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Malaria Mosquito Resistance to Agricultural Insecticides: Risk Area Mapping in Thailand

Hans J. Overgaard



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Cover photograph by Simen Sandve shows insecticide application in a tangerine fruit orchard in a malaria endemic area in Chiang Dao district, Chiang Mai province, northern Thailand.

Inset photograph by James Gathany, Centers for Disease Control and Prevention (CDC), Atlanta, USA, shows an *Anopheles minimus* mosquito, a malaria vector of the Orient, as she was feeding on a human host.

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Acronyms

A1	Perennial malaria transmission, according to the Thai malaria stratification system
A2	Periodic malaria transmission, according to the Thai malaria stratification system
ADI	Acceptable Daily Intake
AESA	Agro-Ecological Systems Analysis
B1	High-risk non-transmission areas, according to the Thai malaria stratification system
B2	Low-risk non-transmission areas, according to the Thai malaria stratification system
Bti	Bacillus thuringiensis israelensis
Bsph	Bacillus sphaericus
DANIDA	Danish International Development Agency
DOA	Department of Agriculture
DDT	Dichloro-Diphenyl-Trichloroethane
EFTA	European Free Trade Association
EIQ	Environmental Impact Quotient
EIR	Entomological Inoculation Rate
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FFS	Farmer Field School
GAP	Good Agricultural Practices
GIS	Geographical Information System
GST	glutathione S-transferase
IA	Integration Area, according to the Thai malaria stratification system
IPM	Integrated Pest Management
IPVM	Integrated Pest and Vector Management
IRAC	Insecticide Resistance Action Committee
IRM	Insecticide Resistance Management
IRS	Indoor Residual Spraying
ITM	Insecticide-Treated Materials
ITN	Insecticide-Treated Nets
IVM	Integrated Vector Management
LDD	Land Development Department, MOAC
MOAC	Ministry of Agriculture and Cooperatives, Thailand
MOPH	Ministry of Public Health, Thailand
MRL	Maximum Residue Level
PA	Pre-integration Area, according to the Thai malaria stratification system
POP	Persistent Organic Pollutant
RISKMODEL	Predicting the RISKS of MOSquito-borne DisEases from Land use change in Northern Thailand (EU project 2001-2005)
RBM	Roll Back Malaria
SEARO	South-East Asia Regional Office (WHO office in New Delhi, India)
Sida	Swedish International Development Cooperation Agency
ULV	Ultra-low volume
UNDP	United Nations Development Programme
UNEP	United Nations Environment Programme
UNESCAP	United Nations Economic and Social Commission for Asia and the Pacific
UNICEF	United Nations Children's Fund
VBDO	Vector-Borne Disease Control Office, Department of Communicable Disease Control, MOPH
WHO	World Health Organization

Summary

Intensive use of insecticides in agriculture has caused concern for the development of insecticide resistance in disease vectors, potentially undermining vector-borne disease control. The purpose of this study was to identify risk areas in Thailand where insecticide resistance in malaria mosquitoes might develop as a consequence of crop protection activities in agriculture. The study provides guidelines on how to delineate risk areas. A review of insecticide resistance in disease vectors and the potential role of agricultural insecticides is presented.

Land use and malaria endemic areas were mapped in four provinces in Thailand: Chiang Mai, Mae Hong Son, Tak, and Kanchanaburi. Land use classes were assigned a value reflecting its insecticide use. Malaria endemic maps reflect vector distribution. Land use and malaria endemic maps were overlaid to identify areas with potential increased risk for resistance development in malaria vectors due to insecticide-intensive agriculture.

Crops with the highest insecticide use were fruit and vegetables. There were small and

scattered areas where malaria mosquito insecticide resistance might develop through exposure to agricultural insecticides, apart from some larger, relatively contiguous, areas in northern Chiang Mai province.

A potential higher risk of vector control failure may be expected in the identified risk areas due to development of insecticide resistance in malaria mosquitoes. Despite of the relatively small and scattered risk areas identified in this study, current agricultural pest control may become a threat to malaria vector control in Thailand and neighboring countries, particularly considering the present expansion and intensification of agriculture in the region.

The report emphasizes the importance of collaboration between the agriculture and health sectors to improve resistance surveillance and to initiate integrated pest and vector management interventions to avoid or minimize double insecticide exposure to insect vectors and to reduce risks to human and environmental health.

Malaria Mosquito Resistance to Agricultural Insecticides: Risk Area Mapping in Thailand

Hans J. Overgaard

Introduction

Malaria is a serious health problem in many tropical and subtropical countries. Vector control is an important component of malaria control. The main methods to control malaria mosquitoes are chemical-based, such as indoor residual spraying or impregnated bednets. The available insecticides used to control malaria mosquitoes are increasingly becoming less effective due to resistance development in mosquito populations.

Evolution of insecticide resistance in an insect population arises when there is an increase in the frequency of one or more resistance genes in the population following exposure to insecticides. Natural selection and genetic drift act on genetic variation in the population that is created by mutation, genetic recombination and gene flow.

Many disease vectors are present in agricultural areas and are therefore likely exposed to insecticides used to control agricultural pests. Approximately 90 percent of all insecticides worldwide are used for agricultural purposes. The

intensive use of insecticides in agriculture has caused concern for increased selection pressure for insecticide resistance development in disease vectors. This may have negative implications for vector-borne disease control.

The purpose of this study was to identify risk areas – target areas – for insecticide resistance developing in malaria mosquitoes as a result of crop protection activities in agriculture in Chiang Mai, Mae Hong Son, Tak, and Kanchanaburi provinces in western and northern Thailand. The study provides guidelines and recommendations on how to delineate such risk areas. These guidelines will help governmental agencies introduce combined integrated pest and vector management strategies through intersectoral collaboration, including resistance management and surveillance programs. The document also presents a general review of insecticide resistance in disease vectors and the potential role of agricultural insecticides in the Southeast Asian region in particular, and in other regions in general.

Background

Malaria and Malaria Control

The most recent estimates of worldwide malaria burden are described in the first comprehensive report of the Roll Back Malaria Partnership (WHO/

UNICEF 2005). According to the report, malaria is endemic in 107 countries with some 3.2 billion people living in risk areas. It further states that each year there are about 350-500 million clinical cases of malaria worldwide with over one million

deaths. About 59 percent of all clinical cases occur in Africa, 38 percent in Asia, and 3 percent in the Americas. Malaria mortality is also highest in Africa with 89 percent of all deaths, whereas 10 percent occurs in Asia and less than 1 percent in the Americas. Of all malaria cases caused by *Plasmodium falciparum*, the most deadly human malaria species, 74 percent are in Africa, 25 percent in Asia, and 1 percent in the Americas.

The countries most seriously affected by malaria in Southeast Asia are Myanmar with 716,000 reported cases (15 per 1,000 population), Cambodia with 71,000 cases (5 per 1,000 population), and Lao PDR (People's Democratic Republic) with 19,000 cases (4 per 1,000 population) in 2003 (WHO/UNICEF 2005). Other countries in the region where malaria is still regarded a considerable public health problem are the Philippines with 43,000 cases (< 1 per 1,000 population), Thailand and Vietnam with more than 37,000 cases each (< 1 per 1,000 population), and the two southern Chinese provinces Yunnan and Hainan together with about 22,000 cases (< 1 per 1,000 population) (WHO/UNICEF 2005). Malaria, apart from affecting the health of individuals, also has a socioeconomic impact resulting from work days lost, reduced school attendance, reduced agricultural productivity, and impacts on tourist potential (WHO/UNICEF 2005). Malaria is likely to continue to be an important regional problem in Southeast Asia, because of high levels of population movements and drug and insecticide resistance.

The World Health Organization (WHO) is the international organization whose mission is to define standards for the prevention, control and possible elimination of major international disease problems. The Roll Back Malaria (RBM) Partnership was launched in 1998 by the World Health Organization (WHO), the World Bank, the United Nations Children's Fund (UNICEF) and the United Nations Development Programme (UNDP), also including malaria-endemic countries, their bilateral and multilateral development partners, the private sector, academia, and international organizations. The overall goal of the RBM

Partnership is to halve the burden of malaria by 2010 (Nabarro and Taylor 1998). The current WHO recommendations to control malaria are based on the Global Malaria Control Strategy adopted in 1992 (WHO 2005a). The strategy has four components: (1) Early diagnosis and prompt treatment; (2) Selective and sustainable preventive measures, including vector control; (3) Early detection, containment or prevention of epidemics; and (4) Strengthening of local capacities in research to assess the ecological, social and economic determinants of disease. Vector control remains the most generally effective measure to prevent malaria transmission (WHO 2005b). There are many methods to control vectors. They differ in their applicability, cost-efficiency, and outcome sustainability. Choosing an appropriate vector control method depends on the degree of the malaria burden and the feasibility of applying effective and sustainable interventions. WHO recommends an Integrated Vector Management (IVM) approach, which is based on knowledge of the local situation and includes Indoor Residual Spraying (IRS), Insecticide-Treated Materials (ITM), and other methods (WHO 2005b).

Integrated Vector Management (IVM) is a decision-making process to manage vector populations, so as to reduce or interrupt transmission of vector-borne diseases (WHO 2004; WHO 2005b). IVM consists of: (1) Selection of methods based on knowledge of local vector biology, disease transmission and morbidity; (2) Using a range of interventions, often in combination and synergistically; (3) Intra- and intersectoral collaboration; (4) Engagement with local communities and other stakeholders; (5) A public health regulatory and legislative framework; (6) Rational use of insecticides; and (7) Good management practices. An IVM approach takes into account the available health infrastructure and resources and integrates all available and effective measures, whether chemical, biological, or environmental.

The main methods to control malaria mosquitoes are still chemical-based, such as Indoor Residual Spraying (IRS) and Insecticide-

Treated Nets (ITN). Other vector control measures are environmental management, biological control, larviciding, personal protection, etc. IRS is a valuable intervention to control malaria in areas with a high percentage of housing structures having adequate sprayable surfaces and where the majority of vectors are endophilic, i.e., rests indoors. ITNs are effective in areas where coverage rates are high and a large proportion of human-biting by local vectors takes place after people have gone to sleep. Both methods require that vectors are susceptible to the insecticide in use. The use of IRS and ITNs has repeatedly been shown to reduce severe disease and mortality due to malaria in endemic regions (e.g., Mbaso et al. 2004; Binka et al. 1996; Nevill et al. 1996). Vector control by IRS in selected areas and epidemic preparedness and surveillance are the key control strategies in all malaria endemic countries in Southeast Asia (WHO/UNICEF 2005).

Malaria and Malaria Control in Thailand

In Thailand, as in many other Southeast Asian countries, malaria is associated with poor, marginalized communities in hilly-forested environments and forest fringes along the national borders (Malaria Division 1993). In these areas, extensive human migration occurs for political, socioeconomic, and personal reasons, which seriously complicates malaria transmission and control (Kondrashin et al. 1991). In the hilly forested areas, perennial malaria transmission is primarily maintained by *Anopheles dirus*, which mainly breeds in small pools, such as rock pools, in humid shaded forested locations. It may also use a variety of animal or man-made breeding places, such as hoof prints or wells. In the lower foothills and in more populated agricultural areas close to the forest fringe, *An. minimus* and *An. maculatus* are the primary malaria vectors (Malaria Division 1993). *Anopheles minimus* breeds in shaded slow-moving streams and *An. maculatus* is found in sunlit streams, ponds, tanks and riverbed pools (Meek 1995). Secondary

vectors in Thailand are *An. sudaicus*, which breeds in brackish water in coastal areas; *An. aconitus*, a rice field breeder; and *An. pseudowillmori*, which has been incriminated in the north of the country (Green et al. 1991; Malaria Division 1993). Other studies have suggested that members of the *An. barbirostris/campestris* group might be important secondary vectors of vivax malaria in eastern Thailand (Somboon et al. 1994; Limrat et al. 2001; Apiwathnasorn et al. 2002). Although *An. annularis* is an important malaria vector in the foothills of Assam and other parts of India (Prakash et al. 2004), it is only considered a suspected vector in Thailand (Prapanthadara et al. 2000).

In 2003, there were 37,355 cases of malaria and 325 deaths reported in Thailand (WHO/UNICEF 2005). Most of these cases were reported from provinces along the western border to Myanmar and the majority of cases being foreign nationals, i.e., Burmese migrants or refugees. During the last 50 years there has been a general decline in malaria in Thailand, mainly due to an improved health care system with prompt treatment of cases, information campaigns, and effective vector control (Malaria Division 1993). It has also been suggested that a reduced forest cover could be a factor explaining reduced malaria rates (Rosenberg et al. 1990), because the primary malaria vectors are forest-associated species. Another change that has occurred in Thailand during the last 40 years is a proportional increase of *Plasmodium vivax* compared to *P. falciparum* cases. *P. vivax* increased from less than 20 percent in 1965 to more than 50 percent in 2002 (Sattabongkot et al. 2004). The reasons for this could be that *P. falciparum* has been relatively easy to control through drug treatment and that drug-resistant *P. falciparum* has been effectively controlled. Another reason could be changes in vector potential, i.e., changes in the composition and abundance of vectors that have a high affinity to transmit *P. vivax* (Sattabongkot et al. 2004). This pattern has been observed in eastern Thailand at the border to Cambodia, where the abundance of

An. dirus decreased and the abundances of members of the *An. barbirostris/campestris* group increased (Limrat et al. 2001). *An. dirus* is the main *P. falciparum* vector and the *An. barbirostris/campestris* group is susceptible only to *P. vivax* (Somboon et al. 1994; Limrat et al. 2001; Apiwathnasorn et al. 2002; Sattabongkot et al. 2004).

The nationwide Malaria Control Program in Thailand adopted the insecticide control strategy in 1951 using DDT indoor residual spraying (Malikul 1988). In 1983, DDT was banned for agricultural use, following environmental and public health concerns. However, DDT was still used in vector control until it was phased out between 1995 and 1999. Chareonviriyaphap et al. (1999) reviewed the status of insecticide resistance in Thailand and listed the types of insecticides and biocides used for vector control in the country (table 1). From 1992, synthetic pyrethroids became the insecticide of choice in malaria vector control. The current vector control consists of IRS with five percent deltamethrin Wettable Powder (WP), using 20 milligrams per square meter (mg/m^2). IRS is conducted twice a year in perennial transmission areas (A1) and once a year in periodic transmission areas (A2) covering the transmission season (see chapter Malaria Stratification, p. 27, for definitions of malaria transmission areas). Approximately six percent of the Thai population lives in malaria transmission areas and 67 percent in risk areas (table 2). Insecticide-Treated Nets (ITN) have been introduced as a supplement to IRS. In areas where public acceptance to IRS is low and net coverage is higher than 60-70 percent, ITN usage replaces IRS. In high malaria transmission areas government staff help villagers to treat their own nets free of charge. Nets are distributed to the poor who cannot afford to purchase nets. Nets are treated by dipping with permethrin 0.3 grams per square meter (g/m^2), twice a year. Other chemicals have been tested and compared with permethrin, e.g., lambda-cyhalothrin, alphacypermethrin, and deltamethrin. Another pyrethroid, etofenprox, was also used for small-scale control of malaria vectors.

Thermal fogging has a relatively limited role. It has been applied during malaria outbreaks and in areas with uncontrolled transmission. Thermal fogging is usually applied once a week for four consecutive weeks. Malathion was used for thermal fogging, but now deltamethrin (esbioallethrin + deltamethrin + piperonyl butoxide) is used. In the past, chemical larviciding with temephos was a method to control malaria vectors in urban areas, but has now been abandoned. The organophosphate temephos is currently the main insecticide for treatment of containers to control the larvae of dengue vectors (*Aedes aegypti*). Adult dengue vectors are controlled using ultra-low volume sprays during disease outbreaks or peak periods of adult populations with fenitrothion and malathion (both organophosphates). Some carbamates, such as propoxur, pirimiphosmethyl, and bendiocarb, have also been applied in dengue and malaria control in Thailand. *Bacillus thuringiensis israelensis* (Bti), a widespread soil bacterium with insecticidal properties, has been used in *Aedes* larvae control in Thailand. Bti is particularly lethal for dipterans and there are no reported adverse environmental effects (e.g., Burges et al. 1981; Lacey and Mulla 1990).

Insecticide Resistance

Insecticide resistance is a complex evolutionary phenomenon, which can potentially cause large problems in the control of agricultural insect pests and disease vectors. According to a database of arthropods resistant to pesticides – maintained by the Center for Integrated Plant Studies, Michigan State University – there are at least 533 arthropod species resistant to one or more of the main groups of insecticides (organochlorines, organophosphates, pyrethroids, and carbamates) (Michigan State University 2005). Sixty percent of these are agricultural pests and the remaining 40 percent are arthropods of medical importance (Mota-Sanchez et al. 2002). In 1946 only two anophelines were known to be resistant to DDT (Warrell and Gilles 2002), but today at least 63 species of *Anopheles* are recorded as being

TABLE 1.
Insecticide use and target organisms in disease vector and agricultural pest control in Thailand.

