E,Z)-7,9-Dodecadien-1-yl acetate, is the pheromone that targets EGVM. It is the active ingredient in Isomate®-EGVM and constitutes approximately 75.7 % by weight of the pheromone formulation in the device (Pacific Biocontrol Corp., 2010b). Other SCLPs in the device are impurities that are inherent to the manufacturing of the active ingredient.

(E,Z)-7,9-Dodecadien-1-yl acetate, like many SCLPs, is susceptible to degradation by UV light and oxidants in the air (Ideses et al., 1982). In order to ensure the pheromone is effective over a long period of time, small amounts of butylated hydroxytoluene (BHT), an anti-oxidant, and bumetrizole, a UV-blocker, are added to the device (US EPA, 2010).

Figure 1. Photo of an Isomate®-EGVM pheromone dispenser. The dispenser, consisting of an aluminum wire and a hollow tube, is attached to a white plastic hanger.

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 determine if health effects can occur in humans, experimental animals are exposed to chemical concentrations many times higher than those expected to be experienced by humans. In order to estimate potential health effects, scientists must estimate human exposures and compare them with what has been learned from animal studies.

The approach used in this evaluation is similar to that in the "Human Health Risk Assessment of Isomate®-LBAM Plus" (OEHHA, 2009). 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 could 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, BHT, and bumetrizole. Sources of information included data published in the scientific literature, as well as data submitted to the United States Environmental Protection Agency (US EPA) and California Department of Pesticide Regulation for registration purposes.

(1a) Toxicity evaluation of the SCLPs

The US EPA defines SCLPs as biochemicals, which are "*naturally occurring compounds, or identical or substantially similar synthetic compounds, designated by an unbranched aliphatic chain (between 9 and 18 carbons) ending in an alcohol, aldehyde, or acetate functional group and containing up to 3 double bonds in the aliphatic backbone*." US EPA has made two relevant determinations about these

chemicals: 1) that they are sufficiently similar toxicologically to be considered as a group (i.e., 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, 2006a). In this assessment, we used toxicity data specific to (E,Z)-7,9-dodecadien-1-yl acetate as well as those on other SCLPs.

(i) Acute Toxicity of SCLPs

Overall, SCLPs have very low acute inhalation, oral, and dermal toxicity in mammals. As an initial screen, toxicologists describe the acute toxicity to test subjects in terms of LD_{50}, or the dose estimated to kill half of the test animals. The LD_{50} value cannot be determined when the test animals survive an extremely high dose of chemical (referred to as the "limit dose"). In such case, the LD_{50} value cannot be determined and is expressed as "greater than" (>) the limit dose. This was indeed the case with some of the acute toxicity studies performed for SCLPs as described 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). "Low Toxicity" and "Very Low Toxicity" are examples of US EPA-derived toxicity categories, which 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, exposure duration of 4 hours is recommended for acute inhalation toxicity studies (US EPA, 1998).

Beroza et al. (1975) exposed rats to several pure SCLPs, such as (Z)-7-hexadecen-1-ol acetate, (Z)-7-dodecen-1-ol acetate, and (Z)-7-dodecen-1-ol, in aerosol form (1 to 10 micrometer (μm) droplets) for an hour and found no deaths or adverse effects at concentrations between 3.8 and 6.7 microgram/liter (mg/L). Acute inhalation toxicity of SCLPs in rats was reviewed by Inscoe and Ridgway (1992). The LC_{50} values 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_{50} 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®-EGVM, the pheromone active ingredient within the dispenser has an acute inhalation LC_{50} >5 mg/L in rats (Pacific Biocontrol Corp., 2010a). The acute inhalation toxicity value of >5 mg/L is based on the "*data available to the Agency (Federal Register Notice 1/26/94) on lepidopteran and other arthropod pheromones*" as quoted by Bolan (2010), see US EPA (1994). This determination is based on the US EPA's assessment that SCLPs have low acute inhalation toxicity with a median LC_{50} generally >50 mg/L. For the purpose of this evaluation, a no-observed-adverse-effect level (NOAEL) of 5 mg/L or 5,000 mg/m^3 is assumed for the acute inhalation exposure. Furthermore, an acute inhalation NOAEL of 229 milligrams/kilogram body weight-hour (mg/kg-hr) is estimated for SCLPs as follows, assuming (1) complete absorption via the lung; (2) breathing rate of 0.22 m^3/day or 0.00917 m^3/hr (US EPA, 1988); and (3) body weight of 0.2 kg for an adult rat (US EPA, 1986):

$$\text{Acute inhalation NOAEL} = \frac{5000\,\text{mg/m}^3 \times 0.00917\,\text{m}^3/\text{hr}}{0.2\,\text{kg}} = 229\,\text{mg/kg} - \text{hr}$$

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.

For the purpose of this evaluation, it is assumed that the acute oral NOAEL for the EGVM pheromone active ingredient is 5,000 mg/kg. This determination is based on the US EPA's assessment that SCLPs have low acute oral toxicity of LD_{50} >5,000 mg/kg (US EPA, 1994).

Acute eye irritation

SCLPs vary in their potential to cause eye irritation in rabbits. Materials are tested by instilling the chemical directly onto the eye and holding it 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 and 48 hours after treatment. Nearly complete recovery was noted at 72 hours after instillation (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).

For the purpose of this evaluation, it is assumed that the pheromone active ingredient within the dispenser can cause slight to moderate eye irritation.

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. The chemicals were tested on the bare skin of animals by direct application, and holding the material in place for a specific duration. Mortalities of test animals were not observed with (Z)-7-hexadecen-1-ol acetate and (Z)-7-dodecen-1-ol at doses up to 2,025 mg/kg. 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 animals exposed to the other two SCLPs. However, at the doses tested, the chemicals caused local skin reactions such as redness, pustulation, erythema, or edema. Necropsies revealed no abnormal findings other than these dermal alterations.

