POTENTIAL HEALTH EFFECTS OF BIOMIST 4 + 12 ULV MOSQUITO SPRAY IN THE CELEBRATION COMMUNITY DEVELOPMENT DISTRICT, FLORIDA

FLORIDA DEPARTMENT OF AGRICULTURE AND CONSUMER SERVICES

DIVISION OF AGRICULTURAL ENVIRONMENTAL SERVICES

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This review evaluates potential human health risks resulting from Ultra Low Volume (ULV) mosquito control activity in the Celebration Community Development District in Celebration, Florida. Conclusions drawn in this review are based on the available information regarding the use of a specific pesticide product at a particular locale within the State of Florida, and do not necessarily apply to other exposure scenarios in which different environmental conditions may be present. The Department utilized information from a wide variety of sources in formulating the conclusions contained within this report. These sources include research findings obtained from publicly available scientific literature, and reports from federal authorities, international governing bodies, pesticide registrants, and agencies both within and outside of the State of Florida. This review includes both quantitative and qualitative information. The Scientific Evaluation Section welcomes comments and discussion of these issues. Mention within this document of any particular pesticide product or other brand of products by name does not constitute an endorsement of those products by the Florida Department of Agriculture and Consumer Services. Mention of a trademark or a proprietary product does not denote a guarantee or a warranty of the product by the Florida Department of Agriculture and Consumer Services, and does not imply its approval to the exclusion of other products that may also be available.

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Executive Summary

Background

On December 29, 2008, the Florida Department of Agriculture and Consumer Services (FDACS) Bureau of Entomology and Pest Control received a letter from the Celebration Community Development District (Hereafter referred to as "Celebration") requesting a programmatic review of Celebration's current mosquito control program. On January 8th and 9th of 2009, another Celebration representative sent follow-up correspondence requesting that FDACS conduct environmental sampling in the Celebration Community to test for the presence of permethrin and piperonyl butoxide (PBO). These are compounds present in Biomist 4 + 12 ULV, a mosquito adulticide product that reportedly has been used over the years since the inception of the Celebration Community in the 1990's. In addition, Celebration has also requested for FDACS to review the scientific evidence on potential carcinogenic and endocrine disrupting effects of permethrin and other components present in the Biomist 4 + 12 ULV mosquitocide. Of particular concern to the Celebration representative was the recent U.S. Environmental Protection Agency (USEPA) change in permethrin's cancer classification from "possible carcinogen" to "likely human carcinogen." The Celebration representative is concerned that the mosquito spray chemicals may be responsible for many of the reported adverse health effects in the community.

The FDACS Bureau of Entomology and Pest Control contacted the Bureau of Pesticides Scientific Evaluation Section (SES) to evaluate and address these concerns based on the best and most recent available scientific evidence. SES is not aware at this time as to whether the Celebration board has contacted the Florida Department of Health to request a cancer cluster evaluation in order to determine whether age-adjusted cancer rates in the area are elevated when compared to the rest of Florida.

Mosquitoes can transmit diseases to humans such as encephalitis, dengue fever, malaria and West Nile Virus, and a variety of other diseases to wildlife and domestic animals. The USEPA and FDACS review and register pesticides and their labeling to ensure that the pesticides used to protect public health are applied by methods which minimize the risk of human exposure and adverse health and environmental effects.

Carcinogenic Potential of Permethrin and Piperonyl Butoxide

- The USEPA has classified permethrin as a "likely human carcinogen" based on results of long-term, high concentration permethrin feeding studies in rodents. These studies show that permethrin causes benign lung and liver tumors in some but not all species or strains of tested rodents. Piperonyl butoxide is classified as a "possible human carcinogen" by the USEPA based on liver tumors observed in rodents.
- The USEPA cancer classification for these compounds does not imply that the Agency believes intermittent, low-level inhalation and dermal exposure following ULV mosquito control activity causes cancer in humans. To the contrary, the Agency has determined that the amount of exposure from mosquito control activity is sufficiently low that there is negligible cancer risk.
- There is no consensus among the various U.S. and international governmental agencies and other authoritative bodies regarding the potential for permethrin to cause cancer in people. The USEPA is alone among recognized authorities in classifying permethrin as a "likely human carcinogen."
- Available evidence from epidemiological studies has not demonstrated that permethrin causes cancer in people.

Endocrine Disruption

- Some, but not all, permethrin studies using human cell lines or experimental animals are suggestive of and consistent with a possible weak endocrine disrupting effect. However, the overall evidence from these studies and their relevance to whole human organisms remains inconclusive.
- The USEPA does not consider permethrin or piperonyl butoxide to be endocrine disruptors at this time, although the Agency has planned additional confirmatory endocrine disruption studies for these compounds because of their high volume of use.
- There is no evidence that exposure to low-level permethrin from ULV mosquito control activities causes endocrine disruption effects in people.

Governmental Agency Toxicological Evaluations of Permethrin for Mosquito Control

U.S. Environmental Protection Agency (USEPA)

The USEPA states, "Pyrethroids, when applied at mosquito control rates, are low in toxicity to mammals...Mosquito control formulations of permethrin break down in the environment, and high temperatures and sunlight accelerate this process" (USEPA, 2002a).

The USEPA evaluated human health risks from permethrin following outdoor activities after mosquito abatement public health ULV adulticide application by truck fogger and aerial spray. Risks were assessed for adults and children living in residential areas. The Agency calculated post-application permethrin risks through the dermal and inhalation routes for adults and children. Oral risks (*i.e.*, hand-to-mouth, object-to-mouth and soil ingestion) were also calculated for children. The Agency's calculations assumed the following:

- Application rates are in the range of 0.007 to 0.1 lb permethrin per acre, as specified on permethrin labels;
- Exposure durations are expected to be 20 minutes;
- The amount of permethrin available for inhalation exposure is 1% of the product released based on aerial dilution;
- The breathing rate values utilized (per NAFTA) for moderate adult activity is 1.6 m^3/hour and the toddler breathing rate for light activity is 0.8 m^3/hour)

Both non-cancer and cancer risks were determined by the USEPA to be well below levels of concern (USEPA, 2007a). For ULV truck-fogger applications, the exposure levels were hundreds of times less than the USEPA's level of potential concern. The USEPA assessed exposure to permethrin in mosquito ULV truck fogger spray up to 288 days and the Agency determined that the benchmark of one in a million additional theoretical cancer cases was not exceeded (USEPA, 2006a; USEPA, 2005a).