Insecticide	Vector control ¹	Agricultural pest control ²
Pyrethroids		
Deltamethrin	Adult malaria mosquitoes, IRS	<u>Mango</u> : Mango leafhoppers <u>Cruciferous</u> ³ : Diamondback moth, cabbage looper <u>Onions</u> ⁴ : Onion leaf miner <u>Chrysanthemum</u> : Composite thrips
Permethrin	Adult malaria mosquitoes, ITN	<u>Mango</u> : Mango leafhoppers
Lambda-cyhalothrin	Adult malaria mosquitoes, ITN	<u>Mango</u> : Yellow tea thrips, mango leafhoppers <u>Lychee</u> : Lychee stink bug <u>Cruciferous</u> ³ : Diamondback moth, cabbage looper, cabbage centre grub <u>Soybean</u> : Lima bean podborer, cotton bollworm, cluster caterpillar, leaf rollers, soybean webworm, soybean aphid <u>Chrysanthemum</u> : Composite thrips
Etofenprox	Adult malaria mosquitoes	<u>Rice</u> : Brown plant hopper, white plant hopper, green rice leafhopper, zigzag leafhopper
Cyfluthrin	Not used	<u>Pomelo</u> : Citrus moths <u>Lychee</u> : Lychee stem-end borer <u>Onions</u> ⁴ : Onion leaf miner <u>Soybean</u> : Cotton bollworm
Cypermethrin	Not used	<u>Pomelo</u> : Citrus moths <u>Lychee</u> : Lychee stem-end borer <u>Banana</u> : Fruit flies <u>Cruciferous</u> ³ : Diamondback moth, cabbage looper, cabbage leaf miner <u>Onions</u> ⁴ : Onion leaf miner <u>Soybean</u> : Cotton bollworm, cluster caterpillar <u>Orchid</u> : Melon thrips, vandal thrips, midges <u>Chrysanthemum</u> : Composite thrips
Organophosphates		
Temephos	Dengue mosquito larvae, used in containers	
Fenitrothion	Adult dengue mosquitoes, ULV spray during disease outbreaks	<u>Rice</u> : Plant hoppers and leafhoppers (see etofenprox), lawn armyworm, northern armyworm
Malathion	Adult dengue mosquitoes, ULV spray during disease outbreaks	<u>Rice</u> : Oriental rice thrips, lawn armyworm <u>Banana</u> : Fruit flies
Chlorpyrifos	Not used	<u>Rice</u> : Paddy bug, yellow stem borer, darkheaded riceborer, striped riceborer <u>Soybean</u> : Soybean fly, bean fly, cotton bollworm

(Continued)

TABLE 1.
Continued.

Insecticide	Vector control ¹	Agricultural pest control ²
Carbamates		
Propoxur	Malaria and dengue mosquitoes	
Piriphosmethyl	Malaria and dengue mosquitoes	
Bendiocarb	Malaria and dengue mosquitoes	
Carbaryl	Not used	<u>Tangerine</u> : Pacific fruit-piercing moth <u>Mango</u> : Yellow tea thrips, mango leafhoppers, mango leaf cutting weevil <u>Lychee</u> : Lychee stem-end borer, lychee stink bug <u>Cruciferous</u> ³ : Leaf beetles <u>Peanut</u> : Blister beetles <u>Rice</u> : Plant hoppers and leafhoppers (see etofenprox), oriental rice thrips
Carbosulfan	Not used	<u>Cruciferous</u> ³ : Leaf beetles, cabbage leaf miner <u>Soybean</u> : Silverleaf whitefly, leaf rollers, soybean webworm, soybean aphid <u>Peanut</u> : Tomato thrips, yellow tea thrips, melon thrips, leafhoppers, cowpea aphid, blister beetles <u>Rice</u> : Plant hoppers and leafhoppers (see etofenprox), paddy bug, yellow stem borer, darkheaded riceborer, striped riceborer, black bug, big-headed ants <u>Chrysanthemum</u> : Composite thrips
Carbofuran	Not used	<u>Soybean</u> : Soybean fly, bean fly
Biocides		
Bacillus thuringiensis israelensis (Bti)	Dengue mosquito larvae	<u>Tangerine</u> : Leaf rollers <u>Cruciferous</u> ³ : Diamondback moth, cabbage looper, lesser armyworm, leaf beetles <u>Onions</u> ⁴ : Lesser armyworm

Sources: Chareonviriyaphap et al. 1999; DOA 2004

Notes: ¹ All insecticides used in vector control according to Chareonviriyaphap et al. (1999)

² A selection of insecticides and crops according to DOA (2004)

³ Cruciferous: cauliflower, Chinese kale, Chinese cabbage, leaf mustard, Chinese radish, etc.

⁴ Onions: shallot, multiplier onion, onion, garlic

resistant to insecticides (Michigan State University 2005).

True insecticide resistance can be defined as a genetic change in the ability of a population to tolerate the exposure of insecticides (Hoy 1990; Roush and Tabashnik 1990). Evolution of insecticide resistance in an insect population arises when there is an increase in the frequency of one or more resistance genes in the population following exposure to insecticides. Natural selection and genetic drift act on genetic variation in the population that is created by mutation, genetic recombination and gene flow. These

evolutionary forces are affected by biological, physical, and chemical factors in the ecosystem.

Resistance can be either physical or behavioral. Physical resistance means that the insect acquires increased resistance through physiological or morphological changes. The various forms of physical resistance are: (1) Target resistance, where the site of action of the active substance – i.e., the molecular target in the pest – has changed (amino acid alterations) so much that the active substance is no longer effective; (2) Metabolic resistance, where the resistant insect can degrade or detoxify the

TABLE 2.
Population in malaria stratification areas in Thailand, 1998.

Area stratification	Population	%
1. Control area with transmission		
Perennial transmission (A1)	729,000	1.29
Periodic transmission (A2)	2,666,000	4.71
Total	3,396,000	6.00
2. Control area without transmission		
High risk area (B1)	9,761,000	17.25
Low risk area (B2)	28,252,000	49.93
Total	38,013,000	67.18
3. Pre-integration area (PA)	2,936,000	5.19
4. Integration area (IA)	12,237,000	21.63
Total population	56,582,000	100.00

Source: Ministry of Public Health 2005

active substance before it has a chance to express its toxicity; and (3) Resistance to penetration, where the resistant insect takes up the active substance more slowly and/or in lower quantities than the normal, sensitive insect. Before explaining the target and metabolic resistance mechanisms in more detail, a brief account of behavioral resistance is given.

Avoidance behavior, also termed excito-repellency, can be either natural (protective avoidance) or developed (behavioral resistance) (Muirhead-Thomson 1960). Protective avoidance implies that insects have an innate irritability that enables them to escape from contact with treated surfaces before they have acquired a lethal dose of the insecticide. Behavioral resistance is present where a genetic change in an insect population occurs that makes it predisposed to avoid contact with insecticides (Roberts and Andre 1994). This change is a result of insecticide selection pressure that increases the frequency of genes conferring insecticide avoidance behaviors. The term excito-repellency is commonly used today and describes avoidance behaviors that include both contact irritancy and non-contact repellency (Roberts and Andre 1994). Behavioral resistance is difficult to prove, because of the difficulty to ascertain if the avoidance behavior is caused by genetic changes

or through individual natural variation in the population. Related to this and in contrast to true resistance is the concept of natural tolerance to insecticides which is caused by e.g., thicker cuticula, higher fat content, and/or larger body size. Tolerance is not based on genetic changes, but through natural variation in individual insects to resist the effects of toxic compounds (Hoy 1990). Tolerance may vary due to seasonal variation in physiological and morphological characteristics.

Insecticide resistance mechanisms have a biochemical basis (Brogdon and McAllister 1998). As mentioned, the two major groups of mechanisms involved in biochemical resistance in insects are target site resistance and detoxification enzyme resistance. Three target sites have been identified:

- (1) Acetylcholinesterase (AChE) breaks down the neurotransmitter acetylcholine in the nerve synapses. AChE is the target site for organophosphates and carbamates, which inhibit the function of AChE. At least five point mutations in the acetylcholinesterase insecticide-binding site (Ace) have been identified causing reduced sensitivity to organophosphates and carbamates in *Drosophila melanogaster* (Mutero et al. 1994). In *An. gambiae*, and other mosquito species, there are two different acetylcholinesterase proteins that are encoded by two different genes, *ace-1* and *ace-2* (Weill et al. 2002). A single mutation in the *ace-1* gene explains resistance in *Anopheles gambiae* and *Culex pipiens* (Weill et al. 2004).
- (2) Voltage-gated sodium channels in the nerve sheath conduct electrical information throughout the nervous system. The sodium channels are the target site for DDT and pyrethroids, which give rise to so-called knockdown resistance (*kdr*). A few specific point mutations in the *kdr*-gene results in resistance to the synthetic pyrethroids in a variety of insect species (Soderlund and Knipple 2003), including *Anopheles* species (Martinez-Torres et al. 1998; Enayati et al. 2003).

- (3) Ligand-gated ion channels receive chemical signals from neurotransmitters, such as γ -amino butyric acid (GABA). The signals are converted into electrical signals via the opening of ion channels. The ion channels are the target site of cyclodienes (e.g., dieldrin) and fipronil. Resistance to dieldrin seems to be related to amino acid replacements coded by single point mutations in the GABA-receptor-subunit gene (termed Resistance to dieldrin gene, or Rdl) in several insect species (French-Constant et al. 2004).

The detoxification enzyme-based resistance occurs when enhanced levels or modified activities of esterases, oxidases, or glutathione S-transferases (GST) prevent the insecticide from reaching its site of action. These enzymes are known to detoxify all major groups of insecticides. The genetic and molecular basis for insecticide resistance in mosquitoes through the detoxification mechanisms has also been widely studied. Increased activity of the esterase detoxification enzymes is associated with an amplification of the corresponding structural gene (Mouches et al. 1990; Vaughan et al. 1997; Hemingway et al. 1998). The up-regulation of both oxygenases and GSTs in resistant mosquitoes is due to the effects of a single major gene in each case (Hemingway et al. 1998).

Any mutation in a gene responsible for reduced sensitivity in a specific target site induces cross-resistance to all insecticides acting on that site. Cross-resistance between DDT and pyrethroids is known for many mosquito vectors (Prasittisuk and Busvine 1977; Chandre et al. 1999a; Brogdon et al. 1999; Ranson et al. 2000; Enayati et al. 2003). Cross-resistance has also been found between organophosphates and pyrethroids; e.g., Rodriguez et al. (2002) found that *Aedes aegypti* selected for temephos resistance also conferred resistance to deltamethrin probably associated with elevated GST activity. There have also been reports on multiple resistance (several resistance mechanisms present in one population), because of sequential exposure to insecticides from different chemical groups (Georghiou 1990a; Brogdon and McAllister 1998).

There are many and complex factors that control the dynamics of resistance development of a population. Each resistance is unique and depends on several genetic, biological, ecological and insecticide factors.

The main genetic factors affecting the dynamics of resistance development are the initial R-allele frequency, the dominance level, rates of mutation, and fitness costs. Insect populations develop resistance quicker if the initial R-allele frequency in the population is high. Dominance is also a factor that can affect the rate of resistance development. The concept of dominance relates to the relative position of the heterozygote phenotype (RS) to the two homozygotes on a dose-response curve (Bourguet et al. 2000). High dominance in a population indicates that the heterozygote phenotype (RS) is close to the homozygote phenotype (RR) resulting in a relatively high proportion of heterozygotes surviving under strong insecticide selection pressure and thus retaining the S-alleles in the population. Therefore, resistance will develop at a slower rate. On the contrary, at low dominance levels (RS is closer to SS), the heterozygotes will not survive high insecticide concentrations and the S-allele frequency will decrease in the population leading to increased rates of resistance development. The presence of avoidance behavior, size of insecticide dose, and degree of dominance further complicates these considerations (as discussed in e.g., Curtis et al. 1999). High mutation rates may also increase the rate of resistance development. The presence of resistance genes can confer fitness costs to insects. Resistance genes coding for either an overproduced detoxifying esterase (locus Ester) or an insensitive acetylcholinesterase target (locus ace-1) apparently induced subtle behavioral responses in *Culex pipiens*, which increased the probability of predation (Berticat et al. 2004). Another study showed that the presence of ace-1 alleles in *Culex pipiens* were associated with a longer larval development time and shorter adult wing length (Bourguet et al. 2004). Fitness costs in combination with high predation may affect the rate of insecticide resistance development.

Biological factors that may affect resistance development are life history, fertility, generation time, and insect behavior. Generally, resistance develops quicker in populations with short generation times, high fertility rates, and behaviors that lead to higher insecticide exposure. Furthermore, if insects from natural populations under low insecticide exposure and with high S-allele frequencies migrate to populations under strong insecticide selection (gene flow) the rate of resistance development may decrease. Selection pressure for insecticide resistance is also determined by the insecticide concentration, the frequency of insecticide applications, the proportion of the population that is exposed, and the repellency effect of the insecticide.

Pest damage and vector-borne diseases are often associated with specific seasons due to seasonal differences in insect population densities. This leads to seasonal variations in insecticide applications and may result in seasonal variations in selection pressure acting on the population. There may also be large geographical differences in the resistance development in insect pests and disease vectors. This is exemplified by the worldwide resistance in *Culex pipiens* to organophosphates (Raymond et al. 2001) and small-scale variations in insecticide resistance in *Anopheles albimanus* in Guatemala (Brogdon et al. 1988). In the latter case, the presence or absence of resistance, as well as level of resistance and dominant mechanism, varied in locations only a few kilometers apart.

Insecticide Resistance Management

Monitoring of vector resistance to insecticides should be an integral component of the planning and evaluation of both agricultural pest and vector-borne disease control programs. Such monitoring should be standardized to ensure comparability of data from different sources. The use of standard test kits and procedures, including discriminating concentrations, is recommended by the WHO (2006). These recommendations suggest that resistance is present if mortality is less than 80 percent in an insect

population exposed to a discriminating concentration of an insecticide (WHO 1998). Mortalities between 80 and 97 percent indicate the possibility of resistance and further studies should be conducted. Mortalities higher than 98 percent indicate susceptible populations.

Effective resistance management depends on early detection and rapid assimilation of information on the resistant insect population, e.g., knowledge of vector susceptibility to insecticides, changing trends of resistance and their operational implications, so that rational insecticide choices can be made. The following suggestions might be considered in managing resistance in disease vector control (WHO 2006):

- Use of non-chemical control methods, either alone or as a supplementary measure, in the seasons or areas in which they are applicable and cost-effective;
- Limitation of pesticide use to areas with high levels of disease transmission;
- Use of adulticides, which kill only adult females, rather than larvicides, which kill both sexes, resulting in approximately half the selection pressure for resistance;
- Rotation among unrelated insecticides according to a pre-arranged plan based on knowledge of the likelihood of resistance developing to each compound;
- Choice of a compound that has been found by experience to select for a narrow spectrum of resistance rather than a broad one; and
- Use of mixtures or mosaic treatments with unrelated compounds, so that individuals resistant to only one of the components are killed by the other.

The Insecticide Resistance Action Committee (IRAC) provides a practical definition of resistance related to resistance on the population level, namely that resistance is a heritable change in the sensitivity of a pest population that is reflected in repeated failure of a product to achieve the expected level of control when used according to the label recommendations for that

pest species and where problems of product storage, application and unusual climatic or environmental conditions can be eliminated (IRAC 2005a). To help reduce the negative effects of resistance in agriculture IRAC suggests the use of Insecticide Resistance Management (IRM). The objective of IRM is to prevent or delay the evolution of resistance to insecticides or to help regain susceptibility in already resistant insect populations (IRAC 2005a). IRM is an integral part of Integrated Pest Management (IPM) (see chapter Agricultural Pest Control, p. 13, for a definition of IPM) and involves three basic components: (a) monitoring pest population densities and trends; (b) focusing on economic thresholds; and (c) integrating control strategies. By following the progress of pests it is possible to determine if and when control measures are warranted. Insecticides should only be considered if pests become numerous enough to cause economic losses that exceed the cost of the insecticide plus application. However, in modern IPM the focus on economic threshold levels has changed to a focus on Agro-Ecological Systems Analysis (AESA), which is a flexible tool to make crop management decisions, based on a larger range of agro-ecological observations and an understanding of interactions between physical and biological factors (Bijlmakers 2005).

The Insecticide Resistance Action Committee (IRAC) has developed a Mode of Action Classification of insecticides which takes into consideration cross-resistance (IRAC 2005b). The classification groups chemically related insecticides that act on the same target site, so that users can select which insecticide should follow in sequence to avoid the risk of cross-resistance. IRAC also recommends the following integrated strategies: use of biological insecticides, beneficial insects (predators/parasites), transgenic plants, pest resistant crop varieties, and chemical attractants or deterrents; and varying cultivation practices and rotating crops (IRAC 2005a). The timing of spraying and details of insecticide application are also important aspects.