US EPA (2006a) and Health Canada (2002) classified SCLPs as Category III (Low Toxicity) for acute dermal toxicity, as there were no mortalities 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.

US EPA (1996) reported that (E+Z)-4-tridecenyl acetate had an acute dermal LD_{50} of >5,000 mg/kg in rabbits.

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 determination is based on the US EPA's assessment that SCLPs have low acute dermal toxicity with a LD_{50} >2,000 mg/kg (US EPA, 2004 & 2006a).

Based on the information available, it is assumed that the pheromone active ingredient in the dispenser can cause slight to moderate skin irritation. After reviewing toxicity studies of SCLPs, Beroza et al. (1975), Inscoe and Ridgway (1992), and the US EPA (1994) considered SCLPs to be mild to moderate skin irritants in rabbits.

According to the MSDS provided by the manufacturer of Isomate®-EGVM, the pheromone active ingredient within the dispenser is not considered to be a skin sensitizer in guinea pigs (Pacific Biocontrol Corp., 2010a).

(ii) Sub-chronic toxicity of SCLPs

There are four sub-chronic animal toxicity studies on SCLPs, i.e., two inhalation and two oral route studies. Some of the characteristics of the studies are summarized in Table 1.

Table 1. 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	Exposure duration	NOAEL and reported health effects	Reference
1-nonanol	Pregnant rats	Inhalation, 30 mg/kg-day	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, 17 mg/kg-day	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, 34 mg/kg-day	14 weeks	34 mg/kg-day (LOAEL* not described)	WHO (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 (1998)

*LOAEL = lowest observed adverse effect level

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 NOAELs calculated for 1-nonanol and 1-decanol were >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, that identified a NOAEL of 33.9 mg/kg-day. Many study details, such as the number of animals per dose group, the dosage used, 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, the chemical was administered in the diet of male and female rats at 0, 100, 500, or 2000 mg/kg-day for 37 days [Hansen (1992), as cited in OECD (1998)]. 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 any of the doses. There was a statistically significant decrease in total 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 observed, making it difficult to assess the toxicological significance of this finding. Based on this observation, a NOAEL of 100 mg/kg-day was identified 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 (2006a) has used the results of a 90-day feeding study of a commercial blend of branched acetates (even though this does not strictly meet US EPA's 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, histopathological 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.

(iii) 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 conjugating with glucuronide and being excreted by the kidneys (OECD, 2002a).

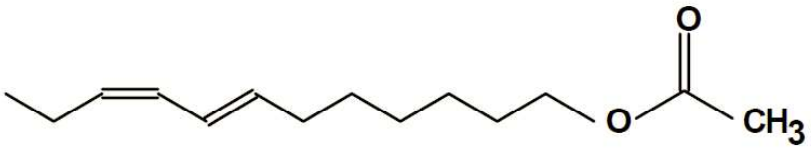
(iv) Genotoxicity of SCLPs

The California Department of Pesticide Regulation (CDPR) 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). Also, 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, 2006a).

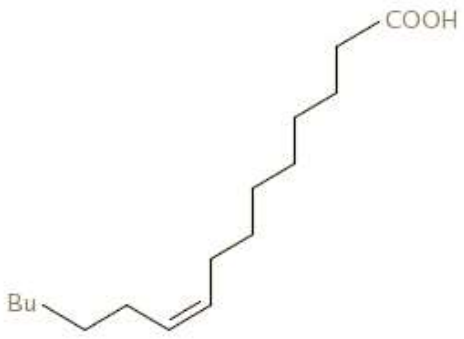
(v) Chronic toxicity of SCLPs

In our literature research, we could not locate any chronic animal toxicity or cancer studies of SCLPs. However, the concern that any adverse health effects may be 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 that SCLPs are mutagenic. In addition, the SCLPs are structurally similar to many fatty acids commonly encountered in food and cosmetic products, and are likely to be metabolized by the body into by-products that have no known toxicological concern.

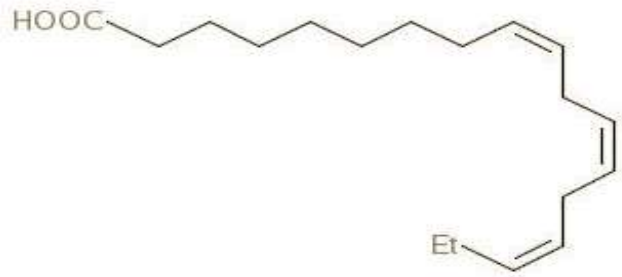
Figure 2. Chemical structure of (E,Z)-7,9-dodecadien-1-yl acetate and three fatty acids found in food.



(E,Z)-7,9-dodecadien-1-yl acetate [CAS# 55774-32-8], is an acetate (ester) with a 12-carbon chain and two double bonds. It is the pheromone in the Isomate®-EGVM.



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 oils from animal, vegetable, and marine products.



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, cow, and goat milk.

(1b) Toxicity evaluation of BHT

The anti-oxidant in Isomate® - EGVM is called butylated hydroxytoluene (BHT) or 2,6-bis(1,1-dimethylethyl)-4-methylphenol or 2,6-di-*tert*-butyl-*p*-cresol (CAS# 128-37-0). At room temperature, BHT is a colorless solid with a melting point of 70 ºC. At 20 ºC, the chemical has a density of 1.03 g/cm^3 and a vapor pressure of 1.1 Pa [Bayer AG (1986, 1973), as cited in OECD (2002b)]. BHT has a very low solubility in water, in the range of 0.6 to 1.1 mg/L at 20-25 ºC [Bayer AG (1986), as cited in OECD (2002b)]. It is susceptible to photo-degradation and has an estimated half-life of approximately 7 hours in air. BHT has a Henry's law constant of 4.12E-06 atm-m^3/mol at 25 ºC (US EPA, 2005). A chemical is considered to be sufficiently volatile if it's Henry's Law Constant is $\geq$ 1E-05 atm m^3/mol (US EPA, 2004). Therefore, the inhalation route of exposure is determined to be an insignificant pathway for BHT, especially when used in the twist tie formulation where the chemical is sealed inside a plastic tube.