U.S. Centers for Disease Control and Prevention (CDC)

The CDC published a study in which urinary metabolites of permethrin were measured in people following mosquito control activities with products containing permethrin and piperonyl butoxide (CDC, 2005). The results showed that the amount of permethrin exposure from ULV spraying was very small. Permethrin metabolite levels among people in mosquito control areas were comparable to levels in people in the general population. The report concluded, "These findings suggest that ULV application of naled, permethrin, and d-phenothrin is safe to humans as part of integrated vector control. The findings are noteworthy because ULV applications of pesticides that kill adult mosquitoes are an important tool in the public health response to West Nile Virus."

U.S. Agency for Toxic Substances and Disease Registry (ATSDR)

The ATSDR states, "No indication exists that permethrin has a significant adverse effect on humans when used as recommended" (ATSDR, 2005).

U.S. Food and Drug Administration (FDA)

The FDA makes the following recommendation to avoid adverse health effects from mosquitoes and other pests: "Treat camping gear, clothes, and shoes with permethrin, which repels and kills ticks, mosquitoes, and other insects. Clothing that is pre-treated with permethrin is also commercially available" (FDA, 2008).

U.S. National Institute for Occupational Safety and Health (NIOSH)

NIOSH recommends the use of permethrin on clothing to protect outdoor workers from mosquitoes, which can carry West Nile Virus (NIOSH, 2005).

Florida Department of Health (FDOH)

"At the levels used in mosquito control, no health affects in humans are expected. The amount of permethrin used in mosquito control is many times lower than the amount of permethrin that causes adverse effects in animals or that would cause health effects in humans" (FDOH, 2004).

"Since permethrin is most effective at killing adult mosquitoes when airborne, applications are made to minimize the amount of permethrin that settles. Therefore, little permethrin is likely to settle in your pool.

In addition, any permethrin that may reach the water would be significantly diluted and broken down quickly. You can cover your pool before the spraying occurs; however, no special precautions or waiting periods are required for swimming pools" (FDOH, 2004).

California Department of Health Services (CDOH)

The California Department of Health Services (CDOH, 2005) has stated that mosquito control pesticides are relatively safe when applied by ULV spraying according to label instructions for the following reasons:

1. Permethrin and piperonyl butoxide rapidly break down in the environment
2. Very low pesticide application rates are used with ULV spraying
3. Permethrin and piperonyl butoxide are poorly absorbed through the skin
4. There is no evidence that people are exposed to any measurable level of these pesticides as a result of ULV mosquito spray activities
5. There is little evidence of any population health effects following mosquito control spraying activities

New York City Department of Health and Mental Hygiene (NYCDOH)

A detailed public health analysis conducted by the NYCDOH determined that no significant adverse public health impacts would be expected from exposure to the mosquito adulticides when applied for the purposes of mosquito control. The quantitative human health risk assessment included evaluation of both cancer and non-cancer health endpoints for permethrin and piperonyl butoxide for adults and children. The NYCDOH states, "As reported in the literature, only permethrin doses many times larger than levels expected from spraying have been found to produce toxic effects associated with skin, ingestion and inhalation exposures." (NYCDOH, 2001).

Biomist 4 + 12 ULV Mosquito Adulticide

Biomist 1.5 + 7.5 ULV consists of 1.5% permethrin (a pyrethroid insecticide), 7.5% piperonyl butoxide (a synergist), and 91% inert ingredients which include "petroleum distillates" (Biomist MSDS, 2005). The Biomist 1.5 + 7.5 ULV label contains the signal word "Caution," which is the least severe acute toxicity category designated by the USEPA (NPIC, 2008). The product is applied as an ultra-low volume aerosol

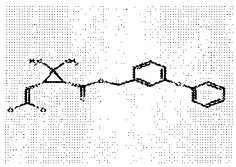
at a rate of a few ounces of formulated product per acre. This is equivalent to 0.00087 up to 0.007 pounds of permethrin per acre and 0.00437 up to 0.035 pounds of piperonyl butoxide per acre (Biomist Label, 2009), or a maximum of 3.18 grams per acre of permethrin and 15.9 grams of piperonyl butoxide per acre.

Petroleum distillates are comprised of a mixture of numerous compounds which may vary greatly in composition and toxicity (ATSDR, 1995). The Biomist 1.5 + 7.5 ULV MSDS does not provide a CAS registry number that specifies which type of petroleum distillate mixture is present in the formulation. However, the USEPA has listed "White mineral oil (petroleum)" as a minimal risk inert ingredient that may be used in food-use pesticides (USEPA, 2008).

Ultra Low Volume (ULV) technology allows for the use of very low amounts of pesticides. The practice of spraying between dusk and dawn, when most people are indoors, helps to minimize exposure to these pesticides. Permethrin has very low volatility, and is not expected to be found in air once it settles to the ground (Williams et al., 2008). In contrast, petroleum distillates are volatile and may remain in the air for longer periods until they are dissipated by the wind or are degraded by environmental factors such as heat, light, oxidation and microbial degradation (ATSDR, 1995).