Insecticide Resistance in Vector Control

The large reductions in malaria cases during the WHO Global Malaria Eradication Program in the 1950s and 1960s, particularly in India and Sri Lanka, and the complete end of malaria transmission in parts of Europe and North Africa, were mainly attributed to the large-scale use of DDT residual spraying. Africa south of the Sahara was not included in the Eradication Program, apparently because of the overwhelming effort needed to eradicate malaria there. Eventually, eradication was not achieved due to the rise of insecticide resistance and various logistical problems. Malaria eradication was officially given up in 1969 and was substituted with a malaria control policy. During the 1970s malaria cases again rose to pre-eradication campaign levels. There are several reasons for the worldwide resurgence of malaria, e.g., the economical crises during the 1970s and 1980s, armed conflicts and civil unrest, human migration, climatic and environmental changes, vector behavioral changes, high birth rates giving rise to susceptible populations, and various technical and operational issues related to the campaign itself (Kager 2002). However, perhaps the most important reasons for the failure of the eradication campaign and the subsequent increase in malaria rates were the emergence and spread of vector resistance to insecticides and parasite resistance to drugs.

According to the WHO/UNICEF (2005) Southeast Asia has the highest rates of drug and insecticide resistance in the world. Thus, insecticide resistance is a real threat to the control of vector-borne diseases in the region. The reason for the high insecticide resistance in the region is probably the continuously profound reliance on various insecticide-based vector control strategies. Other reasons could be that most countries in the region are predominantly agricultural-based economies and recent economic growth in many Southeast Asian countries has led to intensification of the

agricultural sector, with increased pesticide use, potentially affecting vector resistance (see chapter Importance of Agricultural Insecticides for Vector Resistance, p. 17). Cross-resistance may also compromise future vector control efforts, if the agricultural insecticides act on the same target site as those used for vector control.

According to Chareonviriyaphap et al. (1999), there was no evidence of insecticide resistance in mosquito vectors in any region of Thailand in 1985. However, data compiled from routinely performed bioassays undertaken by regional offices of Vector-Borne Disease Control, Ministry of Public Health showed that resistance to DDT in the primary malaria vectors *An. minimus*, *An. dirus*, and *An. maculatus* had developed in northern Thailand between 1990 and 1997 (table 3). Insecticide resistance has also developed in several other malaria vectors in Southeast Asia (table 3). Most resistance studies have been undertaken on DDT, because of its frequent use during the eradication campaign.

Despite the many reports showing evidence of widespread resistance to many insecticides in the region, there are also reports of disease vectors still being susceptible to insecticides. Somboon et al. (2003), for example, found that *An. minimus* collected in northern Thailand was still susceptible to DDT and permethrin except in some areas where a slight tolerance to DDT was observed. There are similar results for *An. minimus* and *An. dirus* in northeast India, where DDT is still used in vector control (A. Prakash, Regional Medical Research Centre, N. E. Region, Assam, India, personal communication 2005). Here *An. minimus* did not develop DDT resistance even after 20 years of house spraying, although this species is highly endophilic there (Georghiou 1990b). Similarly, full susceptibility of *An. minimus* to DDT was reported in upper Assam, India (Kumari et al. 1998). However, Kumari et al. (1998) emphasized that very few bioassays have been undertaken on *An. minimus* and almost no data exist for *An. dirus*, because

of the lack of sufficient mosquitoes to do bioassays on. One study, however, reported full susceptibility of *An. dirus* to DDT, dieldrin and malathion (Prakash et al. 1998). Another study from Thailand reported that *An. balabacensis* (now considered as one of the sibling species in the *Anopheles dirus* complex) was susceptible to DDT in some districts but tolerant in others (Ismail and Phinichpongse 1980). *An. maculatus* in Malaysia was susceptible to DDT in 1989 (Loong et al. 1989) and to lambda-cyhalothrin in 1990-92 (Vythilingam et al. 1993).

Apart from local differences in insecticide susceptibility, e.g., due to variable exposure to agricultural insecticides, the highly variable results on insecticide susceptibility in the species mentioned could be a result of incomplete resistance surveillance. Further, these variations could also be explained by the presence of cryptic sibling species with no gene exchange that exhibit differences in biology, behavior, and insecticide tolerance. Few resistance studies have considered the fact that *An. minimus*, *An. dirus*, and *An. maculatus* are all species complexes (Green et al. 1985; Baimai 1988; Sucharit et al. 1988; Green et al. 1990; Sharpe et al. 1999; Walton et al. 1999). However, Hii (1984) showed that *An. dirus* (species A) was susceptible to discriminating doses of DDT, dieldrin, fenitrothion, malathion, and propoxur, whereas *An. dirus* (species B) was resistant to DDT and fenitrothion and *Anopheles balabacensis* (species C) had reduced susceptibility to DDT. These results may not be comparable, though, since the tested specimens were collected from populations in different locations (species A from Thailand, species B from Malaysia, and species C from Sabah); i.e., the observed differences could be a result from variations in insecticide exposure.

These studies indicate that mosquito resistance must be continuously monitored to stay a step ahead of resistance development, since the main vector control methods in the region are still chemically based.

TABLE 3.
Reports of insecticide resistance in vectors of malaria and dengue in Southeast Asia.

Species	Insecticide	Country	Notes	Reference
An. minimus	DDT	Thailand	Detected by routine bioassays performed by Ministry of Public Health during 1990 and 1997.	Chareonviriyaphap et al. 1999
An. minimus	DDT	Thailand	DDT resistance correlated with increased DDase activity.	Prapanthadara et al. 2000
An. minimus	DDT	Thailand	Slight resistance in some districts.	Somboon et al. 2003
An. minimus	DDT	Thailand	Resistant larvae.	Yasuno and Kerdpibule 1967
An. minimus	Permethrin	Thailand	Detected by routine bioassays performed by Ministry of Public Health in 1992 (only one year after the introduction of synthetic pyrethroids for malaria control).	Chareonviriyaphap et al. 1999
An. dirus	DDT	Thailand	Detected by routine bioassays performed by Ministry of Public Health during 1990 and 1997.	Chareonviriyaphap et al. 1999
An. balabacensis (now An.dirus)	DDT	Thailand	Resistant in some districts and susceptible in others.	Ismail and Phinichpongse 1980
An. dirus Species B	DDT/ Fenitrothion	Malaysia		Hii 1984
An. balabacensis	DDT	Sabah, Malaysia		Hii 1984
An. maculatus	DDT	Thailand	Detected by routine bioassays performed by Ministry of Public Health during 1990 and 1997.	Chareonviriyaphap et al. 1999
An. maculatus	Methyl parathion	Thailand	Resistance due to organophosphates used for controlling pests in fruit orchards.	Overgaard et al. 2005
An. sundaicus	DDT	Indonesia	Resistance detected in 1954, 2-4 years after the start of the malaria control programme.	Soerono et al. 1965
An. sundaicus	Dieldrin	Indonesia	Resistance detected in 1959 in Java after two cycles of spraying.	Soerono et al. 1965
An. aconitus	DDT	Thailand	Detected by routine bioassays performed by Ministry of Public Health during 1986 and 1991.	Chareonviriyaphap et al. 1999
An. aconitus	Dieldrin/ DDT	Indonesia	Dieldrin resistance occurred in Central Java after 3 years of spraying (1-2 cycles/yr). Double resistance to DDT/dieldrin widespread in 1965.	Soerono et al. 1965; Kirnowardoyo and Yoga 1985
An. annularis	DDT	Thailand	DDT resistance correlated with increased DDase activity.	Prapanthadara et al. 2000
An. philippinensis	DDT	Thailand	Detected by routine bioassays performed by Ministry of Public Health during 1986 and 1991.	Chareonviriyaphap et al. 1999
An. nivipes	DDT	Thailand	Detected by routine bioassays performed by Ministry of Public Health during 1986 and 1991.	Chareonviriyaphap et al. 1999
An. culicifacies	DDT	Thailand	Detected by routine bioassays performed by Ministry of Public Health during 1986 and 1991.	Chareonviriyaphap et al. 1999

Agricultural Pest Control

It is estimated that worldwide, approximately 90 percent of all insecticides are used for agricultural purposes (WHO 1986). In 2002, the total global market for chemical crop protection was approximately US\$25 billion (CropLife International 2003). Herbicides consisted of about 50 percent of the market, insecticides 25 percent, and fungicides almost 22 percent. The Asian pesticide market is approximately 22 percent of the global market (CropLife International 2003). The pesticide market of Latin America is almost 16 percent of the total global market. Pesticide use in Africa is very low.

In Asian developing countries, the area devoted to agriculture is approximately 50 percent of the total land area (FAO 2004). Some of the most important crops in Asian developing countries are paddy rice, wheat, maize, cotton, soybean, and fruit (table 4). There is a large number of small-scale subsistence farmers. The region is densely populated, has high population growth rates, and increasing economic expectations, leading to an intensification of crop production activities, particularly in terms of fertilizer and pesticide inputs. Of the developing nations in Asia, the largest pesticide consumers are China, Vietnam, Indonesia, and India. Although figures vary from region to region, the Asian crop protection market by crop is roughly: rice (ca., 40%), fruits and vegetables (30%), plantation crops (10%), cotton (8%), and soybean (3%) (Mengech et al. 1995).

The facts that chemical crop protection is intense in Asia and that many countries suffer from high malaria transmission rates in certain areas indicate that this region is highly susceptible for resistance development in mosquitoes due to exposure to agricultural insecticides.

In 2000, Thailand imported about US\$50 million worth of insecticides and the total insecticide consumption was estimated to 5.3 million tonnes (FAO 2004). The Thai pesticide market is liberal and the import and sale is operated by the private sector. The large amount

TABLE 4.
Harvested area (in million ha) of most important crops (by area) in Asian developing countries in 2002 (in descending order).

Group	Selected crops	Area
1. Cereals	Paddy rice	128.9
	Wheat	80.6
	Maize	42.2
	Millet	14.3
	Sorghum	11.7
	Total all cereals	290.4
2. Oil crops	Cotton seed	17.2
	Soybeans	16.8
	Groundnuts	15.1
	Rape seed	13.4
	Coconut	9.0
	Total all oil crops	92.3
3. Pulses	Beans, dry	12.4
	Chickpeas	9.3
	Total all pulses	33.9
4. Vegetables	Total all vegetables	32.4
5. Fruits	Apples	3.9
	Citrus	2.8
	Mango	2.5
	Banana	1.8
	Total all fruits	21.9
6. Fibre crops	Total all fibre crops	19.4
7. Roots and tubers	Potatoes	6.9
	Sweet potatoes	6.8
	Cassava	3.4
	Total all roots and tubers	17.4
8. Others	Forage crops	13.1
	Sugarcane	8.7
	Natural rubber	6.9

Source: According to FAO 2004

of pesticide trade names and formulations may be confusing to the consumers. The largest agricultural market shares of insecticides in Thailand are citrus (21%), vegetables (18%), and rice (16%) (Jungbluth 1996). A diversification of the Thai agricultural sector has led to an increase in more pesticide intensive cropping systems, such as fruit cultivation. Most pesticides are imported and in 1997 seventy-three percent fell into the WHO categories Ia (extremely hazardous) and Ib (highly hazardous) (Agrow 1997). The three main insecticides used in agriculture in 1997 were

the organophosphates monocrotophos, methamidophos and methyl parathion (Agrow 1997). These insecticides were banned in May 2000, April 2003, and October 2004, respectively (table 5). Most of the banned pesticides were banned in 2000 or later because of their high acute toxicity (table 5). The main insecticides used in tangerine (*Citrus reticulata* Blanco) fruit orchards in Thailand are dimethoate, cypermethrin, metamidophos, flufenoxuron, methomyl, monocrotophos, imidacloprid, and carbosulfan (Jungbluth 2000). All of these, except flufenoxuron, belong to the highly hazardous (Ib) and moderately hazardous (II) pesticide categories according to the WHO classification.

The Department of Agriculture (DOA), MOAC has produced guidelines for the use of pesticides in various crops showing details on insecticide names, active ingredients, dosages, and application methods (DOA 2004). Similar insecticides are often used in both agricultural and vector pest control, particularly the pyrethroids (table 1). However, agricultural pesticide use is generally much more diverse and intensive. The DOA also promotes the practice of Good Agricultural Practices (GAP) and has produced GAP guidelines in Thai language for several crops. GAP is defined as the application of available knowledge to the utilization of the natural resource base in a sustainable way for the production of safe, healthy food and non-food agricultural products, in a humane manner, while achieving economic viability and social stability (FAO 2002a). GAP includes uses of pesticides that are officially recommended or nationally authorized under actual conditions necessary for effective and reliable pest control. GAP encompasses a range of levels of pesticide applications up to the highest authorized use, applied in a manner which leaves a residue which is the smallest amount practicable (FAO 2002b).

Several Integrated Pest Management (IPM) interventions have been undertaken in Thailand and in the region (e.g., DANIDA 2005; FAO 2005). IPM is defined as the careful consideration of all available pest control techniques and subsequent integration of appropriate measures that

discourage the development of pest populations and keep pesticides and other interventions at levels that are economically justified and reduce or minimize risks to human health and the environment. IPM emphasizes the growth of a healthy crop with the least possible disruption of agroecosystems and encourages natural pest control mechanisms (FAO 2002b).

Pesticide residues in foodstuff samples are regularly monitored by the pesticide monitoring programs of the EU and EFTA (EU 2005). Similar programs are also carried out in other countries. In 2002, 2003, and 2004 the Maximum Residue Levels (MRL) of several insecticides, e.g., metamidophos, methyl parathion, cypermethrin, and endosulfan, were exceeded in several food crops exported to the EU from Thailand (information provided by the Agricultural Regulatory Office, Department of Agriculture, Bangkok, based on data from the EU Food and Veterinary Office [<http://europa.eu.int/comm/food/fvo>]). The MRLs of metamidophos and methyl parathion were exceeded in basil, coriander, spearmint, pepper, chili, beans, black-eyed peas, aubergine, water spinach, lychee, durian, and pomelo. The MRLs of cypermethrin were exceeded in basil, coriander, parsley, spearmint, pepper, chili, beans, yard-long bean, black-eyed pea, water spinach, lychee, durian, longan, and lime leaf.

The EU insecticide residue analyses of foodstuffs show that Thai farmers do not necessarily follow the recommendations of the DOA. The true situation of insecticide use in the field is complicated because of the many factors involved. Agricultural insecticide use is a function of pest presence, pest susceptibility to insecticides, crop type, crop damage, crop stage, weather, season, insecticide availability, farmers' socio-economic status and personal preferences, pesticide policy issues, and other factors. Insecticide use may therefore vary between years and regions, and even between farmers' plots. In addition, chemical crop protection is often subsidized by governments and promoted by agriculture extension services and industry.

TABLE 5.
Banned insecticides in Thailand (as of 2004).

Common name	Effective date	Reasons for banning
Chlordimeform	Apr 1977	Possible carcinogen
Leptophos	Apr 1977	Manufacturer voluntarily withdrew product from the market because it had tendency to have carcinogenic effect
BHC	Mar 1980	Very long residual effect, possible carcinogen
Sodium arsenite	Jan 1981	Persistent in soil, can cause fetotoxic effect
Endrin	Jul 1981	Long residual effect, high risk to users and consumers, exported seed often rejected because residues exceeded MRLs, harmful to non-target organisms and highly toxic to fish
DDT	Mar 1983	Possible carcinogen, long residual effect
Toxaphene	Mar 1983	Possible carcinogen, long residual effect
TEPP	Jun 1984	Very high acute toxicity, high risk to users
Parathion ethyl	May 1988	High acute toxicity to human, especially dermal toxicity
Dieldrin	May 1988	Long residual effect, bioaccumulates in human and animals, higher risk to users than other pesticides in the same group
Aldrin	Sep 1988	Long residual effect, bioaccumulates in human and animals
Heptachlor	Sep 1988	Long residual effect, bioaccumulates in human and animals
Mercury compounds	Aug 1993	High acute toxicity, persistent in environment, toxic to fish and aquatic animals
Aminocarb	Sep 1994	Very low ADI, high risk to users
Bromophos	Sep 1994	Very low ADI, high risk to users
Bromophos ethyl	Sep 1994	Very low ADI, high risk to users
Demeton	Sep 1994	Very low ADI, high risk to users
Chlordane	May 2000	Possible carcinogen, long residual effect, has adverse effects to environment and living organisms
Chlordecone	May 2000	Possible carcinogen
Monocrotophos	May 2000	High acute toxicity, high risk to users
Azinphos ethyl	May 2000	High acute toxicity, high risk to users
Mevinphos	May 2000	Very high acute toxicity, high risk to users
Phosphamidon	May 2000	Very high acute toxicity, high risk to users
Azinphos methyl	Jun 2000	High acute toxicity, high risk to users
Calcium arsenate	Jun 2000	High acute toxicity, high risk to users
Chlorthiophos	Jun 2000	High acute toxicity, high risk to users
Demephion	Jun 2000	High acute toxicity, high risk to users
Dimefox	Jun 2000	High acute toxicity, high risk to users
Disulfoton	Jun 2000	High acute toxicity, high risk to users
DNOC	Jun 2000	High acute toxicity, high risk to users
Fonofos	Jun 2000	High acute toxicity, high risk to users
Mephospholan	Jun 2000	High acute toxicity, high risk to users
Paris green	Jun 2000	High acute toxicity, high risk to users
Phorate	Jun 2000	Very high acute toxicity, high risk to users
Prothoate	Jun 2000	High acute toxicity, high risk to users
Schradan	Jun 2000	High acute toxicity, high risk to users
Sulfotep	Jun 2000	High acute toxicity, high risk to users
Hexachlorobenzene	Oct 2001	Probably carcinogenic to human, extremely persistent in environment
Beta-HCH	Dec 2001	Produces tumors in animals, causes adverse liver effect, produces reproductive and fetotoxic effects, persistent in environment

(Continued)

TABLE 5.
Continued.