BHT was patented in 1947 and was approved as a food additive by the FDA in 1954 (NOSB, 2002). BHT was placed on the U.S. Food and Drug Administration

Generally Recognized As Safe (GRAS) list in 1959. This chemical is used as an anti-oxidant in food products, cosmetics, pharmaceuticals, and many industrial goods and components. For use in food, an Acceptable Daily Intake (ADI) of 0 to 0.3 mg/kg-day has been established (OECD, 2002b).

BHT is readily absorbed through the gastrointestinal tract (US EPA, 2005) and slightly through intact skin (Lanigan and Yamarik, 2002). Oxidative metabolism of the chemical is mediated by the microsomal monooxygenase system. There are significant differences in this process among different species. For example, in rats, rabbits, dogs, and monkeys, oxidation of the *p*-methyl group predominates, but in humans, the *tert*-butyl groups are oxidized. In mice, however, both *p*-methyl and *tert*-butyl groups are oxidized in the metabolism of BHT (Madhavi et al., 1996). An enterohepatic circulation of the metabolite BHT acid and its glucuronide has been observed in rats. In rats, BHT and its metabolites are found in both urine and feces (via bile), while humans excrete BHT and its metabolites (primarily the carboxylic acid of BHT and its glucuronide) mostly in urine. Long-term exposure to BHT resulted in accumulation in adipose tissue with lower levels found in the liver. Elimination half-lives ranged from 7-10 days for the adipose and liver tissues. BHT accumulated in adipose tissue at a greater concentration in humans than in rats when compared on an exposure/body weight basis.

The toxicity data for BHT are summarized in the following sections.

(i) Acute toxicity of BHT

This chemical has a low acute toxicity. In rats, the oral LD_{50} was >2,930 mg/kg. No abnormalities in clinical signs, body weight and gross examination were observed during this acute oral test. The LD_{50} after dermal exposure was > 2,000 mg/kg. No clinical signs, local effects or body weight changes were noted after dermal exposure in rats up to 2,000 mg/kg (IUCLID, 2001). Other acute oral studies were reported in the literature; however, many of them did not provide technical details or noted toxic effects other than the lethal dose values. According to these studies, the acute oral LD_{50}'s for mice, rat, and rabbits ranged from 650 to 2100 mg/kg. Also, an acute oral LD_{50} of 10,700 mg/kg was reported from guinea pigs. The lowest LD_{50} was from a mouse study (650 mg/kg) where the symptoms included tremor and pulmonary edema (reference as cited in RTECS, 2008). We assume that the lowest LD_{50} (650 mg/kg) is equivalent to the acute lowest observable adverse effect level (LOAEL), and the acute NOAEL be derived from the acute LOAEL (650 mg/kg) by applying the factor of 10 (i.e., NOAEL = 65 mg/kg). This NOAEL was used to derive the acute oral RfD.

The lowest reported dose for human intoxication was a case study of woman who ingested 80 mg/kg BHT (a total dose of approximately 4 grams) and experienced gastritis, vomiting and coma (reference as cited in RTECS, 2008). If this dose is

assumed to represent the acute LOAEL, then an acute oral NOAEL of 8 mg/kg can be determined by applying an uncertainty factor of 10.

BHT has been shown to be a mild irritant to the skin and eyes of rabbits. It showed negative results in a skin sensitization test using guinea pigs. When patch tested on more than 15 individuals, the undiluted chemical produced mild skin irritation; a moderate skin reaction 14 days later was interpreted as sensitization (Mallette and von Haam, 1952, as cited in OECD, 2002b). Based on this limited report, and in the view of the widespread public exposure to BHT in consumer products, OECD did not draw a conclusion as to the skin irritation and sensitization properties of BHT (OECD, 2002b). Furthermore, BHT is not normally used in consumer products at elevated concentration as tested by Mallette and von Haam (1952). OECD (2002b) also noted that more recent patch test results from patients and medical surveillance reports of occupationally exposed workers were all negative. For example, allergic tests conducted on 358 patients patch-tested with 2.0 % (w/w) BHT were all negative (i.e., 0/358), and only two patients reported skin irritation (Kanerva, 1999). de Boer et al. (1989) also reported negative results using 2% BHT in a study of 286 metal workers.

(ii) Sub-chronic toxicity of BHT

In several sub-chronic oral studies, high doses of BHT (440-1,000 mg/kg-day) often caused fatal hemorrhagic effects in some mouse and rat strains. Marked strain and species differences were noted. At lower doses, BHT's effect on blood coagulation was found to be reversible in some responsive rat strains. Hemorrhagic effects were not observed in six different mice strains exposed for a week at 847-1,925 mg/kg-day. Also, such effects were not observed in dogs (760 mg/kg-day via diet), guinea pigs (380 mg/kg-day), rabbits (390 mg/kg-day), quails (1,056 mg/kg-day), and in infant and juvenile Rhesus monkeys (500 mg/kg-day).

A 28-day oral study in rats was recommended by the OECD (2002) as the critical study to derive a sub-chronic NOAEL. BHT was given to groups of male rats by gavage at doses of 0, 25, 250, or 500 mg/kg-day for 28 days. Dose-related effects in the liver were noted in the mid- and high-dose groups, which included clinical signs such as hepatomegaly and changes in biochemical parameters. A sub-chronic oral NOAEL of 25 mg/kg-day was determined from this data.