Permethrin

CAS Registry Number 52645-53-1



Permethrin is an insecticide in the pyrethroid class. Pyrethroid compounds are synthetic chemicals manufactured to replicate the insecticidal properties of pyrethrins, naturally occurring substances found in chrysanthemum flowers. Permethrin is considered to be less toxic than the naturally-occurring pyrethrins. Permethrin has been registered by the USEPA since 1977. It has been used as a broad-spectrum insecticide on food crops, as dips, shampoos and sprays for pets and livestock, on clothing, and for mosquito abatement. It has uses both indoors and outside of homes and in various modes of transportation, (USEPA, 2007a). The FDA has approved the use of permethrin (sometimes in combination with piperonyl butoxide) for treating head lice and scabies (FDA, 2003). Post-marketing surveys have documented the relative safety of consumer products containing permethrin (Andrews et al., 1992; Carson et al., 1988). Pyrethroid compounds are the most common pesticides in current use

worldwide for control of agricultural and indoor pests (Saito et al., 2000). Permethrin is the most frequently used pyrethroid insecticide in the U.S. and worldwide (Zhang et al., 2008; Ahn et al., 2006; ATSDR, 2005).

While highly toxic to insects, permethrin exhibits low mammalian toxicity (Kamrin, 1997; Hayes and Laws, 1991). This is attributed to several factors:

- Permethrin is poorly absorbed through the skin. Less than 2% of permethrin is absorbed percutaneously in human studies (Punareewattana, 2000; Fradin, 1998).
- Mammalian livers contain increased levels of detoxifying enzymes which rapidly inactivate permethrin in the body, converting it to inactive metabolites that are quickly excreted from the body (Williams et al., 2008; Fuortes, 1999; Fradin, 1998).
- Mammals have a higher body temperature than insects. Pyrethroids show a negative temperature coefficient of action (Williams et al., 2008)
- Mammals have an inherently lower sensitivity of ion channel target sites compared to insects (Williams et al., 2008).

Permethrin is a class I pyrethroid compound, the least toxic type of pyrethroid (NYCDOH, 2001). The toxicity of permethrin in mammals depends on the composition of isomers, with cis-permethrin being more toxic than trans-permethrin. Undiluted technical grade permethrin (25:75 to 40:60 *cis*:*trans* isomeric mixtures) has low acute toxicity after oral, dermal and inhalation exposure (Hayes and Laws, 1991; NRC, 1994). Permethrin has a dermal LD_{50} (the dose required to kill half of test animals) of over 4,000 mg/kg bw (milligrams of permethrin per kilogram of body weight) in rats. The 4-hour inhalation LC_{50} for rats was greater than 23.5 mg/L indicating that permethrin is practically non-toxic acutely by the inhalation route of exposure. Moreover, the inhalation route of exposure is attenuated because of permethrin's low vapor pressure, which suppresses volatilization in air (Kamrin, 1997; NRC, 1994). Permethrin is mildly irritating to the eyes and slightly irritating to skin. It was not a skin sensitizer when tested by the Magnusson and Kligman method (NRC, 1994). Permethrin is potentially neurotoxic at sufficiently high levels of exposure (WHO, 2005a).

The Agency for Toxic Substances and Disease Registry (ATSDR) recommends the following to reduce exposure to outdoor pyrethroid mosquitocide sprays: "Remaining indoors and closing your windows while your neighborhood is being sprayed will lessen your exposure...keep family pets indoors during this time" (ATSDR, 2005). These precautions intend to provide residents with prudent, common-sense advice to reduce an unnecessary source of pesticide exposure.

Permethrin Concentrations in Air

Using computer simulation modeling (AgDrift), the USEPA calculated an outdoor permethrin concentration of 0.0000029 mg/m^3 (milligrams per cubic meter) following an aerial ULV mosquito treatment. The Agency indicated that the spray would quickly dissipate and that the concentration would diminish within about 20 minutes to an hour of spraying (USEPA, 2006a).

Permethrin is applied at much higher rates for agricultural purposes than for outdoor ULV mosquito control. However, actual measurements of permethrin in ambient outdoor air following agricultural applications show that even with higher agricultural rates, permethrin levels in air are still quite low. For example, in California, the maximum 24-hour level of permethrin was 0.000015 mg/m^3 (CDPR, 2003).

Permethrin and piperonyl butoxide are applied inside of homes in the U.S. Consequently, permethrin is commonly found at low levels in house dust and indoor air (Williams et al., 2008). Indoor permethrin applications occur in a confined area and are more persistent than outdoor treatments. Therefore, indoor permethrin exposure levels are expected to be higher than outdoor exposure levels (USEPA, 2007b; USEPA, 2005a; CDOH, 2005). The maximum reported concentration of permethrin in unventilated indoor air following a broadcast flea treatment was 0.054 mg/m^3 (Koehler and Moye, 1995).

Governmental agencies use No Observed Adverse Effect Levels (NOAELs) obtained from animal studies as a starting point to calculate exposure levels that are considered to be safe levels for people. NOAELs are the highest dose or concentration that caused no toxic effect in the most sensitive animal species tested. In calculating health-based guideline levels or regulatory thresholds, the agencies consider a number of factors, including the potential differences in sensitivity between humans and test animals, potential differences in the sensitivity between people and other sources of uncertainty. The result of the highly conservative assumptions used is that the level considered safe to humans is typically one-hundred to a thousand fold less than the NOAEL in the most sensitive animals tested.

The NOAEL for permethrin in a 13-week inhalation study using rats was 250 mg/m^3 based on transient neurologic effects observed at 500 mg/m^3 (ATSDR, 2005). Although the USEPA has not established an inhalation reference concentration (RfC) for permethrin, the State of New York has developed an Ambient Air Guideline Concentration (applicable to long-term levels in outdoor air) of 0.012 mg/m^3

(NYSDOH, 2000). New York City has calculated an acute Risk Based Concentration of 0.0924 mg/m^3 for permethrin (NYCDOH, 2001). California has used a permethrin screening level of 0.064 mg/m^3 (CDPR, 2003). This demonstrates that following the proper use of ULV mosquito spray applications permethrin concentrations in air are likely to be well below applicable health-based guideline concentrations. Modeled and measured levels of permethrin in air following outdoor permethrin applications are several million times less than the highest levels that caused no observable adverse health effect in the rat inhalation study.