Common name	Effective date	Reasons for banning
Copper arsenate hydroxide	Dec 2001	Risk on mutagenicity, teratogenicity, carcinogenicity, very high acute toxicity, high risk to users
Ethyl hexyleneglycol	Dec 2001	Risk associated with use by pregnant woman on study linked to birth defects
Ethylene oxide	Dec 2001	Probably carcinogenic and mutagenic to human
Lead arsenate	Dec 2001	Risk on oncogenicity, mutagenicity, carcinogenicity, high acute toxicity
Lindane	Dec 2001	Persistent in environment and bioaccumulation in food chain, suspected carcinogen
MKG Repellent	Dec 2001	Adverse effects on reproduction (malformations), reduce ovarian activity, carcinogenicity, development of benign tumors
Mirex	Dec 2001	Probably carcinogenic to human, extremely persistent in environment and biomagnification in food chain
o-dichlorobenzene	Dec 2001	Persistent in environment, mutagenic effects in experimental animals
Strobane	Dec 2001	Persistent in environment and bioaccumulation, possible carcinogen
TDE or DDD	Dec 2001	Possible carcinogen, persistent in environment and fatty tissues of human and animals, nervous system poisoning, affects reproductive process of birds and fishes
Methamidophos	Apr 2003	High acute toxicity, high risk to users
Methyl parathion	Oct 2004	
Endosulfan	Oct 2004	

Source: Adapted from Bartlett and Bijlmakers 2003

To make a comparison with other regions of the world where malaria is endemic, a short review of agricultural pesticide use in Africa and Latin America and the potential consequences for resistance development in mosquitoes is given here.

In African developing countries, the area devoted to agriculture is approximately 35 percent of the total land area (FAO 2004). African agriculture is based mainly on introduced crops, such as rice, cassava, maize, sweet potato, cocoa, and wheat. Only a few of the cultivated crops are indigenous, such as millet, sorghum, coffee, and cotton. Some of the indigenous pests have led to crop losses in, for example, millet, sorghum, and coffee. The major crop pests and diseases in Africa, however, have been introduced accidentally from other continents through increased travel and trade, such as the introduction of cassava mealybug and cassava green mite. Such newcomers often lack natural enemies and may therefore cause severe damage. Another characteristic of African agriculture is that most crops are cultivated in mixtures, such as mixed cropping or intercropping. Mixed cropping systems sometimes

have deterring effects on crop pests, partly because the risk of pest attack is spread on more crops. Furthermore, there is a large population of small-scale subsistence farmers that are often very poor and cannot afford agricultural investments. Poverty, in combination with drought, also contributes to low pesticide inputs. Pesticide use in Africa is therefore low compared to other continents. However, between 1988 and 1993, pesticide use increased by 200 percent, which was, by far, more than Asia and Latin America (Mengech et al. 1995). This was assumed to be primarily related to the control of locusts and grasshoppers. Apart from this use, chemical control is mainly occurring in commercial food crops and industrial crops, such as cassava, cowpeas, rice, millet, sorghum, coffee, cotton, and rice. Since agricultural pesticide use in this region is generally low, it is likely that insecticide resistance in mosquitoes from exposure to agricultural insecticides could be negligible. Insecticide resistance management in vector control should therefore be the main activity to reduce the risk of resistance development in vectors. However, the use of

insecticides in agriculture is increasing and can be substantial in areas of intense agriculture, as, for example, in irrigated rice cultivation, which has typically been associated with high malaria transmission (Carnevale et al. 1999). Therefore, the effect of agricultural insecticides on resistance development in malaria mosquitoes in Africa should not be underestimated and continued resistance surveillance is recommended.

The agricultural area in Latin America is approximately 38 percent of the total land area (FAO 2004). Agriculture is still the main economic activity in the region, in spite of recent industrial developments in many countries. The pattern of agricultural development, such as machinery and chemical inputs, is similar in many Latin American countries. Many endemic crops have been domesticated in this region, e.g., maize, potato, tomato, cassava, peanuts, and pineapple. But many have also been imported, such as coffee, rice, wheat, soybean, citrus, etc. The main cash crops in Latin America are coffee, maize, wheat, soybean, sugarcane, cotton, and fruits. In tropical regions, the most important crops are maize, sugarcane, and fruits (citrus, mango, guava, etc.). Large areas are devoted to raising cattle, especially in Argentina, Brazil, and Uruguay. In Latin America, Brazil is the major consumer of pesticides, accounting for more than 50 percent of the pesticides used and 35 percent of the pesticides are applied on soybeans in this country (Agrow 2002). Brazil is the third largest pesticide user worldwide, after the U. S. and Japan (Agrow 2002). To conclude, pesticide use in Latin America is more intensive than in Africa and, perhaps, also Asia. However, malaria rates in this region are low compared to other regions. The risk of insecticide resistance to appear in malaria mosquitoes as a consequence of agricultural insecticide use is probably low. However, some of the most well-known examples of the agriculture insecticide - mosquito resistance relationships have been reported from this region (Chapin and Wasserstrom 1981; Brogdon et al. 1988).

Importance of Agricultural Insecticides for Vector Resistance

Research on insecticide resistance in disease vectors has mainly focused on insecticides used for public health. This is evidently logical since mosquito vectors are clearly exposed to public health insecticides and thus subjected to resistance selection pressure. However, the facts that most insecticides are used for agricultural purposes and that agriculture has become increasingly resource intensive (e.g., WHO 1986; Jungbluth 1996) deserve attention as to what role agriculture plays in resistance development in disease vectors. Agriculture has often been blamed for insecticide resistance in disease vectors, but few attempts have been made to determine and confirm the direct impact of agricultural insecticides. The problem is noticeable in Southeast Asia, where agriculture is particularly resource intensive and vector-borne diseases are abundant, and where both often coincide spatially.

Lines (1988) and Georghiou (1990a) reviewed the relationship between agricultural insecticides and insecticide resistance in mosquito vectors. They categorized evidence for mosquito resistance selection by agricultural insecticides into six classes: (1) Resistance appearing before application of chemical vector control; (2) Higher resistance in agricultural areas than in non-agricultural areas (correlation in space); (3) Vector resistance corresponding to periods of agricultural spraying (correlation in time); (4) Correlation between intensity of insecticide use on crops and degree of resistance in vectors; (5) Correspondence between vector cross-resistance spectrum and insecticide types applied to crops; and (6) Temporary suppression of mosquito population densities following agricultural sprays (relative exposure).

Resistance development in vectors through agricultural selection pressure has been documented from Central America, Africa, South Asia, and Southeast Asia. Georghiou et al. (1971) found organophosphate resistance in An.

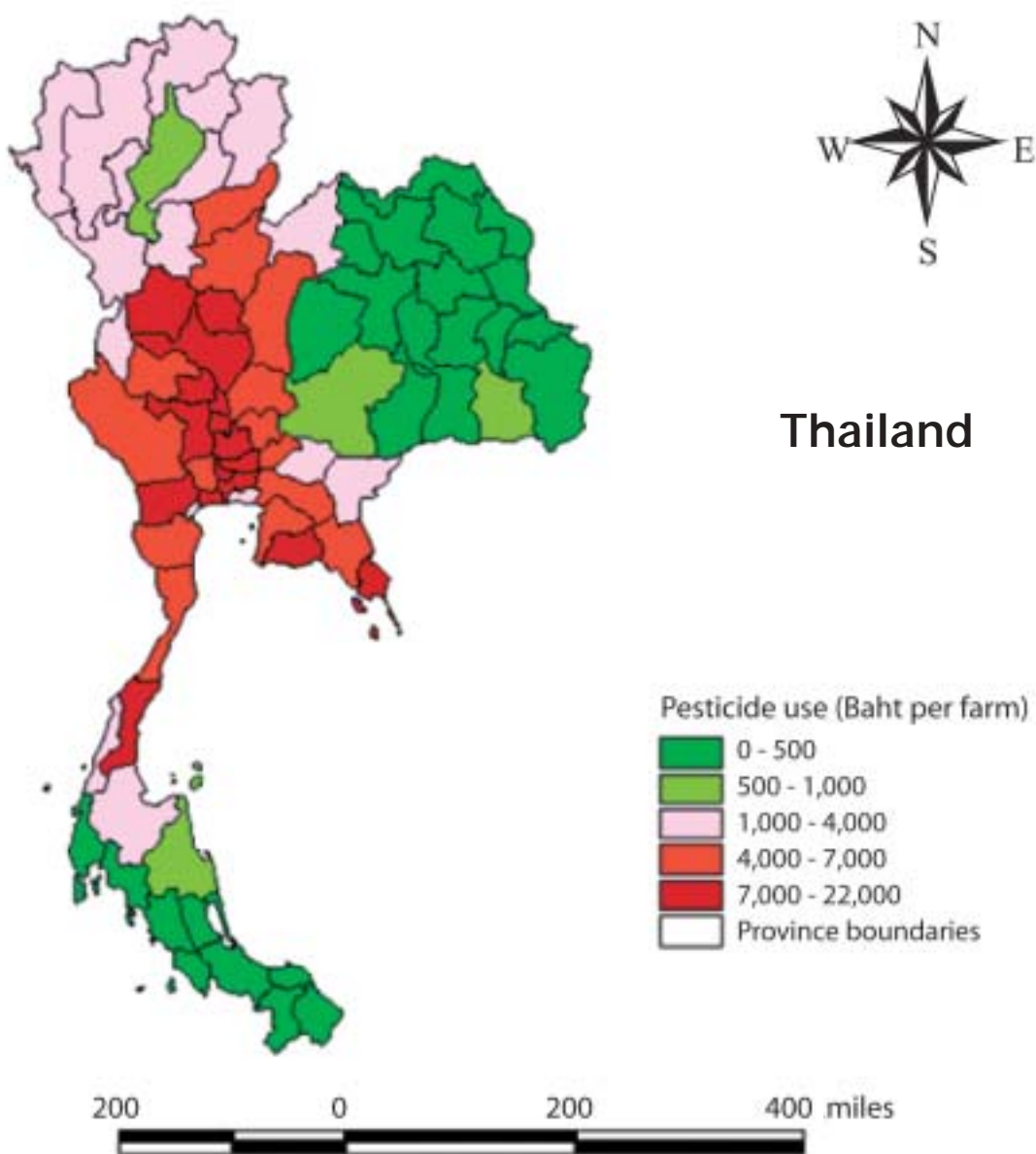
albimanus populations in an area treated intensively with this insecticide against pests on cotton in El Salvador. Chapin and Wasserstrom (1981) related malaria resurgence in Central America and India with agricultural production and intensive insecticide use. Another study associated the presence of the acetylcholinesterase and elevated esterase resistance mechanisms in *An. albimanus* with intensively managed agricultural areas in Guatemala (Brogdon et al. 1988). In Sri Lanka, Hemingway et al. (1986) compared insecticide resistance in *An. nigerrimus*, predominantly breeding in agricultural areas, and *An. culicifacies*, the primary malaria vector in Sri Lanka, breeding in non-agricultural water. They found that *An. nigerrimus* was resistant to organophosphates and carbamates at both the larval and adult stages, whereas *An. culicifacies* was not, indicating that agricultural insecticides was the source for selection pressure for resistance in *An. nigerrimus* (example of category (2) above). Further, the resistance mechanism in *An. nigerrimus* was suggested to be acetylcholinesterase and the resistance gene frequency correlated with the intensity of agricultural insecticide selection pressure (category (4) above). Diabate et al. (2002) found that *An. gambiae* was susceptible to DDT and pyrethroids in a cotton growing area in Burkina Faso during the dry season, when insecticides were not used in agriculture, but that resistance increased during the wet season when insecticides were used to protect cotton plants (category (3) above). Landscape ecological research from rural areas in northern Thailand showed a negative relationship between fruit orchard area and anopheline density (Overgaard et al. 2003). This relationship suggests that mosquito population densities are suppressed as a consequence of the intensive use of insecticides in fruit orchards (category (6) above). The risk of selection of insecticide resistance in mosquitoes would therefore be higher in areas with a high proportion of fruit orchards than in areas with no orchards. Overgaard et al. (2005) confirmed higher resistance to methyl parathion in

An. maculatus s. s. collected in tangerine orchards compared to mosquitoes collected in a comparable area with minimal agricultural insecticide use (correlation in space, category (2) above). Methyl parathion is an organophosphate insecticide commonly used in fruit orchards, but not in vector control.

It is important to identify areas where the risk of insecticide resistance in disease vectors is elevated. In Thailand, attempts have been made to map pesticide contamination and agricultural use of pesticides (Thapinta and Hudak 2003; Bartlett and Bijlmakers 2003). The vulnerability of groundwater to pesticide pollution was studied in four provinces in central-western Thailand, including Kanchanaburi, which is part of the present study (Thapinta and Hudak 2003). The study indicated that well depth, i.e., groundwater level, was the most significant vulnerability factor. The results showed that the study area had an overall groundwater vulnerability rating of 'average'. This average level of pesticide contamination of groundwater was due to deep groundwater levels and fine soils in the agricultural pesticide-intensive areas in the eastern part of the study area and shallow groundwater levels in the generally mountainous and forested western parts of the study area, where less pesticide is applied. However, there were local hot spots throughout the study area, particularly in agricultural areas with shallow groundwater. The IPM-DANIDA project in Thailand has produced a rough map showing pesticide-intensive agricultural areas on a provincial level (figure 1) (Bartlett and Bijlmakers 2003). The map shows that pesticide use is most intensive in the central plain, the northern region, and in the east of Thailand. Areas with relatively lower use of pesticides are in the north eastern and southern regions.

The most urgent threat to vector control is probably the development of pyrethroid resistance. This is because pyrethroids are currently the main stay of current global vector control efforts, used either in indoor residual spraying or treatment of impregnated bednets. However, the amounts of pyrethroids used in vector control are small compared to what is

FIGURE 1.
 Distribution of pesticide use in Thailand based on agricultural statistics for the crop year 2000/2001 (average amount of money spent per farm to purchase pesticides).



Source: Bartlett and Bijlmakers 2003
 Note: 1 mile = 1.609 kilometers

used for agricultural purposes. In Thailand, there are only circumstantial indications of pyrethroid resistance in malaria mosquitoes. Routine bioassays undertaken by the provincial offices of Vector-Borne Disease Control (Ministry of Public Health) showed that permethrin resistance developed in *An. minimus* in 1993, approximately

one year after the introduction of synthetic pyrethroids for malaria control (Chareonviriyaphap et al. 1999). However, these results have been criticized partly because of the inadequate experimental conditions, under which the bioassays were undertaken, e.g., lack of temperature control (Somboon et al. 2003).

Pyrethroid resistance in malaria vectors has been reported from several countries in Africa, such as Cote d'Ivoire, Burkina Faso, Benin, and Kenya (Elissa et al. 1993; Vulule et al. 1994; Chandre et al. 1999b). There is no clear evidence as to how this resistance has developed (Takken 2002), but it is believed that it may be a result of agricultural use of pyrethroids, in particular, in connection with small-scale irrigation practices (Mouchet 1988; Chandre et al. 1999a). Takken (2002) argues that ITNs to control malaria in Africa have, in general, been implemented on such a small scale that it is unlikely that selection for pyrethroid resistance in *An. gambiae* has occurred through the use of ITNs. If pyrethroid resistance was caused mainly by agricultural insecticide use, it is likely that such resistance will evolve regardless of the organized use of pyrethroids in properly managed malaria control campaigns (Chandre et al. 1999a). These kinds of selection pressures are almost impossible to control. Cross-resistance may also be a problem. In areas of predominantly organophosphate agricultural pest control organophosphate-pyrethroid cross-resistance may compromise pyrethroid vector control. Thus, the effect of agricultural insecticides must be considered as a real threat to vector control, as has been pointed out by several authors and organizations (e.g., Lines 1988; Georghiou 1990b; Chareonviriyaphap et al. 1999; WHO 2004).