A sub-chronic dermal study in mice at doses ranging from 145-1,245 mg/kg-day showed that a 4-week exposure to BHT caused lung damage. Between Day 4 and 8 of the study, dose-dependent respiratory distress with subsequent mortality was observed in all dose groups, except for males at 145 mg/kg-day. Autopsies revealed congestion and enlargement of the lung, as well as damage to the alveolar epithelial cells. The skin at the site of application showed epidermal hyperplasia. All other organs appeared normal in all dose groups. A similar

treatment of rats (at 2,000 mg/kg-day) and of hamsters (at 3,100 mg/kg-day) did not show any adverse effects except a slight growth reduction.

(iii) Chronic toxicity of BHT

There are several chronic oral studies in rats. They show that the lungs, liver, kidneys, and thyroid are the main target organs at high doses, i.e., 100 - 900 mg/kg-day (OECD 2002b). Doses above 25 mg/kg-day resulted in thyroid hyperactivity, enlargement of liver, and induction of several liver enzymes. Using these results, a NOAEL of 25 mg/kg-day can be determined for the evaluation of chronic exposures.

(iv) Reproductive and developmental toxicity of BHT

A review by Madhavi et al, (1996) of single and multigeneration reproduction studies in rats, mice, hamsters, rabbits, and monkeys at low doses concluded that BHT exposure had no adverse reproductive or teratogenic effects. The estimated NOAEL for reproductive toxicity was 50 mg/kg. In rabbits administered 3-320 mg/kg-day by gavage during embryogenesis, an increase in intrauterine death was observed at the high doses. At an elevated dose level of 500 mg/kg-day in rats, effects were observed on litter size, number of males per litter, and body weight gain during lactation. Prolonged time to birth of first litters and a reduction in pup numbers and pup weight were also observed in mice at a high dose of 500 mg/kg-day.

According to OECD (2002b), the only effect on reproduction based on a two-generation study in rat conducted by Olsen et al. (1986) was a lower number of litters of 10 or more pups at birth at doses $\geq$ 100 mg/kg-day. No adverse effects on reproductive performance were found in other multi-generation studies quoted by OECD (2002b), which include a three-generation study in mice (Tanaka et al., 1993) and additional two-generation rat studies (Price, 1994 and McFarlane et al., 1997). The NOAEL for reproductive effect was 25 mg/kg-day (OECD, 2002b). There were no evidences of teratogenic effects from BHT from studies using mice or rats (OECD, 2002b). Two teratogenicity tests carried out with mice (Tokyo Metropolitan Research Laboratory of Public Health 1978) revealed no teratogenic potential, i.e., (1) from oral administration of BHT up to 800 mg/kg-d between days 7 and 13 of gestation; and (2) second test with a single administration of 1200 or 1800 mg/kg on day 9 of gestation. However, BHT produced maternal toxicity in mice at oral doses of above 240 mg/kg-day. Two other studies quoted by OECD (2002b) using rats supported the above findings (i.e., Han et al. 1993; Tanaka et al. 1990). OECD (2002b) identified a NOEL of 800 mg/kg-day for developmental toxicity.

In the review conducted by Madhavi et al., (1996), the lowest NOAEL for reproductive and developmental effects was 50 mg/kg-day. However, in a later review, OECD (2002b) determined that the lowest NOAEL for reproductive and developmental effects was 25 mg/kg-day. For the purpose of this evaluation, a more health-protective NOAEL of 25 mg/kg-day is used to evaluate the reproductive and developmental toxicity potential of BHT.

(v) Genotoxicity of BHT

BHT was generally found not to cause gene mutations in a number of short-term bacterial mutagenicity assays (*Salmonella typhimurium* and *Escherichia coli*, with and without metabolic activation), short-term eukaryotic mutagenicity assays (*Saccharomyces cerevisiae* with and without metabolic activation, *Drosophila melanogaster*), and *in vitro* mammalian gene mutation assays (Chinese hamster V79 cells/HGPRT locus) (reviewed by Lanigan and Yamarik, 2002). The negative *Salmonella* data included test strains TA102 and TA104, which were developed to be sensitive to oxidative DNA damage (Hageman et al., 1988). BHT was also generally found to be negative in *in vitro* and *in vivo* chromosomal damage assays (WHO, 1996).

There are also some positive genotoxicity data for BHT. BHT was reported to be positive in the following assays: DNA damage in the COMET assay for colon, glandular stomach, urinary bladder and brain cells from mice treated *in vivo (*Sasaki et al., 2002); mutation in the *Bacillus subtilis* rec assay (Hirano et al. (1978); mutation in L5178Y tk^+/tk^- mouse lymphoma assay (McGregor et al., 1988); chromosomal aberrations in human WI-38 embryonic lung cells (Stanford Research Institute, 1972); and lethality in the dominant lethal assay in Sprague-Dawley rats (Sheu et al., 1986).

(vi) Carcinogenicity of BHT

There are many cancer bioassays on BHT and they provided both positive and negative results. Depending on the dosing schedule, BHT may exert either anti-carcinogenic or tumor-promoting activity at relatively high doses.

BHT was found to be negative in several chronic bioassays of adequate treatment length (approximately lifetime) and sample size using either rats (NCI, 1979) or mice (NCI, 1979; Shirai et al., 1982).