Permethrin Carcinogenicity

Nationally, cancer is the third leading cause of death. The American Cancer Society has determined that the lifetime probability of developing cancer is 45 percent in men and 38 percent in women. Cancer incidence greatly increases with age and may also vary with other factors such as family history of cancer, place of residence, and racial/ethnic background. (Jemal et al., 2008).

For most carcinogens to induce cancer it is necessary for a person to be chronically exposed to doses that are sufficiently high to overwhelm the body's natural repair mechanisms. There is typically a latency period of two or more decades between the advent of exposure and the development of cancer in humans (NTP, 2009).

Approximately half of all chemicals tested in standard high dose animal cancer tests, whether occurring naturally or produced synthetically, are "carcinogens." Plants in the human diet contain thousands of natural pesticides which protect them from insects and other herbivores, and the majority of these which have been tested are rodent carcinogens (Ames and Gold, 1997). Only a small fraction of all cancer cases are attributable to environmental pollutants (Boffetta et al., 2007).

The USEPA requires registrants to conduct chronic/carcinogenicity studies for pesticide active ingredients such as permethrin that are used on food crops. In addition, a number of independently conducted peer-reviewed studies on permethrin carcinogenicity are available in the open scientific literature. Permethrin has caused tumors in some animal studies, although the potential for permethrin to induce cancer in rodents, even at fairly high exposures, is considered to be weak (WHO, 1999; ATSDR, 2005; CDOH, 2005; USEPA, 1989). Permethrin has not been shown to be mutagenic in most *in vitro* and *in vivo* tests, although some studies have reported genotoxic effects such as increased chromosome

aberrations (TEDX, 2009; Meeker et al., 2008; ATSDR, 2003; USEPA, 2002b; Tisch et al., 2002; Rand Corp., 2000; Abu-Qare and Abou-Donia, 2000; WHO, 1999; Surralles et al., 1995; Barreuco et al., 1994; Barrueco et al., 1992; Herrera and Laborda, 1988; USEPA, 1988; Hoellinger et al., 1987; Pluijmen et al., 1984; Woodruff et al., 1983; Miyamoto, 1976).

IARC Permethrin Cancer Classification

The International Agency for Research on Cancer (IARC), considered to be the leading world authority on cancer, stated the following: "One preparation of permethrin (*cis:trans*, 40:60) was tested for carcinogenicity in one study in mice and in one study in rats by oral administration in the diet. In mice, a marginal increase in the incidence of pulmonary adenomas was observed in males. No increased tumour incidence was observed in treated rats...No data were available on the genetic and related effects of permethrin in humans. No effect was observed in the limited number of short-term tests available...There is *inadequate evidence* for the carcinogenicity of permethrin in experimental animals...Permethrin is *not classifiable as to its carcinogenicity to humans (Group 3)*" (IARC, 1991).

USEPA Permethrin Cancer Assessments

The Integrated Risk Information System (IRIS) of the USEPA is a database containing comprehensive reviews of chronic toxicity data that is maintained by scientists from several Program Offices and the Office of Research and Development. IRIS summaries represent a consensus among different program offices within the USEPA. However, the current IRIS summary for permethrin does not include a cancer classification (IRIS, 1987).

In 1988, Health Effects Division of the USEPA Office of Pesticide Programs classified permethrin as a Group C (possible human carcinogen), based on evidence in one species (mouse). The evidence in the second species (Long-Evans rat) was considered to be equivocal, but suggestive. A Scientific Advisory Panel recommended this classification based on permethrin's limited dose-response, relatively weak carcinogenic potency and lack of mutagenicity (USEPA, 1989). More recently, the USEPA classified permethrin as "likely to be carcinogenic to humans" by the oral route. The "likely to be carcinogenic to humans" classification is based on consistent findings of benign lung tumors in female mice and benign liver tumors in male and female mice following chronic oral exposure in repeat studies. There was no evidence of cancer in Wistar rats, and evidence was equivocal for carcinogenicity of permethrin in Long-Evans rats. Although there were no malignancies found and an increase in benign tumors was found in

only one species, the USEPA Draft Guidelines for Carcinogenic Risk Assessment (July 1999) supported the current classification of permethrin as "likely to be carcinogenic to humans" (USEPA, 2002b). The USEPA Cancer Assessment Review Committee indicated that the following factors were considered in the decision to place permethrin in this cancer class:

1. Two tumor types were observed in one species.
2. Lung tumors in female mice had an early onset and were not reversible.
3. Tumor findings in the Long-Evans rat were equivocal.
4. Permethrin shares a structure activity relationship with cypermethrin, which is classified as a "possible human carcinogen" based on lung tumors in female mice.

As previously stated, the USEPA conducted both cancer and non-cancer risk assessments for permethrin used in outdoor ULV insecticide spray activity. The Agency carefully considered the amount of permethrin to which people would be exposed through ULV spraying. In addition, aggregate risks were assessed for all approved food uses for permethrin. The Agency concluded that human health risks to adults and children, residential bystanders and workers would not exceed the USEPA levels of concern (USEPA, 2005a; USEPA, 2005b). Independently conducted research on cancer risks from permethrin following ULV spray treatments agrees with the USEPA conclusion that this activity does not pose any significant cancer risk (Macedo et al., 2007; Peterson et al., 2006). This conclusion is consistent with the fact that people are exposed to very low levels of permethrin following outdoor ULV mosquito treatment.

Permethrin Cancer Classifications Assigned by Other Governmental Agencies

The ATSDR has stated, "Data do not indicate that pyrethroids should be considered a carcinogenic concern to humans" (ATSDR, 2005). The U.S. National Toxicology Program (NTP), the Occupational Safety and Health Administration (OSHA) and the NIOSH have not assigned carcinogenicity classifications for permethrin. The Florida Department of Environmental Protection (FDEP) has not identified cancer as an important toxicological endpoint for permethrin (FDEP, 2005).