Rationale of Study

As described above, the dynamics of resistance development is complex and varies from species to species and from area to area. However, the fundamental requirements for an insect population to develop resistance are exposure to insecticides and genetic variation in insecticide susceptibility. It is relatively easy to assess the geographical extent of insecticide exposure (compared to assessing the geographical extent of genetic population variation). Based on this fact it is possible to develop simple maps showing overlapping areas of particularly

insecticide-intensive cropping systems and areas of high endemicity of disease vectors. Such maps show risk areas where insecticide resistance is likely to develop in vectors, as well as in agricultural pests. Identifying risk areas should focus on land use specific pesticide use to determine local or regional variations in pesticide use and intensity. Maps showing risk areas – or target areas – may be particularly helpful for assessing potential locations for the implementation of resistance management and integrated control strategies. Such strategies could be action plans to reduce or replace insecticides used in pest and disease vector control or coordination of Integrated Pest Management (IPM) and Integrated Vector Management (IVM) activities.

At a workshop on "Sustainable Approaches for Pest and Vector Management and Opportunities for Collaboration in Replacing POPs Pesticides" held by the UNEP/FAO/WHO in 2000, the need was expressed for an inventory identifying such target areas, as well as areas for undertaking pilot field studies and training of IPM/IVM trainers (UNEP 2000). Implementation of action plans and/or resistance management options through coordinated approaches between sectors could thus be made more efficient.

An inter-country workshop on insecticide resistance in mosquito vectors held in Indonesia in 1997 by WHO Southeast Asia Region stated that the reappearance of several mosquito vectors in most member states was attributed to the failure of chemical control as a result of insecticide resistance (WHO/SEARO 1997). Mosquitoes had developed resistance to all the major groups of insecticides, including biocides. It was concluded that selective vector control following WHO guidelines should be adapted to local conditions with special emphasis on the rational use of insecticides, and that it is necessary to prevent or delay insecticide resistance resulting from excessive or improper use. This may require inter-ministerial policy and program coordination involving health and agricultural ministries as well as municipalities and local administrations.

The UNEP, FAO, and WHO are currently in the process of producing a training compendium (partly written by H. J. Overgaard) for developing action plans to replace POP insecticides in pest and disease vector control in accordance with the Stockholm Convention. This compendium will be a complement to the UNEP/FAO/WHO document 'Reducing and eliminating the use of persistent organic pesticides – Guidance on alternative strategies for sustainable pest and vector management' (UNEP 2002). These documents will assist planners and decision-makers to assess the specific needs for considering alternatives to pesticides; to identify relevant stakeholders; and to address advantages and disadvantages of different alternative pest/vector control approaches in different target areas.

The extent of intensively managed agroecosystems varies from country to country and from region to region and is different depending on what insecticide is in focus. There are various ways of mapping areas where insecticide resistance in disease vectors may develop as a consequence of exposure to agricultural insecticides. Each way depends on the availability and quality of background data, how government agencies store collected data, etc. In this study, the approach (developed by H.

J. Overgaard) outlined in the unpublished UNEP/FAO/WHO training compendium was adopted. GIS was applied to identify the spatial extent of malaria transmission areas, including information on vector distributions that coincide spatially with insecticide-intensive agroecosystems.

A particularly problematic issue is the difficulty to acquire reliable information on what kind of insecticides and the amounts that individual farmers use. Prior to the current study, a survey of farmers' agricultural practices was undertaken in the Chiang Mai and Kanchanaburi provinces of Thailand (H. J. Overgaard unpublished data). It was found that farmers, particularly large-scale farmers, were suspicious and reluctant to provide reliable answers, probably as a response to recent publicity of adverse human health effects from pesticides used in fruit cultivation. The ambiguity of relying on farmers' answers, in addition to the relatively high costs to acquire such information were partly avoided in this study by directly assessing land use specific insecticide use. This assessment was based on the fact that certain cropping systems generally require more insecticide input than other systems and on the assumption that insecticides are evenly applied in each land use. However, it was not possible to investigate the details of specific insecticides used in each cropping system.

Materials and Methods

The focus of this study was the four provinces Chiang Mai, Mae Hong Son, Tak, and Kanchanaburi in western and northern Thailand, which are situated along the border to Myanmar (figure 2). These provinces are, in general, mountainous and forested. The most populated areas are located along the major river valleys. The river valleys are typically cultivated with paddy rice and other crops. The study areas have the highest malaria rates in the country (Malaria Division 1993) and are also under considerable

agricultural development financed by the government and wealthy landowners (Jungbluth 1996). The land area of Chiang Mai is 22,090 square kilometers (km²), Mae Hong Son is 12,740 km², Tak is 17,260 km², and Kanchanaburi is 19,410 km², making up a total study area of 71,500 km². The administrative units in Thailand are province (jangwat), district (amphoe), sub-district (tambon), and village (muu ban). The extent of separate villages is arbitrary and not set by well-defined borders.

FIGURE 2.
Study areas in Thailand.



Classification of Land Use

Digitized land use maps (ArcView shapefiles) from 2003 of the study area were acquired from the Land Development Department (LDD), Ministry of Agriculture and Cooperatives (MOAC), Thailand. The LDD land use classification, consisting of more than 1,600 single and multiple land use classes, was modified into a simplified classification comprising 18 land use classes to account for the purposes of this study (table 6).

The LDD land use classification allows for recording of multiple land uses in any patch, e.g., intercropping or various agroforestry systems. In cases where there were patches (polygons) with multiple land uses, the primary land use class was used in the reclassification. The primary land use class, according to LDD, is the major land use that covers at least 50 percent of the area. The LDD classification lacked some detail, which was detected by studying the ArcView land use database and observing the true conditions in the field. Some land uses observed in the field were not recorded in the LDD database, partly because of too small areas of cultivation and that the cultivation patterns of Thai farmers changed from year to year. Additionally, sometimes several crops existed in one patch and were therefore lumped into the categories 'Mixed field crops' or 'Mixed swidden cultivation'. There was also an abundance of crops grown near houses in built-up areas, e.g., in homegardens. The insecticide use in homegardens was expected to be low, since farmers often hesitate to use large amounts of pesticides around their houses or on crops which are intended for own consumption. All land uses present in the LDD database for the four provinces are found in table 6. This exercise aimed at producing a general overview of the present situation and it was not possible to undertake a more detailed analysis than this.

The areal extent of fruit orchards was, in reality, much larger than shown here, because fruits were often mixed together with other crops or grown in homegardens. In such cases, where secondary land uses comprised less than 50 percent of any patch, the total area of those land uses was underestimated. Another limitation was

that areas classified as 'bush fallow' and 'abandoned field' might become under cultivation in the season after the survey.

Assessment of Agricultural Pesticide Use

To assess the magnitude of crop-specific insecticide use in Thailand three reports were used (see table 7 and below for details). The reports give information on insecticide use by (1) Amount per area, (2) Market share per area, and (3) Ordinal classification. Data on insecticide use in crops that were not present in the current study are shown in table 7 for information purposes.

(1) Amount per area (Jungbluth 1996)

The first source was an analysis of the crop protection policy of Thailand and included crop-specific insecticide use from the Thai-German Plant Protection Program from 1993. These data were rather old, but could still be indicative of present insecticide use. Insecticide intensity was measured as the amount of insecticide used in a specific crop divided by the planted area of that crop (kilograms per rai (kg/rai); 1 rai = 0.16 hectares (ha)). There was no mention of specific insecticides or active ingredients in this source. For the present purposes, insecticide intensity in the land use 'Fruit' was calculated by taking the average of insecticide use in tangerine, mango, and durian. Insecticide intensity in "Legumes" was calculated by taking the average of insecticide use in soybean, peanut, and green beans.

(2) Market share per area (UNESCAP 2000)

The second source was a report from the Department of Agriculture, MOAC presented at an international workshop on IPM and Green Farming in rural poverty alleviation under the auspices of UNESCAP. The report gives information on the estimated pesticide market shares of various crops by pesticide companies in Thailand in 1998. Insecticide

TABLE 6.

Land uses in Chiang Mai (CM), Mae Hong Son (MHS), Tak (TAK), and Kanchanaburi (KB) provinces of Thailand according to Land Development Department (LDD), Ministry of Agriculture and Cooperatives and the conversion of LDD codes and names to the new land use codes and names used in this report.

LDD code	LDD land use name	New code	New land use name	Presence
A101	Transplanted paddy field	1	Paddy rice	All
A102	Broadcasted paddy field	1	Paddy rice	KB
IA101	Transplanted paddy field (irrigation)	1	Paddy rice	CM
A209	Soybean	2	Legumes	CM, MHS
A609	Soybean (swidden cultivation)	2	Legumes	CM, MHS
A610	Peanut (swidden cultivation)	2	Legumes	TAK
A612	Black bean, red bean (swidden cultivation)	2	Legumes	TAK
A202	Maize	3	Cereals	CM, MHS, TAK
A213	Sorghum	3	Cereals	KB
A216	Upland rice	3	Cereals	KB
A602	Maize (swidden cultivation)	3	Cereals	All
A616	Upland rice (swidden cultivation)	3	Cereals	All
A203	Sugarcane	4	Sugarcane	TAK, KB
A204	Cassava	5	Cassava	KB
A205	Pineapple	6	Pineapple	KB
A223	Cabbage	7	Vegetables	CM
A229	Chili	7	Vegetables	KB
A502	Truck crop (vegetables)	7	Vegetables	CM, TAK, KB
A623	Cabbage (swidden cultivation)	7	Vegetables	CM, MHS, TAK
A201	Mixed field crop (various crops)	8	Mixed crops	All
A601	Mixed swidden cultivation (various crops)	8	Mixed crops	CM, MHS, TAK
A313	Tea	9	Tea	CM
A503	Floriculture	10	Floriculture	CM
A100	Abandoned paddy	11	Bush fallow/abandoned field	CM, KB
A600	Bush fallow	11	Bush fallow/abandoned field	CM, MHS, TAK
A301	Mixed perennial	12	Perennial	TAK, KB
A302	Para rubber	12	Perennial	KB
A304	Eucalyptus	12	Perennial	TAK, KB
A305	Teak	12	Perennial	CM, KB
A306	Magosa	12	Perennial	KB
A307	Casuarina	12	Perennial	KB
A308	Acacia	12	Perennial	CM
A315	Bamboo	12	Perennial	KB
A318	Rain tree	12	Perennial	CM, TAK
A4	Orchard	13	Fruit orchard	KB
A401	Mixed orchard	13	Fruit orchard	All
A402	Orange	13	Fruit orchard	CM, TAK
A403	Durian	13	Fruit orchard	CM
A406	Litchi	13	Fruit orchard	CM
A407	Mango	13	Fruit orchard	CM, TAK
A411	Banana	13	Fruit orchard	CM, TAK
A413	Longan	13	Fruit orchard	CM
A423	Sub-tropical fruit	13	Fruit orchard	CM, MHS

(Continued)

TABLE 6.
Continued.

LDD code	LDD land use name	New code	New land use name	Presence
F100	Disturbed evergreen forest	14	Forest	All
F101	Moist evergreen forest	14	Forest	CM, TAK, KB
F102	Dry evergreen forest	14	Forest	CM, TAK, KB
F103	Hill evergreen forest	14	Forest	CM, MHS, TAK
F104	Tropical pine forest	14	Forest	CM, MHS
F200	Disturbed deciduous forest	14	Forest	All
F201	Mixed deciduous forest	14	Forest	All
F202	Deciduous dipterocarp forest	14	Forest	All
F300	Disturbed forest plantation	14	Forest	CM
F301	Mixed forest plantation	14	Forest	All
F302	Pine	14	Forest	CM, MHS, TAK
F304	Eucalyptus	14	Forest	CM
F305	Teak	14	Forest	CM, TAK, KB
M101	Grass	15	Grass/scrub	KB
M102	Scrub, grass and scrub	15	Grass/scrub	CM, TAK, KB
M103	Bamboo	15	Grass/scrub	TAK, KB
A703	Poultry farm house	16	Various	CM
A704	Swine farm house	16	Various	CM
M2	Wetland	16	Various	CM, TAK, KB
M3	Mine, pit	16	Various	CM
M300	Abandoned mine	16	Various	KB
M301	Mine	16	Various	CM, TAK, KB
M302	Laterite pit	16	Various	KB
M303	Sand pit	16	Various	KB
M4	Other landuse	16	Various	CM
M402	Beach	16	Various	TAK
U1	City, town, commercial and service	17	Urban	All
U200	Allocated land project	17	Urban	CM, TAK, KB
U201	Lowland village	17	Urban	All
U202	Highland village	17	Urban	CM, MHS, TAK
U3	Institutional land	17	Urban	All
U4	Transportation, communication and utility	17	Urban	TAK
U401	Airport	17	Urban	CM, MHS, TAK
U502	Factory	17	Urban	CM, TAK, KB
U6	Other urban and built-up land	17	Urban	TAK
U601	Recreation area	17	Urban	CM, KB
U602	Golf course	17	Urban	CM, KB
U603	Cemetery	17	Urban	KB
U604	Refugee camp	17	Urban	TAK
A8	Aquatic plant	18	Water	KB
A801	Mixed aquatic plant	18	Water	KB
A901	Mixed aquacultural land	18	Water	KB
A902	Fish farm	18	Water	CM, KB
W101	River, canal	18	Water	CM, TAK, KB
W102	Lake	18	Water	CM, TAK, KB
W201	Reservoir	18	Water	All
W202	Farm pond	18	Water	CM, TAK, KB

TABLE 7.

Classification of insecticide use in land uses in Chiang Mai, Mae Hong Son, Tak, and Kanchanaburi provinces, Thailand. The eighteen land use classes used in this report are shown in bold. For land use codes, see also table 6.

Land use name (assigned code)	Insecticide use ¹	Insecticide market share ²		Insecticide use classes ³		New classification of insecticide use
	kg/rai ⁴	baht/rai ⁴	relative to rice	1-5 scale	1-4 scale	Name
Grapes (n. p.)	24.630	4,800.00	377.66	4.00	-	-
Citrus/Tangerine (incl. in 13)	4.920	1,023.39	80.52	2.00	-	-
Mango (incl. in 13)	0.270	133.06	10.47	2.00	-	-
Durian (incl. in 13)	0.730	135.66	10.67	n. d.	-	-
Fruit orchard (13)	1.973	n. d.	n. d.	2.00	4	High
Chilli, pepper (incl. in 7)	1.180	n. d.	n. d.	4.00	-	-
Onion, garlic (incl. in 7)	0.770	n. d.	n. d.	n. d.	-	-
Vegetables (7)	4.730	n. d.	n. d.	5.00	4	High
Floriculture (10)	n. d.	n. d.	n. d.	4.00	4	High
Soybean (incl. in 2)	0.120	n. d.	n. d.	3.67	-	-
Peanut (incl. in 2)	0.098	n. d.	n. d.	3.67	-	-
Green beans (n. p.)	0.040	n. d.	n. d.	n. d.	-	-
Legumes (2)	0.086	27.95	2.20	n. d.	3	Medium
Paddy rice (1)	0.140	12.71	1.00	4.67	3	Medium
Maize (incl. in 3)	0.011	0.58	0.05	3.33	-	-
Cereals (3)	n. d.	n. d.	n. d.	n. d.	2	Low
Mixed crops (8)	n. d.	n. d.	n. d.	n. d.	2	Low
Tea (9)	n. d.	n. d.	n. d.	n. d.	2	Low
Pineapple (6)	n. d.	9.60	0.76	2.00	2	Low
Cassava (5)	n. d.	0.00	0	2.33	1	Negligible
Sugarcane (4)	0.020	0.00	0	2.67	1	Negligible
Para rubber (incl. in 12)	n. d.	0.00	0	n. d.	1	-
Oil palm (n. p.)	0.014	14.14	1.11	n. d.	1	-
Bush fallow/abandoned field (11)	n. d.	n. d.	n. d.	n. d.	1	Negligible
Perennial (12)	n. d.	n. d.	n. d.	1.00	1	Negligible
Forest (14)	n. d.	n. d.	n. d.	1.00	1	Negligible
Grass/scrub (15)	n. d.	n. d.	n. d.	1.00	1	Negligible
Various (16)	n. d.	n. d.	n. d.	1.00	1	Negligible
Urban (17)	n. d.	n. d.	n. d.	1.00	1	Negligible
Water (18)	n. d.	n. d.	n. d.	n. d.	1	Negligible

Sources: Jungbluth 1996; UNESCAP 2000; Thapinta and Hudak 2003

Notes: ¹ Insecticide use according to Thai-German Plant Protection Program cited by Jungbluth (1996). 'Fruit' was estimated as the average of tangerine, mango, and durian. 'Legumes' was estimated as the average between soybean, peanut, and green beans. The types of vegetables in the 'Vegetables' category, were not provided

² Estimated insecticide market share of various crops in Thailand, based on figures from pesticide companies and planted crop area in 1998 (UNESCAP 2000)

³ Classification of land cover and insecticide use (average of carbofuran, dicofol, and endosulfan) from 1 (lowest use) to 5 (highest use) (Thapinta and Hudak 2003). Figures in italics indicate that the particular land use was included in one of three general categories: 'Horticulture' (flowers, grapes, pepper, strawberry, passion fruit, and raspberry), 'Fruit' (orange, mango, tamarind, jack fruit, rose apple, lime, and banana), and 'Perennial' (eucalyptus, casuarinas, acacia, bamboo)

⁴ 1 rai = 0.16 hectares

n. d. = no data

n. p. = not present in the four provinces of this study

intensity was measured as the crop market shares divided by the planted area of each crop (baht/rai; baht is the Thai currency, 1 rai = 0.16 ha). The magnitude of crop-specific insecticide use relative to rice was also calculated as a comparison. It was not possible to separate insecticides into insecticide groups or active ingredient.