Carcinogenicity data for BHT were reported in both rats and mice. Olsen et al. (1986) exposed male and female Wistar rats to 0, 25, 100 or 500 mg/kg/day BHT for 13 weeks, mated the exposed animals, then continued to expose the pregnant females (F_0 generation) through pregnancy and lactation. Offspring of both sexes (F_1 generation) were maintained post-weaning on the same exposure levels, with

the exception that the high-dose level was reduced to 250 mg/kg-day because of renal toxicity in the F_0 generation. Test animals were sacrificed at 141-144 weeks of age. Survival was 44% and 39% in treated males and females, respectively, in the high-dose F_1 group, as compared to 16% and 17% in the control males and females, respectively. High-dose F_1 males and females demonstrated statistically significant increases in incidence of hepatocellular adenoma and carcinoma compared to control group. Liver tumors were reported only in rats of more than 115 weeks old; however, no liver tumors occurred prior to this time. According to OECD (2002b), the oncogenicity of BHT at terminus of these studies may be due to the toxic effects of BHT at high doses and persistent cell proliferation. The conventional study duration of a cancer bioassay is 104 weeks for rats and mice.

Inai et al. (1988) exposed male and female B6C3F_1 mice to BHT in their diet at concentrations of 1% and 2% (i.e.,1,640 and 3,480 mg/kg-day in males; and 1,750 and 4,130 mg/kg-day in females) for 104 weeks. Treated animals were examined after a 16-week recovery period. A significant increase of hepatocellular tumors were noted in the BHT-treated male mice. A clear dose-response was noted for hepatocellular adenomas. The incidence of male mice with a hepatocellular carcinoma was not different from that of the concurrent controls. Hepatocellular tumors were not observed in the female mice.

According to OECD (2002b), BHT is not a genotoxic carcinogen. The non-genotoxic carcinogenic effects such as hepatocellular tumors observed in a long-term study were thought to be due to specific test conditions, i.e., (1) adaptive response of the liver and liver enzymes (e.g., mixed function oxidase) to lifetime treatment with xenobiotics as a “late” phenomenon (e.g., as with phenobarbitone); and (2) malnutrition due to deficiency of choline in the diet during lactation. Nevertheless, OECD concluded that the potential for non-genotoxic carcinogenicity due to persistent cell proliferation from the hepatoxic effect caused by elevated and chronic doses of BHT could not be completely ruled out.

BHT is not listed as a carcinogen under Proposition 65, and has been placed by IARC in its Group 3 category: i.e., not classifiable as to carcinogenicity to humans, based on limited evidence for the carcinogenicity of BHT in experimental animals (IARC, 1986).

Recently, US EPA (2005) conducted a human health hazard assessment on BHT and other antioxidants using available toxicity information, including mutagenicity and carcinogenicity data. The assessment considered aggregate exposure and concluded that BHT does not pose a significant health risk.

(1c) Toxicity evaluation of Bumetrizole

The UV-blocker in Isomate® - EGVM is 2-(2'-hydroxy-3'-tert-butyl-5'-methylphenyl)-5-chlorobenzotriazole (CAS# 3896-11-5). It has other names, such as Sumisorb 300®, Tinuvin 326, bumetrizole, and 2-(5-chloro-2-benzotriazolyl)-6-tert-butyl-p-cresol. It is a pale yellow solid and has a melting point of 137-142 ºC. The chemical is practically insoluble in water and soluble in many organic solvents. The chemical has a low vapor pressure of 7.9E-8 mm Hg at 25 ºC. As an UV absorber, the chemical functions as an energy transfer agent by absorbing the energy of the protected chemical and dissipating it as thermal energy before photochemical degradation can occur. Other benzotriazoles are used as corrosion inhibitors and anti-foggants in photographic media, and some of them are also used in aircraft deicing fluids. Bumetrizol has been approved for use in food packaging, dental resin composites, textiles, various plastic polymers and cosmetics (UC SAREP, 2003).

Toxicity data on the chemical are limited and most of the information described is obtained from studies reported by the Bioresearch Center Corporation in Wajima, Japan, and a document compiled by the University of California Sustainable Agriculture Research and Education Program (UC SAREP, 2003) titled, "Sumisorb 300, for use in crop protection."

(i) Acute toxicity of Bumetrizole

According to the UC SAREP report, the acute oral LD_{50}s in rats and mice were both greater than 5,000 mg/kg. In an acute inhalation study in rats, it was estimated that the LC_{50} was >0.27 g/m^3 (4 hr-exposure). The actual LD_{50}s in these studies are likely to be higher but little useful scientific information can be gained by testing beyond these elevated dose levels. The Bioresearch Center Corporation studied acute oral toxicity of bumetrizole in rats and found the LD_{50} to be above 2,000 mg/kg (JBC, 2007a). The study result showed no mortality, no change in body weights, and no abnormalities from the necropsy of animals. For the purpose of this evaluation, the acute oral NOAEL was assumed to be 2,000 mg/kg.

Bumetrizole was an eye irritant in rabbits. It was not a skin sensitizer when tested in humans.

(ii) Sub-chronic toxicity of Bumetrizole

According to the report of UC SAREP (2003), the NOAEL for rats fed with the chemical over three months was 2,500 ppm. Beagles fed at >2,500 ppm mixed with feed over three months showed weight loss and increased liver weight.

The Bioresearch Center Corporation studied sub-chronic, reproductive and developmental toxicity of bumetrizole in rats. Animals were exposed by repeated daily oral administration by gavage of 0, 62.5, 250, or 1,000 mg/kg for various durations. The sub-chronic oral administration study showed no abnormalities in test animals (i.e., mortality rates, general health, changes in body weight and food intake, Functional Observational Battery (FOB) observations, hematology and blood biochemistry, organ weights, and in histopathology for both sexes at all dose levels were comparable to control groups).

The combined reproductive and developmental testing did not show any difference between the treated and control groups of F0 and F1 generations. Many parameters were investigated including but not limited to: copulation rate, number of fertilized female, pregnancy period, birth rate, number of corpus luteum, implantation rate and indices, number of death at birth, viable number of offspring, and sex ratio. Based on the study results, the NOAEL was >1,000 mg/kg-day for sub-chronic oral toxicity as well as reproductive and developmental toxicity (JBC, 2007b).