Permethrin *in vivo* (Experimental Animal) Carcinogenicity Studies

An oral carcinogenicity study was conducted using Charles River CD-1 mice. Groups of 75 mice of each sex were fed technical permethrin in their diet for twenty-four months. Males were given permethrin at 0, 20, 500 and 2000 ppm (0, 4, 75, and 300 mg/kg/day); females were dosed with 0, 20, 2500 and 5000 ppm (0, 4, 375, and 750 mg/kg/day). The cis/trans ratio of the technical permethrin was not stated. Increased

rates of hepatomas and bronchioalveolar adenomas were observed in female mice in the two highest dose test groups, and there was also a possible increase in hepatocellular carcinomas in male mice (USEPA, 1988; USEPA, 1982; USEPA, 1980). In a Supplementary Shimkin Mouse Lung Bioassay, A/J mice were dosed with either 285, 475, 713.5 or 1425 mg/kg of permethrin for three days per week for eight weeks. There was no evidence of increased lung adenoma formation (USEPA, 1988).

CFLP Swiss-derived mice were dosed with either 0, 10, 50, or 250 mg/kg/day of permethrin (25% cis/ 75% trans) for 92 weeks. There were some indications of lung carcinogenicity in this study (USEPA, 1988). In another study, Swiss-derived mice were maintained for their lifetime (80% mortality by 98 weeks) on diets containing 0, 250, 1000, or 2500 ppm (375 mg/kg/day) of permethrin. A slight elevation in benign lung tumor incidence was observed in males only at 2500 ppm permethrin but was not considered by the Agency to represent a carcinogenic effect (USEPA, 1988; Ishmael and Litchfield, 1988).

Long-Evans rats were fed diets containing 0, 20, 100 and 500 ppm permethrin (40% cis/ 60% trans) for 2 years. The incidence of alveologenic lung tumors was significantly elevated in males treated with permethrin compared to untreated males. No other tumor type was significantly elevated in either sex. The review concluded that "an oncogenic effects appears to be present, but appears to be of low potency." However, inconsistencies were noted in the histological methodologies that were used to prepare the lung tissue for analysis (USEPA, 1981; USEPA, 1988).

Wistar rats were dosed with either 0, 10, 50 or 250 mg/kg/day of permethrin (25% cis/75% trans) for two years. The USEPA concluded that there were no indications that permethrin was oncogenic (USEPA, 1988). In another study, Wistar rats were fed diets containing 0, 500, 1000 or 2500 ppm permethrin (125 mg/kg/day) for 2 years. No evidence of a carcinogenic effect was seen in the rat study (USEPA, 1988; Ishmael and Litchfield, 1988).

Eight pesticides were tested in a medium-term bioassay based upon the induction of preneoplastic lesions in the liver. Rats were initially given diethylnitrosamine intraperitoneally at a dose of 200 mg/kg body weight and two weeks later were treated with the pesticides for six weeks and then killed; all rats had a partial hepatectomy at week three. Hepatocarcinogenic potential was assessed by comparing the number and area of glutathione S-transferase placental form positive foci in the liver with those of controls given diethylnitrosamine (DEN) alone. Permethrin (mixture of 25% cis form and 75% trans form) gave negative

results, whereas permethrin (mixture of 39% cis form and 61% trans form) showed borderline results (Hakoi et al., 1992).

Additional information can be obtained from the World Health Organization, which has summarized in detail the available experimental laboratory animal cancer studies for permethrin (WHO, 1999).

Permethrin Human Epidemiological Cancer Studies

The Agricultural Health Study (AHS) examined exposure of 55,323 pesticide applicators to 45 different pesticides through the use of a self-administered questionnaire (Alavanja et al., 2006; Alavanja et al., 2005; Alavanja et al., 2003). Cancer incidence was determined from 1993 to the end of 2002. The overall cancer incidence among farmers was 12% lower than cancer rates among the general population, although there were small increased rates for some cancers. No exposure response relationship was observed for permethrin and prostate cancer, but among those exposed to permethrin who also had a family history of prostate cancer, statistically significant raised risks of prostate cancer was found. While this study reinforces the known link between prostate cancer and family history of prostate cancer, this type of finding in which something appearing in only a subgroup of the entire study population is particularly difficult to interpret, since it could result from chance or from differences between subgroups other than their use of pesticides.

In one study, a single case of congenital leukemia is described with 11q23/MLL genetic rearrangement in a preterm female newborn. Because of arachnophobia, the mother had heavily abused aerosolised permethrin. Permethrin's potential to induce cleavage of the MLL gene in cell culture was confirmed with incubation of a BV173 cell line with 50 μM permethrin (Borkhardt et al., 2003).

In contrast, in another study which included thousands of people in four U.S. states, residential use of permethrin was not associated with an increased risk of non-Hodgkin lymphoma (Colt et al., 2005).

Permethrin Endocrine Disruption Potential

In its toxicological profile on pyrethroid insecticides, the ATSDR stated the following (ATSDR, 2003): 'Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with

this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the Environmental Protection Agency (EPA) to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), which in 1998 completed its deliberations and made recommendations to EPA concerning *endocrine disruptors.* In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens... These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior... Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis...'

Since many endocrine disruptors are thought to affect sex hormone function, and therefore reproduction, the findings in multi-generation animal studies, currently required for pesticide registration by the USEPA, can provide strong evidence of the potential for endocrine disruption. The relationship between hormonal imbalance and cancer is complex. For example, estrogen is a natural hormone in humans but is nevertheless classified as a known human carcinogen (IARC, 1987). Even though it is present at some level in all people, not everyone gets cancer as a result of its presence. Likewise, there are natural chemicals in plants that have hormone-like activity. These chemicals, mostly phytoestrogens, are found in high levels in broccoli, cauliflower, soybeans, carrots, oats, rice, onions, legumes, apples, potatoes, beer, and coffee. Most phytoestrogens have weak activity (low potency) and people who consume diets rich in these substances may have a *reduced* risk of developing some hormone related diseases, including some

types of cancer (EXTOXNET, 1998; European Commission, 1999). Although the relationship between human diseases of the endocrine system and exposure to environmental contaminants is poorly understood and scientifically controversial, some prescription pharmaceutical compounds with potent hormonal activity such as diethylstilbestrol are known to have caused devastating reproductive damage and cancer in humans (USEPA, 2007c). Many biologically potent pharmaceutical compounds are directly consumed by Americans in large amounts and are also present at trace levels in the environment (USEPA, 2001).