(3) Ordinal classification (Thapinta and Hudak 2003)

The third source showing the most recent estimates were from a scientific paper on the assessment of groundwater pollution potential of pesticides in Central Thailand. Crop-specific insecticide intensity was ranked on an ordinal scale from 1 (lowest use) to 5 (highest use) according to the use of three insecticides/acaricides: carbofuran (carbamate), dicofol (organochlorine), and endosulfan (organochlorine) and two herbicides. Here the average ratings of the three insecticides/acaricides were used to assess insecticide use. In the paper by Thapinta and Hudak (2003), several crops were grouped into categories. Thus, 'Horticulture' consisted of flowers, grapes, pepper, strawberry, passion fruit, and raspberry; 'Fruit' consisted of orange, mango, tamarind, jack fruit, rose apple, lime, and banana; and 'Perennial' consisted of eucalyptus, casuarinas, acacia, and bamboo.

Each of the 18 land use classes was assessed in terms of insecticide input by ranking and grouping according to insecticide intensity. A new classification on an ordinal scale from 1 to 4 based on the three reports was used as an overall estimate of general insecticide use in land uses present in the four provinces (table 7). The new classification indicated 1 for 'Negligible', 2 for 'Low', 3 for 'Medium', and 4 for 'High' pesticide use.

Using this classification fruit, vegetables, and floriculture were classified as having high insecticide use; paddy rice and legumes were classified as having a medium use of insecticides; and cereals, mixed crops, pineapple,

and tea were classified as low insecticide use. The other land uses were estimated as having negligible insecticide uses. In cases where there were no available data a rough classification was undertaken, thus for cereals and mixed crops, the value for maize was used. Considering the lack of information on insecticide use in tea and the few and small areas of this crop it was assigned as low insecticide use.

In the evaluation of the new classification, a higher emphasis was put on the exact numbers provided by the Jungbluth (1996) and UNESCAP (2000) sources than on the ordinal scale of Thapinta and Hudak (2003). However, in some cases the more recent estimates of UNESCAP were used since crop protection practices change as a response to technology development. The increased use of improved plant varieties, for example in cassava, has reduced the use of insecticides as a means of plant protection. Many of the crops listed in table 7 did not appear in the LDD land use maps of the four provinces of this study; therefore, they were not listed in the final classification. Cotton, tobacco and tomato, which are normally quite insecticide-intensive land uses, were not present in the LDD database of the four provinces and were therefore not included in the land use classification.

Malaria Stratification

In this study, malaria and vector distribution was determined by using yearly malaria area stratification records of the governmental Vector-Borne Disease Control Offices (VBDOs). Malaria stratification follows the guidelines of the Thai Malaria Division (1993) and forms the basis for malaria control efforts for the next year. The number of malaria cases is recorded each year, including an assessment of vector presence. The smallest unit of record is the village level. Based on these records malaria transmission was assessed by stratifying areas into four basic categories: (1) Control area with transmission (A1 and A2); (2) Control area without transmission (B1 and B2); (3) Pre-integration areas (PA); and (4)

Integration areas (IA). PA and IA are virtually free of malaria and vectors and no control is undertaken in these areas. Active malaria and vector control is only undertaken in the first two categories, which are further divided into two sub-categories:

(A) Control area with transmission

- (1) Perennial transmission areas: transmission occurs every year during at least 6 months of the year (A1)
- (2) Periodic transmission areas: transmission occurs every year but during less than 6 months of the year (A2)

(B) Control area without transmission

- (1) High-risk non-transmission areas: no transmission for at least three consecutive years; primary malaria vectors present (B1)
- (2) Low-risk non-transmission areas: no transmission for at least three consecutive years; only suspected vectors present (B2)

In this study, data were compiled for each administrative level above village level, i.e., the tambon or sub-district. Each sub-district was assigned a number reflecting its malaria status, 1=A1, 2=A2, 3=B1, 4=B2, and 5=PA. Integration areas (IA) were not present in the study areas. Malaria stratification data for fiscal year 2004 were acquired from Vector-Borne Disease Control Offices (VBDO), Ministry of Public Health. VBDO No. 10 in Chiang Mai provided data for Chiang Mai and Mae Hong Son provinces, VBDO No. 8 in Nakhon Sawan provided data for Tak province, and VBDO No. 4 in Kancharaburi provided data for Kancharaburi province.

In some cases, a sub-district contained several stratification areas, e.g., different villages within the sub-district might have been assigned different stratification categories, such as A1, A2, etc. Since, it was not possible to map separate villages due to the lack of identifiable village borders, a decision had to be made as to what category should be assigned to that sub-district. In such cases, the highest category was used, e.g., if one village in a sub-district was considered as A1 (perennial transmission), but the rest of the sub-district was A2 (periodic transmission) or B1 or B2 (risk areas), the sub-district as a whole was categorized as A1.

GIS and Maps

Administrative borders for sub-districts were acquired from the LDD database and from a digitized database from the Irrigation Department, MOAC. These two databases were adjusted to fit the malaria stratification data from the VBDOs.

Land use maps were produced from the LDD data for each province (Appendices 1-4). Provincial land use specific insecticide intensity was calculated from the land use maps and the insecticide classification developed here (table 7). Insecticide intensity maps are shown together with malaria stratification maps in Appendices 5-8.

The potential risk areas for insecticide resistance in malaria vectors were calculated for each province by overlaying selected features (high and medium insecticide use) in the insecticide intensity maps with selected features (A1 and A2) in the malaria stratification maps to produce maps showing land uses with high insecticide intensity in malaria transmission areas (Appendices 9-12). All GIS work, including overlays, area calculations, and map layouts were undertaken using ArcGIS 9 and ArcView 3.2.

Results

The most insecticide-intensive cropping systems were found to be fruit, vegetables, floriculture, legumes, and paddy rice and are therefore reported here. Land uses referred to in this chapter are those that are located within malaria transmission areas.

Chiang Mai

Perennial malaria transmission was located in the north, west and south of Chiang Mai province (Appendix 5). Periodical malaria transmission was located throughout the province, except close to Chiang Mai city, which were mainly low-risk areas.

Of a total of 24 districts, 21 were recorded with overlapping insecticide-intensive agriculture and malaria transmission as defined here. The total area of insecticide-intensive agriculture in malaria transmission areas in Chiang Mai was 154,283 ha (about 7% of the total area of the

province) (table 8). Mueang Chiang Mai, Saraphi, and San Kamphaeng, three districts around Chiang Mai city, were not included in the analysis due to the malaria stratification criteria, i.e., they were classified as pre-integration areas (PA). The major insecticide-intensive land use systems in transmission areas were situated in the north of the province and along river valleys (Appendix 9).

The total area of fruit cultivation in transmission areas in the province was about 80,400 ha. The largest continuous area of insecticide-intensive agriculture in transmission areas was in the northern districts of Fang, Chai Prakan, and Mae Ai where 25, 16, and 20 percent, respectively, of their district areas were devoted to fruit cultivation. Another district with a concentrated fruit growing area was Wiang Haeng district, which is situated very close to the Myanmar border, where malaria is known to be a serious problem. In the southern part of the province fruit cultivation was limited.

TABLE 8.

Area and cover (% of district) of insecticide-intensive land uses in malaria transmission areas in Chiang Mai province (horizontal divisions show northern, southern, and central districts from top to bottom). Only districts in which insecticide-intensive land use overlaps with malaria transmission areas are displayed. Figures are rounded.

District	Fruit orchard		Vegetables		Floriculture		Legumes		Paddy rice		Sum	
	ha	%	ha	%	ha	%	ha	%	ha	%	ha	%
Fang	20,391	25	0	0	0	0	0	0	7,319	9	27,709	33
Chai Prakan	10,072	20	0	0	0	0	0	0	1,877	4	11,950	24
Mae Ai	11,965	16	0	0	0	0	0	0	7,705	10	19,670	26
Chiang Dao	7,894	4	0	0	0	0	0	0	5,254	2	13,148	6
Wiang Haeng	1,411	2	0	0	0	0	0	0	2,116	3	3,527	5
Chom Thong	7,330	7	1,187	1	0	0	0	0	2,523	2	11,041	10
Doi Tao	2,770	3	84	<1	0	0	3,428	4	1,098	1	7,380	8
Hot	2,479	2	2,447	2	0	0	0	0	2,123	1	7,049	5
Mae Chaem	0	0	5,410	2	0	0	104	<1	5,817	2	11,331	3
Omkoï	24	<1	1,838	1	0	0	0	0	4,633	2	6,495	2
Hang Dong	2,155	8	0	0	33	<1	0	0	712	3	2,899	10
Mae Rim	536	1	0	0	319	1	0	0	774	2	1,629	4
Others (9 districts)	13,397	2	570	<1	18	<1	103	<1	16,368	3	30,456	5
Sum	80,424	4	11,536	1	369	<1	3,634	<1	58,319	3	154,283	7

The total area of vegetable production in transmission areas in Chiang Mai was 11,536 ha and was quite scattered throughout the province. Vegetable crops were mainly grown in the southwest of the province in Mae Chaem, Hot, Chom Thong, and Omkoi districts (table 8). Malaria was also transmitted in these districts.

There were only small areas devoted to flower cultivation in the province. Floriculture was situated close to Chiang Mai city in Mae Rim and Hang Dong districts, where malaria was not transmitted.

Most of the legumes grown in Chiang Mai transmission areas were found in Doi Tao district in the southeast of the province and covered about 4 percent of the district. Some malaria was also reported from Doi Tao district. The total area of paddy rice in malaria transmission areas in Chiang Mai was 58,319 ha. Paddy rice was scattered throughout the province and there was no clear clustering, apart from in the three northern-most districts. Most of the paddy areas were situated along rivers and streams in the central valleys.

Mae Hong Son

Malaria transmission was perennial throughout most of the province (Appendix 6). Eight sub-

districts predominantly situated in the east of the province were categorized as periodic transmission.

Insecticide-intensive agriculture in transmission areas was represented in all seven districts of the province and the total area was 44,367 ha (3.5% of the provincial area) (table 9). Thus, these land uses were small and scattered and mainly situated along the major river valleys in the province (Appendix 10).

There were just a few areas with fruit cropping in Mae Hong Son province and floriculture did not exist at all. Most of the vegetable cropping areas were scattered throughout Mae La Noi and Mae Sariang districts in the southern part of the province. Legumes were grown in small plots throughout the province, mainly as swidden agriculture in upland areas. Paddy fields were found along the central valleys.

Tak

In most of the western part of the province, along the border areas to Myanmar, malaria was perennial with periodic transmission occurring in some sub-districts (Appendix 7). The eastern part of the province was mainly categorized as risk transmission areas, with only a few areas of periodic transmission.

TABLE 9.

Area and cover (% of district) of insecticide-intensive land uses in malaria transmission areas in Mae Hong Son province (districts ordered from north to south). All districts in the province are displayed. Figures are rounded.

District	Fruit orchard		Vegetables		Legumes		Paddy rice		Sum	
	ha	%	ha	%	ha	%	ha	%	ha	%
Pai	132	<1	0	0	0	0	5,851	3	5,983	3
Pang Mapha	0	0	0	0	210	<1	1,204	1	1,414	2
Mueang Mae Hong Son	0	0	0	0	293	<1	4,928	2	5,221	2
Khun Yuam	0	0	8	<1	751	<1	3,852	2	4,611	3
Mae Sariang	0	0	3,703	3	4,746	3	3,718	3	12,167	9
Mae La Noi	56	<1	1,759	1	3,728	1	6,105	2	11,648	4
Sop Moei	22	<1	0	0	1,028	1	2,271	2	3,321	2
Sum	210	<1	5,470	2	10,757	5	27,930	2	44,367	3

The total area of insecticide-intensive agriculture in malaria transmission areas in Tak was 50,447 ha (about 3% of the provincial area) (table 10). Out of a total of eight districts, six had overlapping insecticide-intensive agriculture and malaria transmission. Sam Ngao and Ban Tak, two districts in the northeast of the province, were not included in the analysis due to the malaria stratification criteria (i.e., classified as PA).

There were two major areas of insecticide-intensive land uses in transmission areas in the western and eastern parts of Tak province (Appendix 11), which mainly consisted of paddy rice. Otherwise, the areas were small and scattered along river valleys, as in Mae Hong Son.

There were few fruit and vegetable growing areas. Phop Phra district in the south of the province had a few fruit cultivation areas. The largest areas of vegetables were found in Phop Phra and Umphang districts also in the south of the province. A few vegetable growing areas were also found in Mae Ramat district in central Tak.

Legume cultivation was almost nonexistent. There were extensive areas of paddy fields in the transmission areas. These were mainly located in the western parts of Mae Sot and Mae Ramat districts in central western Tak. A large paddy rice growing area with periodic malaria transmission was located in Mueang Tak district in the eastern part of the province.

Kanchanaburi

Malaria was perennial in a large area in the northern and western parts of the province (Appendix 8). Immediately to the south and east there were periodic transmission areas. In the five eastern districts of the province there was no malaria transmission (PA).

The total area of insecticide-intensive agriculture in transmission areas in Kanchanaburi was 18,467 ha (< 1% of the provincial area) (table 11). Out of a total of 13 districts, insecticide-intensive agriculture and malaria transmission overlapped in eight districts.

Insecticide-intensive cropping systems were most common in the eastern populated area of the province and along the river valleys (Appendix 12). Of the insecticide-intensive land uses there were only fruit orchards, vegetables and paddy rice grown in the transmission areas.

Many fruit orchards were scattered along the Mae Nam Khwae Noi River in Thong Pha Phoom, Sai Yok, and Mueang Kanchanaburi districts. Other clusters of fruit orchards were situated in the eastern part of Sri Sawat district and in Nong Preu district.

There was a rather large clustered area of vegetables grown in the transmission area of Sri Sawat district in central Kanchanaburi. Other vegetable areas were small and scattered and found in Sai Yok and Dan Makham Tia districts in the southwestern part of the province.

TABLE 10.

Area and cover (% of district) of insecticide-intensive land uses in malaria transmission areas in Tak province (districts ordered from north to south; Mueang Tak district is in eastern Tak). Only districts in which insecticide-intensive land use overlaps with malaria transmission areas are displayed. Figures are rounded.

District	Fruit orchard		Vegetables		Legumes		Paddy rice		Sum	
	ha	%	ha	%	ha	%	ha	%	ha	%
Tha Song Yang	0	0	0	0	0	0	3,244	2	3,244	2
Mae Ramat	0	0	242	<1	0	0	6,212	4	6,454	4
Mae Sot	405	<1	17	<1	0	0	15,580	9	16,002	9
Phop Phra	1,031	1	1,489	2	0	0	2,332	2	4,853	5
Umphang	70	<1	645	<1	41	<1	2,446	<1	3,202	1
Mueang Tak	141	<1	0	0	0	0	16,551	6	16,693	6
Sum	1,648	<1	2,393	<1	41	<1	46,366	3	50,447	3

TABLE 11.

Area and cover (% of district) of insecticide-intensive land uses in malaria transmission areas in Kanchanaburi province (horizontal division show western and eastern districts ordered from north to south). Only districts in which insecticide-intensive land use overlaps with malaria transmission areas are displayed. Figures are rounded.

District	Fruit orchard		Vegetables		Paddy rice		Sum	
	ha	%	ha	%	ha	%	ha	%
Sangkhla Buri	11	<1	0	0	254	<1	265	<1
Thong Pha Phoom	1,375	<1	0	0	835	<1	2,210	<1
Sai Yok	4,073	<1	106	<1	0	0	4,179	<1
Mueang Kanchanaburi	2,535	<1	0	0	1,188	<1	3,722	<1
Dan Makham Tia	355	<1	258	<1	545	<1	1,159	<1
Sri Sawat	613	<1	762	<1	0	0	1,375	<1
Nong Preu	336	<1	0	0	684	<1	1,020	<1
Bo Phloi	99	<1	0	0	4,439	<1	4,538	<1
Sum	9,397	<1	1,126	<1	7,944	<1	18,467	<1

The largest single paddy rice growing area in the perennial transmission areas was located in Thong Pha Phoom district. Some smaller paddy rice growing areas were also found in Sangkhla Buri district. A comparably large

proportion of Bo Phloi district was devoted to paddy rice. In this district malaria was periodically transmitted. Few areas along the Mae Nam Khwae Noi River in Sai Yok district were cultivated with rice.