According UC SAREP (2003), when bumetrizole was orally administered to mice on days 6-15 of pregnancy, it did not show any teratogenicity. The NOAEL derived from this study was reported to be 1,000 mg/kg-day.

(iii) Genotoxicity and Carcinogenicity of Bumetrizole

According to UC SAREP (2003), bumetrizole was negative in the Ames test. The Bioresearch Center Corporation investigated the mutagenic potential of bumetrizole by using Salmonella typhimurium (TA100, TA98, TA1535 and TA1537) and *Escherichia coli* reverse mutation assays. Under the test conditions, with or without S9 mixtures, bumetrizole did not induce genetic mutation (JBC, 2006a).
The center also used a mammalian cell culture to study the clastogenic potential of bumetrizole. The test results showed that bumetrizole did not induce chromosomal abnormalities (JBC, 2006b).

Benzotriazoles such as bumetrizole are not biodegradable and tend to persist in the environment due to their UV stability and resistance to oxidation. In the environment, bumetrizole would break down to 5-chlorobenzotriazole (UC SAREP, 2003). Benzotriazol (CAS # 95-14-7), which is the molecular base compound of bumetrizole and other phenolic benzotriazols, is at least ten times more toxic to mammals with an acute oral LD_{50} of 500 mg/kg (i.e., bumetrizole acute oral LD_{50} > 5000 mg/kg; UC SAREP, 2003, p. 8/14; US EPA, 2006b & 2009).

(2) Exposure Evaluation

This section describes how OEHHA estimated human exposure to the chemicals in Isomate®-EGVM twist-ties. When the Isomate®-EGVM is used as described in the product label, acute inhalation, sub-chronic inhalation, and acute 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 a pheromone dispenser and ingests the chemicals inside.

The inert ingredients such as BHT and bumetrizole are either not volatile or have extremely low volatilities; therefore these chemicals are likely to remain inside the dispenser. The potential for dermal contact or inhalation of vapor or particulate of these inert ingredients are therefore not evaluated. A study with codling moth mating disruption dispensers showed that the relative concentration of non-volatile inert ingredients increased as the pheromones volatilized out of a dispenser. In a field-aged dispenser, it can contain up to 75% non-volatile materials (Millar and McElfresh, 1994). The chemical-specific exposure pathways evaluated in this assessment are summarized in Table 2.

Table 2. A summary table indicating exposure pathways evaluated for the SCLPs, anti-oxidant, and UV-blocker.

Chemical	**Exposure Pathway**	**Exposure Duration**	**Exposure Scenarios**
SCLPs	Inhalation	Acute	Adult & child
	Inhalation	Sub-chronic	Adult & child
	Dermal	Acute	Adult & child
	Oral	Acute	Child
BHT	Oral	Acute	Child
Bumetrizole	Oral	Acute	Child

(a) Inhalation exposure

The Isomate®-EGVM is designed to be hung on tree branches or grape vines, approximately four to ten feet off the ground. It is effective for at least 120 days. During that time, the SCLPs in the plastic dispenser 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®-EGVM, it is difficult to measure the chemical concentrations in the field. Even if such measurements were performed, the data only represent air concentrations achievable under a specific set of conditions. The release rate of the pheromone varies with environmental factors, such as temperature and wind velocity, as well as days of deployment 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.

A simple air dispersion model can be used to estimate the air concentrations of chemicals. First, the volume of air that is filled with chemicals released from a single dispenser is estimated. In order for the pheromone dispensers to be effective, the manufacturer of Isomate®-EGVM (Pacific Biocontrol Corp.) recommends a maximum target application rate of 200- 250 dispensers per acre. Assuming a maximum target application rate of 250 per acre or 250 dispensers per 4,046.9 m^2 and a square-shaped grid, this application rate 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®-EGVM is designed to be attached to tree branches or grape vines at a height of 1.2 to 3 m (4 to 10 ft). In the modeling, it is assumed that a pheromone dispenser is hung at a height of approximately 1.4 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).

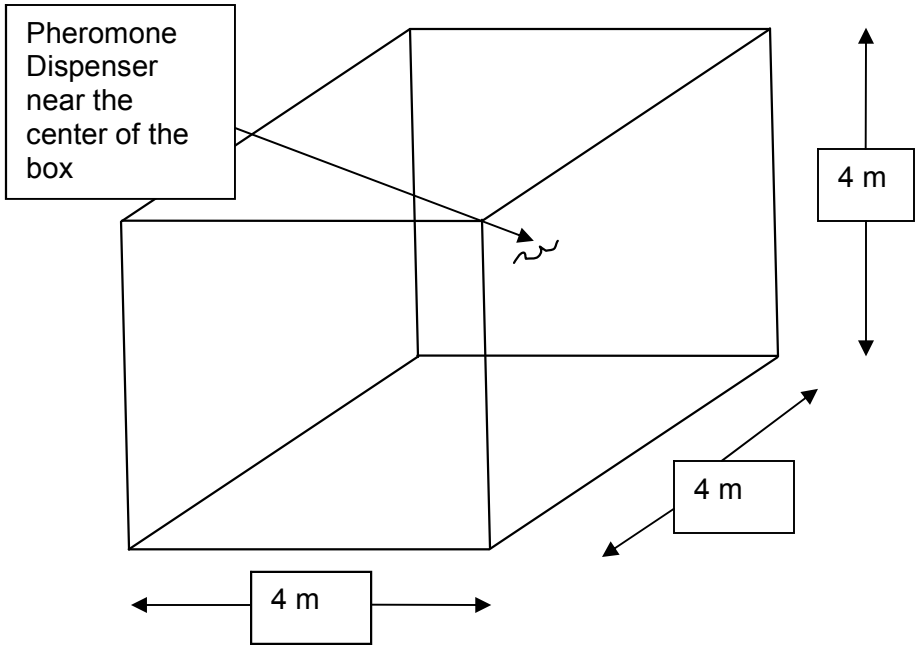


Figure 3. A diagram to show the dimensions used in estimating the concentrations of chemicals that would be in the air.