Pyrethroid pesticides such as permethrin are much less potent endocrine disruptors than hormones such as estrogen and many other pharmaceutical compounds. Moreover, doses of permethrin resulting from ULV mosquito spray activity are many orders of magnitude less than doses of potent endocrine disrupting pharmaceuticals such as diethylstilbestrol that have caused serious reproductive consequences in women.

Available data suggest that, at sufficiently high doses, some pyrethrin and pyrethroid compounds may potentially act as endocrine disruptors. Available *in vivo* data include findings of reduced reproductive organ weights, significantly altered sperm characteristics, reduced plasma testosterone levels, or altered thyroid hormone production in male rats administered high oral doses of pyrethroids (ATSDR, 2003). While some high dose *in vitro* studies using human cell cultures have shown weak androgenic or estrogenic activity of several pyrethroids, other studies have not found these effects (Eil and Nisula, 1990; Kim et al., 2004; Go et al., 1999; Garey, 1998). The outcomes of different studies are sometimes inconsistent because of the inherent variability of the different assays and the use of different experimental conditions by different researchers (Kim et al., 2004). Overall, the available evidence from *in vitro* studies for the estrogenic potential of pyrethroid compounds is equivocal. Results from *in vitro* studies should be carefully interpreted because these studies do not fully represent all of the complex biochemical processes (*e.g.*, absorption, distribution and transformation) and the various mechanisms of detoxification that occur in a whole organism (Saito et al., 2000).

FDACS has reviewed available studies on permethrin endocrine disruption potential (TEDX, 2009; ATSDR, 2003; USEPA, 2007b). Although some studies indicate that permethrin may potentially have endocrine disrupting activity in mammals other studies were unable to confirm endocrine disrupting effects. Overall, the evidence remains equivocal and is therefore inconclusive. There is no evidence that permethrin causes endocrine disruptive effects in humans following exposure to the low doses of permethrin resulting from outdoor ULV mosquito spray activity.

The USEPA has stated the following with regard to permethrin endocrine disruption (USEPA, 2005c): 'EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administration may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and FFDCA authority to require wildlife evaluations, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP). In the available toxicity studies on permethrin, there was no toxicologically significant evidence of endocrine disruptor effects. When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, permethrin may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.'

The Agency also stated that "Developmental and reproductive toxicity studies demonstrated that there is no evidence (qualitatively or quantitatively) for increased susceptibility to infants and children following *in utero* and/or pre/post-natal exposure to permethrin. Additionally, there is no evidence that permethrin induces any endocrine disruption" (USEPA, 2005d).

Nevertheless, the USEPA apparently believes that there is still some uncertainty regarding the question of potential permethrin endocrine disruption. Both permethrin and piperonyl butoxide are on the USEPA "June 2007 Draft List of Chemicals for Initial Tier 1 Screening" for endocrine disruption potential. However, the website for that list states the following: "This page presents an alphabetized draft list of the 73 pesticide active ingredients and HPV/pesticide inert chemicals selected for Tier 1 screening. This draft list was published in a Federal Register Notice in June 2007. Because this list of chemicals was selected on the basis of exposure potential only, it should not be construed or characterized as a list of known or likely endocrine disruptors" (USEPA, 2007d).

The European Commission (Executive Branch of the European Union) published a report entitled *Towards the Establishment of a Priority List of Substances for Further Evaluation of Their Role in Endocrine Disruption in 2000*, which included a large list of suspected endocrine disruptors. The

chemicals were placed into three groups depending on the level of concern and the quality of scientific evidence. Permethrin was included on this list, although it was placed in Group III, compounds for which there was considered to be insufficient evidence of endocrine disruption or for which there was only low concern with regard to exposure (IEH, 2005).

In 1999, the National Research Council produced a report "Hormonally Active Agents in the Environment." That report does not specifically characterize permethrin as an endocrine disruptor (NRC, 1999).

Permethrin *in vitro* Endocrine Disruption Studies

Some researchers have reported that permethrin may be an endocrine-disrupting chemical (Lu et al., 2006), although results from *in vitro* studies testing the estrogenic and androgenic activities of permethrin have been somewhat contradictory (Kim et al., 2005). Permethrin reportedly demonstrated endocrine disrupting potential in an assay using sex hormone-binding globulin (Meulenberg, 2002). Indicative of possible estrogenic activity, permethrin reportedly inhibited the binding of estradiol to the estrogen receptor and induced pS2 expression in the MCF-7 human breast cell carcinoma cell line (Chen et al. 2002; ATSDR, 2003). Permethrin reportedly caused a statistically significant increase in the proliferation of MCF-7 human breast cancer cells compared to estradiol alone (Kakko et al., 2004). Using the uterine Calbindin-D9k (CaBP-9k) gene expression assay, other researchers reported that permethrin exhibited some estrogenic activity (Kim et al., 2005). Another *in vitro* study reported that permethrin metabolites either exhibited no estrogenic activity or only very weak activity that was many orders of magnitude less than the estrogenic activity of 17B-estradiol (McCarthy et al., 2006).