Discussion

Potential risk areas for insecticide resistance development in malaria mosquitoes resulting from chemical crop protection activities in agriculture were identified in four provinces in northern and western Thailand. There were small and scattered areas where such resistance might develop, apart from some larger, relatively contiguous, areas in northern Chiang Mai province. It is likely that there is a potential higher risk of vector control failure in the identified risk areas due to the development of insecticide resistance in malaria mosquitoes. Despite the relatively small and scattered risk areas identified in this study, current agricultural pest control may become a threat to malaria vector control in Thailand and neighboring countries, particularly considering the present expansion and intensification of agriculture in the region.

It has been shown that use of insecticides in agricultural crop protection indeed affects resistance development in disease vectors (e.g., Brogdon et al. 1988; Hemingway et al. 1986; Diabate et al. 2002). Overgaard et al. (2005) demonstrated that the use of methyl parathion (an organophosphate) in a tangerine orchard in northern Chiang Dao district in Chiang Mai province resulted in higher resistance in *An. maculatus* s. s. compared to specimens collected in an area with few fruit orchards and insignificant insecticide use. This resistance was most likely caused by agricultural insecticides because organophosphates have never been used for malaria control in the area. The study location of Overgaard et al. (2005) corresponded with the risk areas identified in the present study. As can be seen in Appendix 9, only a few small and

scattered fruit cultivation areas were identified in northern Chiang Dao district in Chiang Mai province. This indicates that large and continuous areas of insecticide-intensive agriculture are not a prerequisite for resistance to develop in mosquitoes. Overgaard et al. (2005) concluded that in areas of predominantly organophosphate agricultural pest control, cross-resistance between organophosphates (mainly used to control agricultural pests) and pyrethroids (used to control both vectors and agricultural pests) may pose a potential threat to future vector control. Furthermore, it was concluded that – although malaria mosquitoes in Thailand still seem to be susceptible to pyrethroids (Somboon et al. 2003) – vector control may be compromised through intensive and increased use of pyrethroids in agriculture, due to the evident mosquito-insecticide contact in this environment and the ensuing increased risk of insecticide resistance development.

It is not likely, however, that insecticide resistance may spread from one area to another through dispersal of resistant mosquitoes. Although, definite knowledge is still lacking of how far Southeast Asian malaria mosquitoes can fly, a few studies indicate that the flight range is generally limited to approximately 2 kilometers (km) (Rosenberg 1982; Rao 1984; Tsuda et al. 1999). A limited flight range together with the topography and geography of malaria endemic areas in Thailand probably precludes long-range mosquito migration. Furthermore, a potential fitness cost associated with insecticide resistance might give rise to resistant specimens that are less fit for dispersal (Berticat et al. 2004; Bourguet et al. 2004). The ‘spread’ of insecticide resistance is therefore most likely if there is a substantial expansion and intensification of agriculture with associated pesticide inputs, exposing mosquito populations to high selection pressures. Another possibility is the migration of resistant mosquito strains (alleles) to areas with susceptible populations (gene flow) with or without the help of human infrastructure. There are indications that agriculture expands and intensifies as a result of a general improved national economy (Jungbluth 1996). Insecticide-

intensive cropping systems, like fruit and vegetables, are likely to expand into endemic transmission areas, as they already have during the last decades (Jungbluth 1996). Therefore, insecticide resistance in mosquitoes due to agricultural insecticides is a potentially increasing problem in Thailand, as well as in fast developing neighboring countries, such as Vietnam, Laos, and Cambodia.

Insecticides used in both agricultural pest and vector control bring about a double threat for high insecticide resistance selection pressure in disease vectors. The problem is particularly serious in areas where insecticides used for crop protection are similar and have the same mode of action as those used for vector control, e.g., in the case of pyrethroids (see examples of possible combinations in table 1). In such areas, regular monitoring of insecticide resistance and resistance management is very important. Cooperation between the agriculture and health sectors is necessary to initiate integrated pest and vector management and pesticide management interventions. These issues are discussed below.

The study determined that fruit and vegetable cropping systems were the most insecticide-intensive land uses. Paddy rice and legumes constituted medium insecticide-intensive land uses. Flower production was probably also quite insecticide-intensive, but only limited areas were devoted to floriculture.

The largest clustered area of insecticide-intensive cropping systems in malaria transmission areas were located in the three most northern districts in Chiang Mai province where extensive fruit orchards have been planted with various types of fruit, mainly citrus, such as tangerine (*Citrus reticulata* Blanco; som kiaw waan in Thai). Some districts in this region had up to 25 percent of their area covered with fruit crops. The present study showed small district percentages of fruit cultivation in Mae Hong Son, Tak, and Kanchanaburi provinces; however, fruit cultivation was quite common along the Mae Nam Khwae Noi River in Kanchanaburi province. The intense use of pesticides in tangerine orchards in Chiang Mai province and its negative health

effects on farmers and local people have been covered several times by the media (e.g., Bangkok Post, September 7, 2003). It is interesting to observe that fruit orchards are often situated close to forest fringe areas (Sithiprasasna et al. 2005), which are typical habitats for the primary malaria vectors. The most common land use change in the forested foothill areas of northern Thailand is the establishment of fruit orchards (C. Walton, project coordinator of EU-funded RISKMODEL project [2001-2005], University of Manchester, UK, personal communication 2005). Moreover, in the uplands of northern Thailand, traditional subsistence farming is often converted to high-input cash cropping systems (Rerkasem and Rerkasem 1994), leading to high land use conversion and potential high pesticide use.

Vegetable cultivation in transmission areas was mainly found in a few districts in the southern parts of Chiang Mai, Mae Hong Son, and Tak provinces. Although vegetables only covered about 1-3 percent of the district areas, vegetable crops are known for their heavy reliance on pesticides. Several IPM programs have therefore been carried out in vegetable cropping systems (DANIDA 2005; FAO 2005). Legumes were mainly found in Doi Tao district (4% of the district area) in Chiang Mai province and Mae Sariang district (3%) in Mae Hong Son province. Paddy rice is a typical crop in this region. It was present in this study in all four provinces. The largest paddy rice areas were found in Mae Ai (10%) and Fang (9%) districts in Chiang Mai province and Mae Sot district (9%) in Tak province.

Considering the presence of malaria vectors and insecticide-intensive cropping systems in these provinces, some areas are of interest for resistance management and integrated pest and vector management interventions. The following districts and areas are recommended for possible introduction of intervention programs: Mae Ai, Fang, Chai Prakan, Chiang Dao, and Wiang Haeng in Chiang Mai province; and several areas along the Mae Nam Khwae Noi River in Sai Yok district in Kanchanaburi province. The main insecticide-intensive crops in these districts were

fruit orchards and paddy fields. The vegetable growing areas in Mae Chaem and Hot districts in Chiang Mai province, Mae Sariang district in Mae Hong Son province, and Phop Phra district in Tak province could also benefit from intervention programs. The combination of consistently high malaria transmission rates in Mae Sot district, Tak province (Malaria Division 1993) and concomitant large areas of relatively insecticide-intensive rice cultivation also justifies implementation of intervention programs in this district.

The type of intervention program could vary, but should include regular resistance surveillance followed by resistance management in areas where it is considered necessary. Resistance surveillance and management should preferably be undertaken within some form of pesticide management strategy, such as Integrated Pest Management (IPM), Integrated Vector Management (IVM), or in a combination (IPVM). In both plant protection and vector control, effective and sustainable resistance management strategies (such as Insecticide Resistance Management (IRM), see chapter Insecticide Resistance Management, p. 9) should use alternations, sequences, or rotations of compounds with different modes of action. Other integrated strategies should also be considered, such as biological insecticides, beneficial insects, pest resistant crop varieties, chemical attractants or deterrents; and varying cultivation practices and rotating crops. Coordination of chemical control efforts between the public health and agricultural sectors is important to avoid or minimize double insecticide exposure to insect vectors. The agricultural economic threshold model or the Agro-Ecological Systems Analysis (AESAs) methodology discussed earlier (chapter Insecticide Resistance Management, p. 9) could be adapted for vector control purposes by evaluating the risks and socio-economic costs of vector-borne diseases.

A large scale field trial was established in Mexico in 1997 to test and compare different resistance management strategies for malaria vector control with the aim to find the most suitable and effective strategy (Hemingway 2002). The following strategies were tested: single use

of one compound (DDT or pyrethroids); rotational (i.e., temporal) alternation of unrelated insecticides (organophosphates – pyrethroids – carbamates); and mosaics, where adjacent areas were treated simultaneously with different insecticides (organophosphates and pyrethroids). The results showed that pyrethroid resistance was significantly lower in the rotation and mosaic areas compared to areas with single continuous use of pyrethroids. It was concluded that single use of insecticides shortened the effective lifespan of the insecticide, whereas the rotational and mosaic strategies expanded the lifespan of insecticides (A. D. Rodríguez, CIP, National Institute for Public Health, Tapachula, Mexico, personal communication 2003). It was noted that agricultural insecticides may play an important role in the success or failure of a resistance management program. Another study investigated the potential for developing resistance management strategies for mosquitoes resistant to the microbial control agent *Bacillus sphaericus* (Bsph) (Zahiri et al. 2002). The aim of the study was to reverse Bsph resistance in *Culex quinquefasciatus* by using *Bacillus thuringiensis israelensis* (Bti) alone, Bti and Bsph in rotation or in mixture. Partial restoration of susceptibility to Bsph was achieved with Bti alone and a rapid decline in resistance was observed by using Bti and Bsph in rotation or in mixture. All three combinations were promising for use in resistance management strategies for this vector.

The IPM Farmer Field Schools (FFS) approach has been implemented in many countries in Southeast Asia, e.g., through various national IPM programs and the FAO Program for Community IPM in Asia. Farmer Field Schools focus on participatory non-formal education of farmers through field observation and experimentation (Pontius et al. 2002). Reduced pesticide use is often a clear effect of increased farmer expertise attained through FFS training (e.g., van den Berg et al. 2003). Reduced pesticide use is beneficial not only for reducing the negative health effects of farmers and the environment, but may also reduce the selection pressure for insecticide resistance in both agricultural pests and vectors. However, few

studies, if any, have investigated differences in vector resistance in IPM areas and non-IPM areas. This probably relates to the difficulty in finding large areas with only IPM.

Another tool, which has been used in combination with the FFS is the Environmental Impact Quotient (EIQ). The EIQ is an indicator model for pesticide risk assessment and was designed by IPM specialists for farmers in the United States to choose low impact control options (Kovach et al. 1992). In Southeast Asia the applicability of the model has been tested in Vietnam by analyzing farmers' pesticide management practices. The EIQ model proved easy to use by Vietnamese farmers to judge the risk of their crop protection methods and to assess and reduce pesticide loads on pesticide users, consumers, and the environment (Eklo and Dung 2004). The Vietnamese results also showed significantly lower pesticide load in IPM plots compared with non-IPM plots. If properly implemented the EIQ model could help relieve resistance selection pressures in disease vectors.

Combining IPM and IVM requires intersectoral collaboration. Attempts to combine the control of agricultural pests and disease vectors are not widely found, despite the apparent problem of resistance development. Today, there is basically no collaboration between the public health sector and the agricultural or environmental sectors. One exception is an on-going pilot project to assess the feasibility of integrating disease vector management into community-based IPM training initiated in Sri Lanka in 2002 by FAO and UNEP (van den Berg 2004a). The objective of the project was to develop a participatory approach to Integrated Vector Management (IVM) to reduce reliance on chemical methods of control. This is one of few attempts in trying to integrate efforts to manage both agricultural pests and disease vectors. The project is unique in the sense that it uses the established IPM Farmer Field Schools (FFS) as an instrument for transmitting knowledge to farmers about the ecology of disease vectors and how to improve management of mosquito populations. The project showed that farmers benefited from increased knowledge of mosquito vectors and vector control. The approach still

needs to be tested on a large scale to study the effects on reduced vector-borne disease incidence and to investigate long-term compliance of farmer involvement in vector control.

The use of FFS to support inclusion of vector control components in the farmer training sessions was also encouraged by the participants at a WHO/UNEP workshop held in Bangkok in May 2004 (UNEP/WHO 2004) and is also endorsed by WHO in the global strategic framework on IVM (WHO 2004).

Through restriction and control of insecticides it might be possible to easier determine the intensity and type of insecticide used in particular cropping systems. However, restrictions may increase illegal and unmonitored use of insecticides and it is therefore essential that enforcement of regulations are supported and promoted. Alternative practices and tools, such as IPM Farmer Field Schools and the Environmental Impact Quotient (EIQ) can be used to better understand farmers' pest management strategies. Acquiring the trust, interest, and collaboration of farmers is essential in implementing IPM programs to reduce and control pesticide use and the risk of insecticide resistance development in both agricultural pests and disease vectors.

The effect of agricultural insecticides on vectors of other diseases is also an important aspect to consider. Although, *Aedes aegypti*, the primary vector of dengue, is predominantly urban, breeding in man-made containers and apparently not coming into contact with agricultural insecticides, the use of insecticides in urban agricultural areas could affect resistance development also in this species. *Aedes albopictus*, a dengue vector that is becoming increasingly more important, probably serves as a maintenance vector of dengue in rural areas of Southeast Asia (Gratz 2004). Since *Ae. albopictus* is associated with rural areas it is more likely to be exposed to rural agricultural insecticides than *Ae. aegypti*. A recent project undertaken in northern Thailand showed that dengue vectors breed in containers left in fruit orchards and that proximity to fruit orchards

increased the risk of dengue infection in a periurban site (Vanwambeke et al. 2006). Contrary to this, van Bentheim et al. (2005) did not find an increased risk of dengue infection associated with fruit orchards. The transmission dynamics of dengue are evidently complicated and risk factors seem to vary between urban and rural sites (van Bentheim et al. 2005). A recent study investigated susceptibility to permethrin, temephos, and malathion in *Ae. aegypti* and *Ae. albopictus* larvae collected from several areas in Thailand (Ponlawat et al. 2005). The study showed that *Ae. aegypti* was resistant to permethrin from all study sites and to temephos from several sites. *Ae. albopictus* had low levels of resistance to all tested insecticides, but was clearly resistant to permethrin in two of the study sites. The tested insecticides are actively used in dengue vector control, but the authors emphasized that the observed resistance could also have been affected by agricultural insecticides, particularly for *Ae. albopictus*. Dengue vectors should therefore be included in regular surveillance programs of insecticide resistance in risk areas. Dengue vector control consists of chemical control of larvae and adults and community prevention programs to eliminate breeding sites.

Culex tritaeniorhynchus and other *Culex* mosquitoes are vectors of Japanese encephalitis and breed in paddy rice fields and in pools close to rice fields and are thus directly in contact with insecticides used to protect rice plants. Vectors of lymphatic filariasis, such as *Mansonia* species and *Culex quinquefasciatus* (also a vector of Japanese encephalitis), could also be exposed to agricultural insecticides. Other arthropods associated with disease, such as blackflies, sandflies, and ticks, and their relation to agricultural pesticides and resistance development should also be examined.

An interesting phenomenon that needs further enlightenment is the effect of avoidance behavior to insecticides. Avoidance behavior in insects has been reviewed for both disease vectors and agricultural insects (Muirhead-Thomson 1960; Georgioui 1972; Lockwood et al. 1984; Pluthero

and Singh 1984; Sparks et al. 1989; Roberts and Andre 1994; Hoy et al. 1998). Behavioral responses to insecticides have been documented in more than 100 cases (Hoy et al. 1998), but there is still a gap in knowledge as to how avoidance behavior, physiological resistance, genetic variation, and spatial distribution of toxins interact. Further research on these issues could improve the understanding of these relationships and improve integrated vector and pest control approaches.

Below follows a few recommendations for continued actions, studies and research in the field of resistance in disease vectors:

- Continued insecticide resistance surveillance and monitoring, particularly in identified risk areas, including studies on modes of action in disease vectors in general.
- Prospective studies in the identified target areas of this study and other similar studies to confirm the roles of agricultural insecticides in insecticide resistance development in disease vectors and to identify particular crop-insecticide-vector combinations where vector resistance is most likely to develop.
- Mapping risk areas in other countries in the region.
- Development of alternative integrated approaches to combined agricultural pest and vector control (e.g., IPVM), which should also aim at reducing the negative effects of hazardous chemicals on the environment and public health in general. Such studies should include recommendations for specific control options in different crop-vector situations.
- More research is needed to understand the dynamics of mosquito-insecticide contact. How do insecticide application mechanisms affect mosquito behavior? Do agricultural insecticides affect behavioral responses in disease vectors?

- A better understanding is needed on issues related to resting behavior, local breeding site selection, mosquito associations with specific cropping systems, the mechanics and genetics of excito-repellency, and the effects of insecticide run-off and drift on resistance development.

Limitations

In this section, limitations to the analysis and the effect on the results are discussed and improvements suggested. The limitations have been grouped into three categories: (a) Agricultural insecticides and land use classification; (b) Malaria stratification and vector distribution; and (c) Mosquito-insecticide contact.