According to the information provided in the MSDS of Isomate®-EGVM, the maximum emission rate is estimated to be 35 μg of material per hour per dispenser (Pacific Biocontrol Corp. (2010a).

For the purpose of this risk assessment, it is assumed that a dispenser releases 35 μg of pheromone into a volume of 64 m^3 once an hour, and this volume is completely replaced with fresh air once an hour. Also, no dilution or loss of material is assumed prior to each air-exchange. This is equivalent to assuming the air-exchange rate (or ventilation rate) of once an hour (1 hr^{-1}). This assumption is health-protective because the air-exchange rates measured in different types of buildings in different geographical areas are much higher than 1 hr^{-1}. 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, Australia (Pluschke, 2004). Since the pheromone dispenser is only used in an outdoor environment, the assumption that the air-exchange rate used for this modeling (i.e., 1 hr^{-1}) is lower than those measured in residential houses (e.g. 3.7 - 26.3 hr^{-1}) is likely to over-estimate the actual air concentrations of chemicals released by Isomate®-EGVM.

Assuming all of the material released consists of SCLPs, the concentrations of SCLPs in air for acute exposures are calculated as follows:

$$\text{Estimated concentration of SCLPs in air for acute exposure} = \frac{35\,\mu g \times 1.0}{64\,m^3} = 0.55\,\mu g/m^3$$

It is important to note that this value, 0.55 μg/m^3, represents a "high-end" air concentration estimate. It is likely to over-estimate the actual air concentration for the following reasons:

- The calculations assume a maximum application rate of 200-250 dispensers per acre. The actual application rate is much lower. Based upon studies of urban vegetation density, only about 20% of an urban area land use is vegetation. The other 80% is roads, houses, commercial buildings, and open land that cannot be treated. The actual application rate could be as low as 50 dispensers per acre.
- The calculations assume the volatilized material is confined to a relatively small volume (4m x 4m x 4m), no material is lost due to absorption, and there is no dilution due to diffusion or mass air movement within one hour.

To ensure the protection of public health, the "high-end" air concentration estimate of SCLPs will be used in the evaluation of health hazards associated with acute inhalation exposure.

The dispensers are designed to continuously release the SCLPs for about 120-180 days and if the moth infestation is not abated after that time, the spent dispensers are replaced with fresh ones. Since the exposure may last several months it is possible to have a sub-chronic inhalation exposure to the SCLPs. While it is appropriate to assume the "worst case" scenario to be health protective for the acute exposure, exposure to such a "high-end air concentration estimate" for period of months is unlikely to occur. For this reason, a dilution factor of 10 is applied to this "high-end air concentration estimate" for the evaluation of health effects associated with a longer term exposure. An air-exchange rate of ten times an hour (10 hr^{-1}) is a conservative assumption since the monitoring data show that residential air-exchange of homes in a mild-to-warm climate can be as high as 26.3 hr^{-1} (Pluschke, 2004).

Using this reasoning, the estimated air concentration for sub-chronic exposure would be 10 times lower than that estimated for acute exposure using this assumption. The estimated air concentration for evaluating the sub-chronic exposure to SCLPs is 0.055 μg/m^3.

(ii) Estimation of acute inhalation dose for SCLPs

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).

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

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

where:

C_A = concentration in air, μg/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

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

where:

C_A = concentration in air, μg/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

Based on these two equations, the acute inhalation doses of SCLPs for an adult and a child are estimated to be 0.025 and 0.058 μg/kg-hr, respectively.

(iii) Estimations of sub-chronic inhalation dose for SCLPs

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 the acute exposures,

- Individuals have average activity levels and thus average breathing rates, and
- Individuals are exposed continuously for months.

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

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

where:

C_A = concentration in air, µg/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)

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

where:

C_A = concentration in air, µg/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)

The sub-chronic inhalation doses of SCLPs estimated using the above equations for an adult and a child are 0.013 and 0.025 µg/kg-day, respectively.

(b) Dermal exposure to SCLPs

Dermal exposure may occur when individuals handle the pheromone dispensers with their bare hands. Since 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 that 35 µg of SCLP (i.e., 100% of the material released from a dispenser in one hour) is available for dermal exposure.

The estimated acute dermal doses of SCLPs 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:

$$\text{Estimated acute dermal exposure for an adult} = \frac{35\,\mu g \times 1.0}{70\ kg} = 0.5\,\mu g / kg$$

$$\text{Estimated acute dermal exposure for a child} = \frac{35\,\mu g \times 1.0}{18\,kg} = 1.9\,\mu g / kg$$

(c) Oral exposure to SCLPs, BHT, and Bumetrizole

When Isomate®-EGVM is properly used as recommended by the manufacture, the potential for oral exposure to the chemicals inside is very low. Nevertheless, in the unlikely event where a child gets hold of a dispenser and chews the pheromone tube, a conservative estimate would be that up to 25% of the chemical inside is ingested. According to the manufacturer, each dispenser contains 253.4 mg of chemical and 75.7% by weight is EGVM pheromone. The other 24.3% is inert ingredients and chemical by-products, which includes other SCLPs, and straight chained acids and alcohols. For the purpose of this evaluation, it is assumed that 95% by weight is SCLPs and 5% are the two inert ingredients (i.e., BHT and bumetrizole are 2.5% each). The estimated acute oral doses are calculated as follows using 18 kg as the child's body weight:

$$\text{Estimated acute oral dose of the SCLPs} = \frac{253\,mg \times 0.95 \times 0.25}{18\ kg} = 3.3 mg / kg$$

$$\text{Estimated acute oral dose of BHT} = \frac{253\,mg \times 0.025 \times 0.25}{18\,kg} = 0.088\,mg / kg$$

$$\text{Estimated acute oral dose of bumetrizole} = \frac{253\,mg \times 0.025 \times 0.25}{18\,kg} = 0.088 mg / kg$$

(3) Dose-Response Evaluation

In this section, the 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. The acute RfDs are developed and presented in Tables 3 and 4 using this approach with the identified acute NOAELs.