Permethrin reportedly binds to the peripheral benzodiazepine receptor, which stimulates production of testosterone (Ramadan et al., 1988). Permethrin and some other pesticides reportedly activated the cancer biomarker enzyme erbB-2 kinase in human prostate cancer cell lines (Tessier and Matsumura, 2001). Some researchers have reported small, variable androgenic effects of permethrin using three different prostate cancer cell lines (Kim et al., 2006). Another study demonstrated anti-androgenic activity of relatively high concentrations of permethrin and a metabolite in CV-1 African green monkey kidney cells (Sun et al., 2007). Several pyrethroids, including permethrin, have been shown to interact with androgen binding sites in dispersed intact human genital skin fibroblasts, with varying degrees of potency, but at levels comparable to those resulting in the same order of binding observed using cimetidine (an over-the-counter indigestion medication), a known inhibitor of androgen receptor binding (Eil and Nisula 1990;

ATSDR, 2003). Permethrin reportedly exhibited approximately 500-fold less anti-androgenic activity than the prostate medication flutamide in a human androgen receptor yeast screen assay, although some permethrin metabolites produced by yeast exhibited more estrogenic and anti-androgenic potency than permethrin (Tyler et al., 2000). One recent *in vitro* study concluded that permethrin has only weak anti-androgenic properties (Xu et al., 2008).

Other researchers have not found any endocrine-disrupting effects of permethrin using *in vitro* experiments. *In vitro* human endometrial and breast cancer cell lines that produce phosphatase as an indicator of hormonal activity did not show any progestinic or anti-estrogenic activity when exposed to permethrin (Garey and Wolf, 1998; WHO, 2005b). Sumida et al. (2001) reported that permethrin had no binding affinity for progesterone receptors in human breast cancer cells. Kim et al. (2004) reported that permethrin did not induce MCF-7 human breast cancer cell proliferation or increase estrogen receptor protein levels or pS2 mRNA levels. Moreover, permethrin significantly *inhibited* estradiol-induced MCF-7 human breast cancer cell proliferation in that study. Similar negative findings for permethrin were reported earlier by other researchers who concluded that permethrin does not affect estrogen regulation (Kasat et al., 2002; Saito et al., 2000; Go et al., 1999; Kojima et al., 2005). Permethrin did not inhibit macrophage function in bioassays to measure chemical effects on the immune system (Igarashi et al., 2006).

Permethrin *in vivo* (Experimental Animal) Endocrine Disruption Studies

The World Health Organization has concluded that the overall evidence, which includes several "Good Laboratory Practice" (GLP) reproductive and developmental animal studies submitted by pesticide registrants and peer-reviewed non-registrant studies indicate that permethrin is not a developmental or reproductive toxin (WHO, 2005a; WHO, 1999). This is consistent with conclusions reached by the USEPA, although the agency is requiring a study to rule out developmental neurotoxicity (USEPA, 2007a; Shafer et al., 2004). Permethrin did not cause birth defects in animal studies, although the fertility of female rats was reportedly affected when they received very high oral doses of permethrin (250 mg/kg/day) during the 6^{th} to 15^{th} days of pregnancy (Kamrin, 1997). At least one study reported that permethrin exposure caused embryo loss in rats (Spencer and Berhane, 1982). Lesions were induced in sex cells of mice given relatively high-level exposure to permethrin via intraperitoneal or per os route of administration, even though no signs of cytotoxicity accompanied the sperm anomalies (Tyrkiel et al., 2001). One study reported that adrenal ornithine decarboxylase (ODC) enzyme activity was greatly elevated in rats dosed once with permethrin (Bondy and Hong, 1987).

In one recent study, the reproductive toxicity of *cis*-permethrin was evaluated in adult male ICR mice given (0, 35, or 70 mg/kg/day) by oral administration for 6 weeks. Caudal epididymal sperm count and sperm motility in the treated groups were statistically reduced in a dose-dependent manner. Testicular testosterone production and plasma testosterone concentration were significantly and dose-dependently decreased with an increase in luteinizing hormone, and a significant regression was observed between testosterone levels and *cis*-permethrin residues in individual mice testes after exposure. However, no significant changes were observed in body weight, reproductive organ absolute and relative weights, sperm morphology, and plasma FSH concentration after *cis*-permethrin treatment. Moreover, *cis*-permethrin exposure significantly diminished the testicular mitochondrial mRNA expression levels of peripheral benzodiazepine receptor (PBR), steroidogenic acute regulatory protein (StAR), and cytochrome P450 side-chain cleavage (P450scc) and enzyme and protein expression levels of StAR and P450scc. At the electron microscopic level, mitochondrial membrane damage was found in Leydig cells of the exposed mouse testis. The researchers concluded that the insecticide permethrin may cause mitochondrial membrane impairment in Leydig cells and disrupt testosterone biosynthesis by diminishing the delivery of cholesterol into the mitochondria and decreasing the conversion of cholesterol to pregnenolone in the cells, thus reducing subsequent testosterone production (Zhang et al., 2007). Further study by these researchers concluded that the difference in metabolic activity between *cis*- and *trans*-permethrin might contribute to the difference in the reproductive toxicity between both isomers (Zhang et al., 2008).

Subchronic dermal administration of permethrin and N,N-diethyl m-toluamide (DEET) combined with oral doses of pyridostigmine bromide in Sprague-Dawley rats induced apoptosis in testicular germ cells, Sertoli cells, and Leydig cells, as well as in the endothelial lining of the blood vessels (Abou-Donia et al., 2003).

Other researchers have reported that topical permethrin administration affected the thymus and spleen and that it inhibited antibody production and macrophage function in C57Bl/6N mice (Prater et al., 2002; Punareewattana et al., 2001; Punareewattana et al., 2000).

There was no evidence of anti-androgenicity or estrogenicity following repeated oral gavage exposure of castrated male rats (5-day Hershberger assay) and ovariectomized female rats (3-day uterotrophic assay) to permethrin at doses high enough to elicit classical clinical signs of neurotoxicity (Kunimatsu et al. 2002; ATSDR, 2003). On the other hand, other researchers using the same tests concluded that

permethrin does display both estrogenic and anti-androgenic activity (Kim et al., 2005). The researchers in the later study attributed the contradictory results between the two studies to differences in assay protocols.