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

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

Table 4. A summary table showing the calculation of acute oral RfDs for BHT and bumetrizole.

Chemical	Acute NOAEL	UF	Acute RfD
BHT	65 mg/kg	100	0.65 mg/kg
Bumetrizole	2000 mg/kg	100	20 mg/kg

As described in the hazard identification section, a sub-chronic inhalation NOAEL of >17 mg/kg-day was determined for the SCLPs. The sub-chronic inhalation RfD of 0.057 mg/kg-day or 57 µg/kg-day can be calculated by applying an overall UF of 300 to the NOAEL value (17 mg/kg-day). The UF of 300 consists of the following factors: (1) 10-fold for inter-species variability; (2) 10-fold for intra-species variability; and (3) 3-fold for an exposure period of the animal study of less than 90 days.

(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 quotient (HQ) approach is used to estimate this likelihood. A HQ is a ratio calculated by dividing an estimated human exposure with an appropriate RfD. The lower the HQ, 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.

HQs estimated for an adult and a child following acute exposures to SCLPs through the inhalation and dermal routes are summarized in Table 5.

Table 5. A summary table of the hazard quotients (HQs) estimated for an adult and a child resulting from acute exposures to SCLPs through the inhalation and dermal routes.

Exposure Route	Estimated dose	Acute RfD	HQ	Potential Health Risk to Adult or Child
Inhalation exposure (adult)	0.025 µg/kg-hr	2,290 µg/kg-hr	0.000011 (1.1×10^{-5})	Very low to none
Inhalation exposure (child)	0.058 µg/kg-hr	2,290 µg/kg-hr	0.000025 (2.5×10^{-5})	Very low to none
Dermal exposure (adult)	0.5 µg/kg	20,000 µg/kg	0.000025 (2.5×10^{-5})	Very low to none
Dermal exposure (child)	1.9 µg/kg	20,000 µg/kg	0.000095 (9.5×10^{-5})	Very low to none

The estimated HQs for an adult and a child resulting from sub-chronic inhalation exposure are 0.00023 (2.3×10^{-4}) and 0.00044 (4.4×10^{-4}), respectively, based on the sub-chronic inhalation dose estimates calculated (0.013 µg/kg-day for an adult and 0.025 µg/kg-day for a child) and the RfD of 57 µg/kg-day for the SCLPs.

Based on this risk assessment performed for the pheromone dispenser usage as recommended by the manufacture, the potential health risks to an adult or a child exposed to the SCLPs through inhalation and dermal routes are expected to be very low. There should be no oral exposure to the chemicals inside the sealed tube if this device is used in the way it is designed. In the unlikely event that a child gets hold of a pheromone dispenser and ingest part of its content, the HQs for this incident are provided in Table 6.

Table 6. ***A summary table of the HQs estimated for an exposure scenario where a child accidentally ingests 25% of its contents.***

Chemical	Estimated oral dose	Acute oral RfD	HQ	Potential Health Risk to Adult or Child
SCLPs	3.3 mg/kg	50 mg/kg	0.066	Very low
BHT	0.088 mg/kg	0.65 mg/kg	0.14	Very low
Bumetrizole	0.088 mg/kg	20 mg/kg	0.0044	Very low

No adverse health effect is expected when a HQ is below one. While (E,Z)-7,9-Dodecadien-1-yl acetate is the active ingredient of Isomate®-EGVM, there is limited toxicity information specific to this chemical. It belongs to a class of chemicals called SCLPs and they have similar chemical structures and physical properties. US EPA (1994, 2006a) determined that SCLPs are sufficiently similar toxicologically to be considered as a group. In this assessment, potential health effects of (E,Z)-7,9-Dodecadien-1-yl acetate were evaluated by using surrogate toxicity data.

No chronic toxicity or cancer studies of the SCLPs in experimental animals were found in the literature. However, concerns that adverse health effects may be associated with long-term exposure to the SCLPs are mitigated by the very low HQs determined for sub-chronic inhalation exposures. There is no evidence to indicate that the SCLPs are carcinogenic. Furthermore, the SCLPs are structurally similar to some common fatty acids and are likely to be metabolized by the body into by-products without any toxicological concern.

As discussed in the hazard identification section, the pheromone in Isomate®-EGVM in an undiluted form are slight to moderate skin and eye irritants in rabbits. As a precautionary measure, it is advisable to avoid eye or skin contact with the pheromone.

The health risk assessments of the BHT and bumetrizole in Isomate®-EGVM provided above demonstrate that these two chemicals are not likely to pose any health risk to humans. As a precautionary measure, skin and eye contact with these chemicals should be avoided as they have been shown to be mild irritants in animal tests.

The conclusion of this assessment is that pheromones and the two additives in pheromone dispensers will not cause adverse effects in humans, which is consistent with a determination provided from the U.S. EPA (2006). This

conclusion is based on the following factors: (1) general low toxicity and high volatility of pheromones; (2) low application rate; and (3) low human exposure expected from the chemicals in these devices.

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