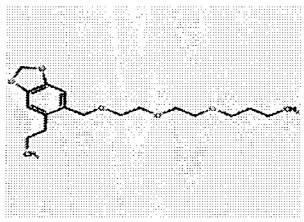
Permethrin Human Reproduction/ Endocrine Disruption Studies

Women who in the first trimester of pregnancy had used a cream rinse for the treatment of head lice containing 1% permethrin did not experience increased rates of adverse pregnancy outcomes compared to a control group of pregnant women that did not have permethrin exposure (Kennedy et al., 2005). Women treated with topical 4% permethrin for scabies during pregnancy did not experience increased rates of adverse effects on pregnancy outcome (Mytton et al., 2007). People living near agricultural areas that applied permethrin reportedly had a reduced risk of having children with hypospadias (Meyer et al., 2006).

One recent study examined the relation between creatine-adjusted urinary concentrations of the pyrethroid metabolite 3-phenoxybenzoic acid in men and concentrations of sex hormones in blood (Han et al., 2008). The study reported finding a positive relation for luteinizing hormone but a negative relation for estradiol.

Piperonyl Butoxide

CAS Registry Number 51-03-6



Piperonyl butoxide (PBO) is a synergist that enhances the pesticidal effects of active ingredients such as pyrethrins, pyrethroids, carbamates and rotenone, allowing for the application of reduced amounts of active ingredients. Researchers developed PBO in 1947 from naturally-occurring safrole. PBO demonstrates low acute dermal, inhalation and oral toxicity (NPIC, 2000; Breathnach, 1998; Williams et al., 2008). Studies of occupational and consumer exposure to PBO have not reported any significant effects on human health (Phillips et al., 1997).

Piperonyl Butoxide Carcinogenicity

Numerous studies and reviews have examined the question of piperonyl butoxide carcinogenicity. Carcinogenic effects in the liver were consistently observed in mice and rats at very high dietary levels that also caused marked acute toxicity, but not at lower doses (Yasuno et al., 2008; Muguruma et al., 2007; Muguruma et al., 2006; BIBRA Working Group, 1998; Butler et al., 1998; Watanabe et al., 1998; Takahashi et al., 1998; Takahashi et al., 1997; Phillips et al., 1997; Tayama, 1996; Takahashi et al., 1994a; Takahashi et al., 1994b; Takahashi et al., 1994c; Fujitani et al., 1993; Maekawa et al., 1985; Cardy et al., 1979; NTP, 1979; Sarles and Vandegrift, 1952).

Permethrin has generally given negative results in a range of genotoxicity tests, including Ames bacterial assays. However, equivocal findings were reported in mice treated by the oral or intraperitoneal routes (in a dominant lethal assay), and in mammalian cells in culture there was evidence of mutagenicity, chromosomal damage and cell transformation (BIBRA Working Group, 1998).

The 2006 USPEA RED for piperonyl butoxide (PBO) states the following with regard to carcinogenicity (USEPA, 2006b): "PBO is classified as a Group C-possible human carcinogen with no cancer quantification required for PBO risk assessments. In a combined chronic/carcinogenic study in rats, positive carcinogenic effects were reported at doses where a high incidence of ileocecal ulcers were noticed in test mammals. Liver adenomas and carcinomas were reported in Fischer 344 rats only when tested at very high doses. A slight increase in thyroid follicular cell tumors was reported in Sprague-Dawley rats. A 1979 National Toxicology Program (NTP) study reported negative effects for carcinogenicity in the same strain of rats and in B6C3F1 mice. In CD-1 mice, PBO tested positive for liver tumor effects."

The IARC has stated, "The available data provide no evidence that piperonyl butoxide is likely to present a carcinogenic risk to humans" (IARC, 1983).

Piperonyl Butoxide Endocrine Disruption Potential

The USEPA stated the following regarding the potential for piperonyl butoxide to cause endocrine disruption (USEPA, 2006b): "In the database for PBO, there was no toxicologically significant evidence of endocrine disruptor effects. When additional appropriate screening and/or testing protocols being

considered under the Agency's EDSP have been developed, PBO may be subject to further screening and/or testing to better characterize effects related to endocrine disruption" (USEPA, 2006b).

Regarding developmental effects of piperonyl butoxide, the Agency stated, "No developmental toxic effects were noted in guideline studies using rats and rabbits. A few developmental studies in the open literature reported limb deformities, increased resorption and decreased number of viable fetuses in rodents at doses close to or higher than the highest dose tested in the guideline studies" (USEPA, 2006b).

Conclusions and Areas of Uncertainty

Synergists such as piperonyl butoxide that are present in the body at sufficiently high levels may inhibit oxidative and hydrolytic activity that is involved in the breakdown of pyrethroid compounds, and therefore synergists may increase the toxicity of pyrethroid compounds (Hayes and Laws, 1991). The USEPA requires pesticide registrants to conduct toxicological studies on animals for acute health effects using whole formulated products (*i.e.*, Biomist formulation containing both permethrin and piperonyl butoxide along with non-active ingredients). By contrast, for non-acute toxicological endpoints (*e.g.*, reproductive toxicity and carcinogenicity), tests are conducted only on the individual active ingredients, typically by the oral route of administration. There is therefore some uncertainty with regard to the extent to which some types of adverse health effects may occur as a result of long-term dermal and inhalation exposure to low-level formulated ULV mosquito control products. However, people are exposed to extremely low levels of Biomist, and USEPA risk assessments for permethrin and piperonyl butoxide have concluded that there is a substantial margin of safety for each of these components when considered alone. It is unlikely that together these components would significantly raise the overall risk of cancer or endocrine effects. The combined doses for each of the components in Biomist are still sufficiently low that it is unlikely that the human body's natural defense mechanisms and ability to detoxify these compounds would be appreciably compromised. The available human epidemiological studies on mosquito control products containing both permethrin and piperonyl butoxide have not found that appropriate use of these products cause adverse health effects in people. Based on the available information, long-term exposure to Biomist mosquito spray according to the legally-binding restrictions of the USEPA-approved label is likely to pose negligible health risks to residents living in the Celebration community.

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