(a) Agricultural insecticides and land use classification

The main problem encountered in the study was the difficulty to find reliable and detailed information on the extent and intensity of specific insecticides used in different cropping systems. As mentioned in the introduction, estimating insecticide use in agriculture is complicated because of the many factors that are involved. The amounts and types of insecticides used in agriculture depends on pest presence, pest susceptibility to insecticides, crop type, crop damage, crop stage, weather, season, insecticide availability, farmers' socio-economic status and personal preferences, pesticide policy issues, etc. The straightforwardness to assess agricultural insecticide use is likely to vary from region to region and from country to country.

Initiatives to reduce farmers' reliance on pesticides (e.g., IPM) and increased pesticide restrictions and control may improve estimates of the amount and types of pesticides used in particular cropping systems, as well as to reduce the risk of insecticide resistance. Data on pesticide use is an important parameter for assessing the

impact of Farmer Field School programs and is regularly collected in IPM Farmer Field School impact evaluations (van den Berg 2004b). Impact evaluations are important to assess the effect of an intervention, but also to acquire information on crop-specific insecticide use.

The classification of land uses in the present study might not represent the true situation, because farmers' cropping patterns change from year to year, although on average this might not be a problem. The land use classification in this study was simplified into 18 classes and it was not feasible, nor desirable, to distinguish any further details than this. A more detailed study in a defined region or area should identify land uses through up-to-date high resolution satellite images or aerial photos, supplemented by detailed ground truthing. Comprehensive investigations of current pesticide use in selected cropping systems would improve the end result. In the current attempt to predict insecticide resistance in mosquitoes from exposure to agricultural insecticides, it was not possible to measure the actual use of insecticides in the land uses present, partly because of lack of resources but also because of the difficulty to acquire up-to-date and precise information on the spatial extent of cropping patterns and the amount of active ingredients used in each crop. Further, the estimated use of insecticides in specific crops was assumed to be equal for the whole area, based on the information from the three available sources on insecticide use in Thailand (i.e., Jungbluth 1996; UNESCAP 2000; Thapinta and Hudak 2003). This might not necessarily be true since, as mentioned earlier, insecticide use varies between farmers, fields, crops, areas, regions, etc.

(b) Malaria stratification and vector distribution

Malaria stratification may seem as an indirect estimate of vector distribution, because it mainly relies on information on the geographical distribution of malaria cases or malaria endemicity. A problem with this is that malaria endemicity is a function of case detection and diagnosis, treatment, preventive measures, and climatic factors. Thus, there might be mosquito

vectors in areas without malaria cases being reported; i.e., the absence of the parasite does not exclude the development of resistance in the mosquito. A stronger risk factor would be true distribution of vector species or vector density. However, in Thailand vector distribution maps only show presence of vector species on a provincial level (Malaria Division 1993). Such maps would be too rough for the purpose of this study. Nevertheless, an assessment of vector presence is made by Ministry of Public Health personnel in the process of malaria area stratification. Consequently, the malaria stratification areas do not only indicate where malaria is transmitted, but also where malaria vectors are present. Thus, the primary vectors are present in transmission areas (A1 and A2) and in high-risk non-transmission areas (B1) and suspected vectors are present in low-risk non-transmission areas (B2). Malaria vectors outside transmission areas may definitely be subjected to resistance selection pressure through exposure to agricultural insecticides. However, adverse effects of insecticide resistance on malaria control in non-transmission areas are considered a lesser problem since transmission has not been reported in these areas for at least three consecutive years. To conclude, it is not possible to find more exact information about the geographical distribution of malaria vectors in Thailand than the data on presence/absence of mosquitoes found in the governmental malaria stratification records.

This study focused only on perennial and periodic transmission areas (A1 and A2). As mentioned, these areas were selected to highlight the potential danger of increased insecticide resistance and potential reduced effects of vector control efforts in malaria transmission areas. However, in some cases perennial malaria (A1), periodic malaria (A2), high-risk area (B1) and low-risk area (B2) were present in the same sub-district. In such cases the whole sub-district was considered as A1. Since the smallest spatial unit was the sub-district (having identifiable borders) and the stratified sub-districts sometimes consisted of several classes, it was not possible to keep such small-scale variations. If more

detailed studies are required GIS tools, such as Thiessen polygons, should be used. Thiessen polygons define the potential area influenced by a condition in a set of points, in this case, villages with available malaria transmission data. The size of the area for each point (village) is determined by drawing polygon borders at mid-distance between the points.

Furthermore, the malaria stratification classification changes from year to year, potentially causing temporal inconsistencies. However, in this study it was not considered an important problem, because primary malaria vectors are present in all areas, except in B2, PA, and IA. Thus, B1 will function as a buffer between areas with (A1, A2) and areas without (B2, PA, IA) primary vectors. It is assumed that the stratified areas seldom change directly from an area with primary vectors to an area without primary vectors.

To acquire a more exact measurement of malaria transmission intensity the Entomological Inoculation Rate (EIR) could be used. The EIR is a function of the anopheline density in relation to humans, the average number of persons bitten by one mosquito in a day, and the proportion of mosquitoes with sporozoites in their salivary glands. Mapping malaria transmission areas using EIR requires a lot more effort than the method used in the present study.

Other possibilities to map transmission areas are to identify the geographical distribution of disease vectors or to identify other potential risk areas, based on environmental evidence (irrigated agriculture, forested or deforested areas depending on region, vector species ecological preferences, variations in local settings, climate, etc.) or socio-economical data (areas with high poverty and poor housing, areas of civil unrest, migration, etc.). Knowledge on ecological requirements and behavior of individual vector species, as well as socio-economic information could be used in countries where malaria or malaria vector distribution are not mapped in detail.

(c) Mosquito-insecticide contact

By including in the analysis mechanisms that bring mosquitoes into contact with insecticides, it might be possible to more accurately map risk areas. Such mosquito-insecticide contact may depend on pesticide application mechanisms and insect behavior. However, it would be extremely difficult to assess the effects of insecticide application mechanisms because the application of pesticides varies according to farm size, economy, investment capabilities, etc. A small-scale farmer often uses hand pumps for applying insecticides whereas large-scale farmers may use tractor-mounted spraying equipment (see front cover). The aerial drift of insecticides of these two application types may vary immensely and is also determined by the climatic conditions, such as wind direction, wind speed, and rainfall, during the time of application. Run-off of pesticides into mosquito breeding habitats may also vary greatly. Pesticide run-off depends on the characteristics of the pesticide and local soil conditions.

By including behavior of mosquitoes into the analysis it might be possible to better understand resistance reactions of specific mosquito species to specific pesticides used in specific cropping systems. Mosquito associations with cropping systems was not considered important in this study, because by selecting malaria stratification areas (A1 and A2) where malaria vectors (the focus organisms of this study) are proven to be present and agricultural areas with high pesticide use it was possible to delineate risk areas (and cropping systems) where the selection pressure for resistance is likely to be particularly high. The effects of agricultural insecticides on excito-repellency behavior in mosquitoes are unknown. It is also not clear if a behavioral response is a natural or acquired trait (Roberts and Andre 1994), i.e., a gene coding for increased behavioral resistance has yet to be identified in mosquitoes. More research is needed to clarify these issues.

Conclusion

This study used a simple GIS approach to delineate potential risk areas – target areas – where insecticide resistance in malaria mosquitoes may develop as a result of crop protection activities in agriculture. Target areas are locations where action is deemed necessary for the implementation of insecticide resistance management and surveillance programs or combined integrated pest and vector management strategies. The study was undertaken in four provinces in northern and western Thailand. The methodology presented in this study is universally applicable and can be used in any country that wishes to identify such target areas.

The study identified several areas which could benefit from specific intervention programs. The largest, relatively contiguous, risk areas identified were located in northern Chiang Mai province, where insecticide-intensive fruit cultivation was common in malaria transmission areas.

It is recommended that resistance surveillance should first be focused in areas where malaria transmission and intensive agricultural pest control coincide, because these areas are most likely to develop insecticide resistance in mosquito vectors. Such resistance surveillance should be undertaken by the Offices of Vector-Borne Disease Control, Ministry of Public Health, preferably in collaboration with agricultural authorities. Insecticide Resistance Management (IRM) in combination with Integrated Pest and Vector Management (IPVM) strategies are important to avoid or minimize double insecticide exposure to insect vectors and to reduce risks to human and environmental health. It is recommended that the effect of agricultural insecticides on other disease transmitting insects, such as *Aedes* and *Culex* mosquitoes, should also be investigated.

The limitations of the approach were mainly related to acquiring reliable information on crop specific pesticide use. To overcome such limitations more detailed and up-to-date studies can be undertaken in limited areas where action is considered most necessary and where reliable background information is available. In such areas, and if sufficient funds are available, farmers can be interviewed on their plant protection practices and soil and plant samples analyzed for insecticide residues. Furthermore, more detailed vector studies could be undertaken in these areas.

Another limitation to studies of this kind is that often the only available information on malaria transmission is based on passive case detection records from hospitals and malaria clinics. Such information only provides an indirect estimate of vector distribution. This will result in risk maps that omit all non-transmission areas although such areas might be under strong selection pressures and harbor resistant mosquito populations. These areas might be important because of the potential migration of resistant alleles to areas where mosquitoes are still susceptible. However, information on the number of malaria cases in an area is often the only information available. This should not restrict the development of risk maps as has been shown here, because it is in the transmission areas where insecticide resistance constitutes the most significant threat to vector control.

With a focus on Asia, this report gives a review of insecticide resistance in malaria mosquitoes and the potential effects of agricultural insecticides on mosquito resistance development. The report identifies a number of areas in Thailand, which would benefit from integrated pest and vector management interventions.

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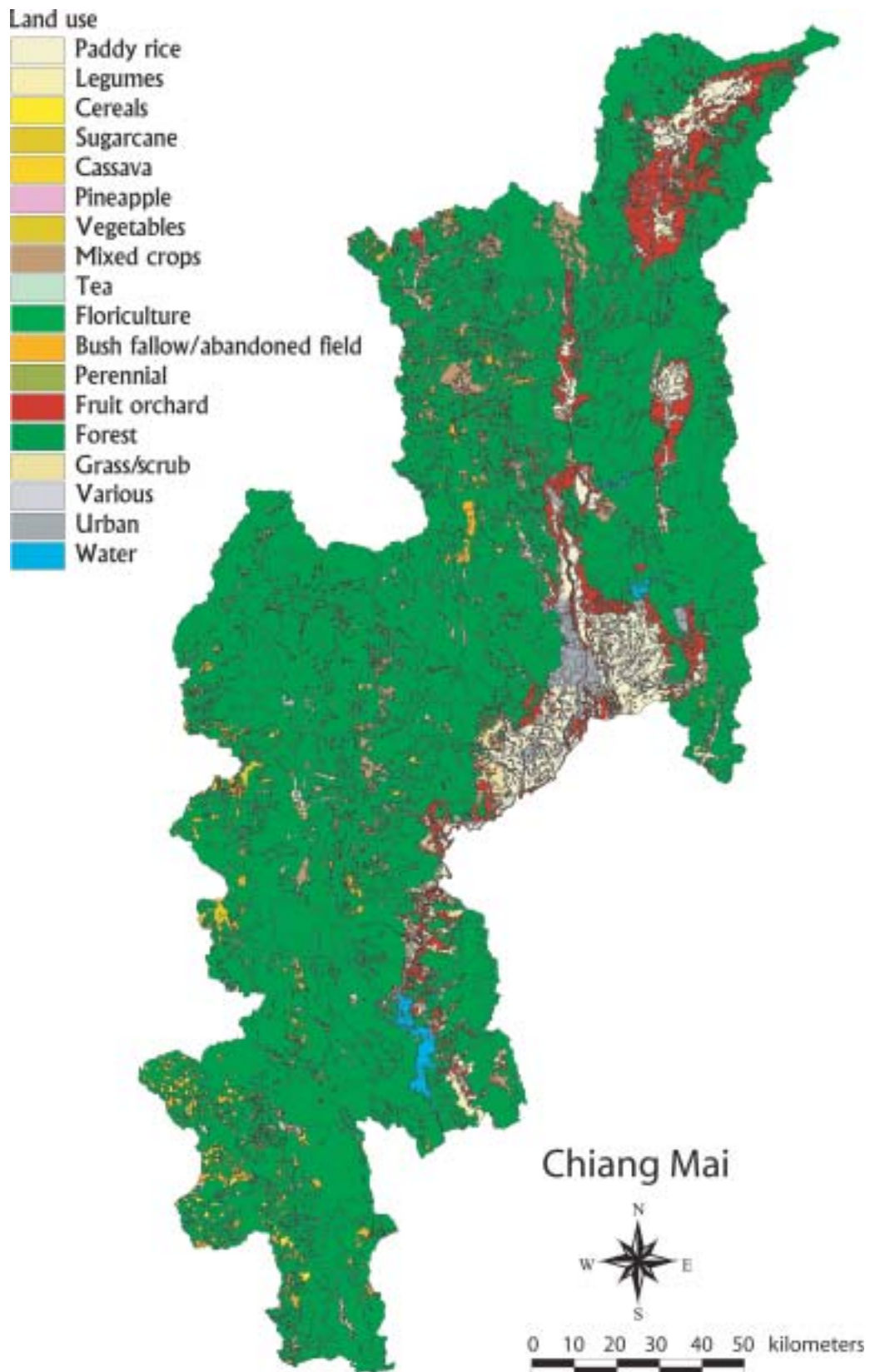
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APPENDICES

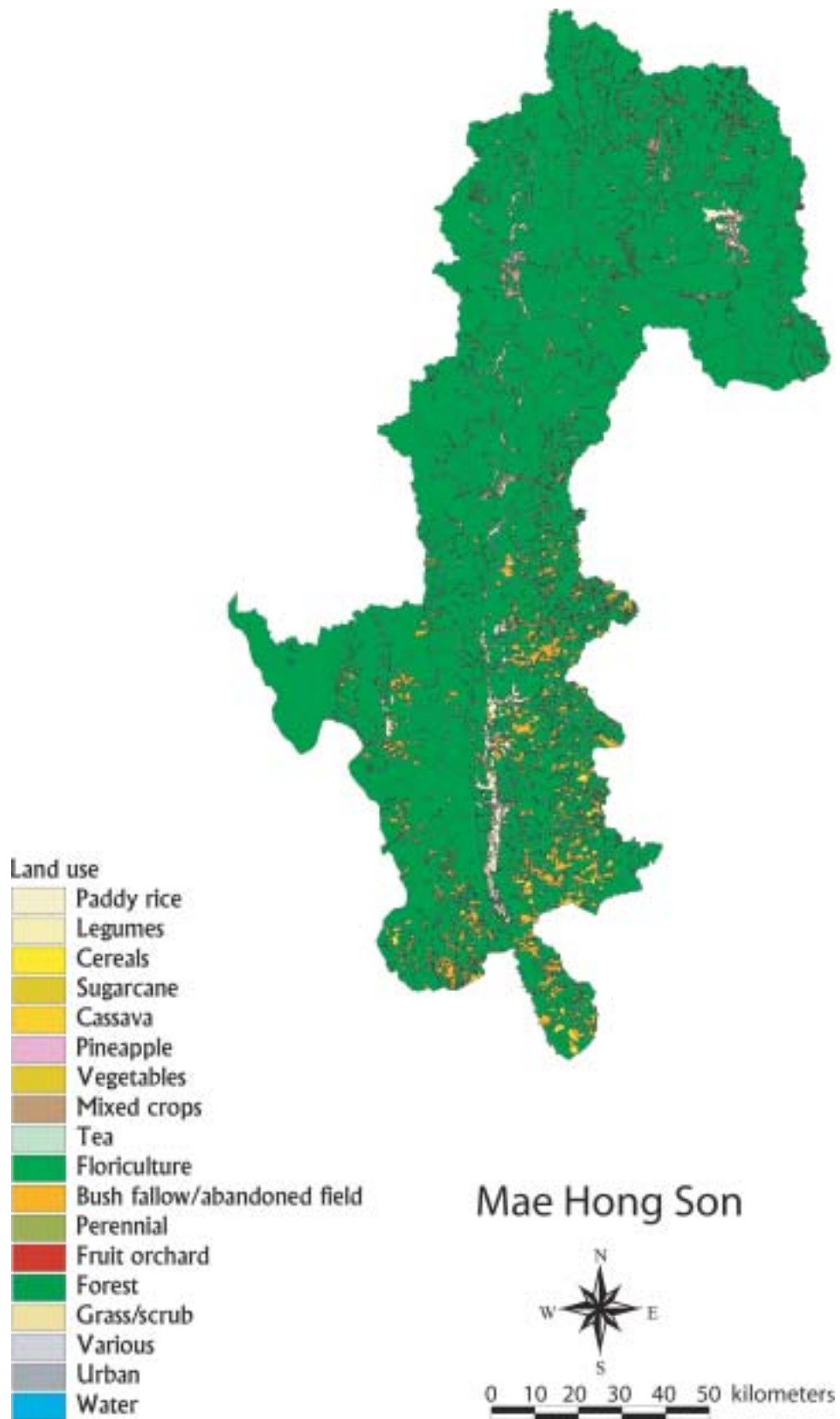
Appendix 1.

Land use in Chiang Mai.



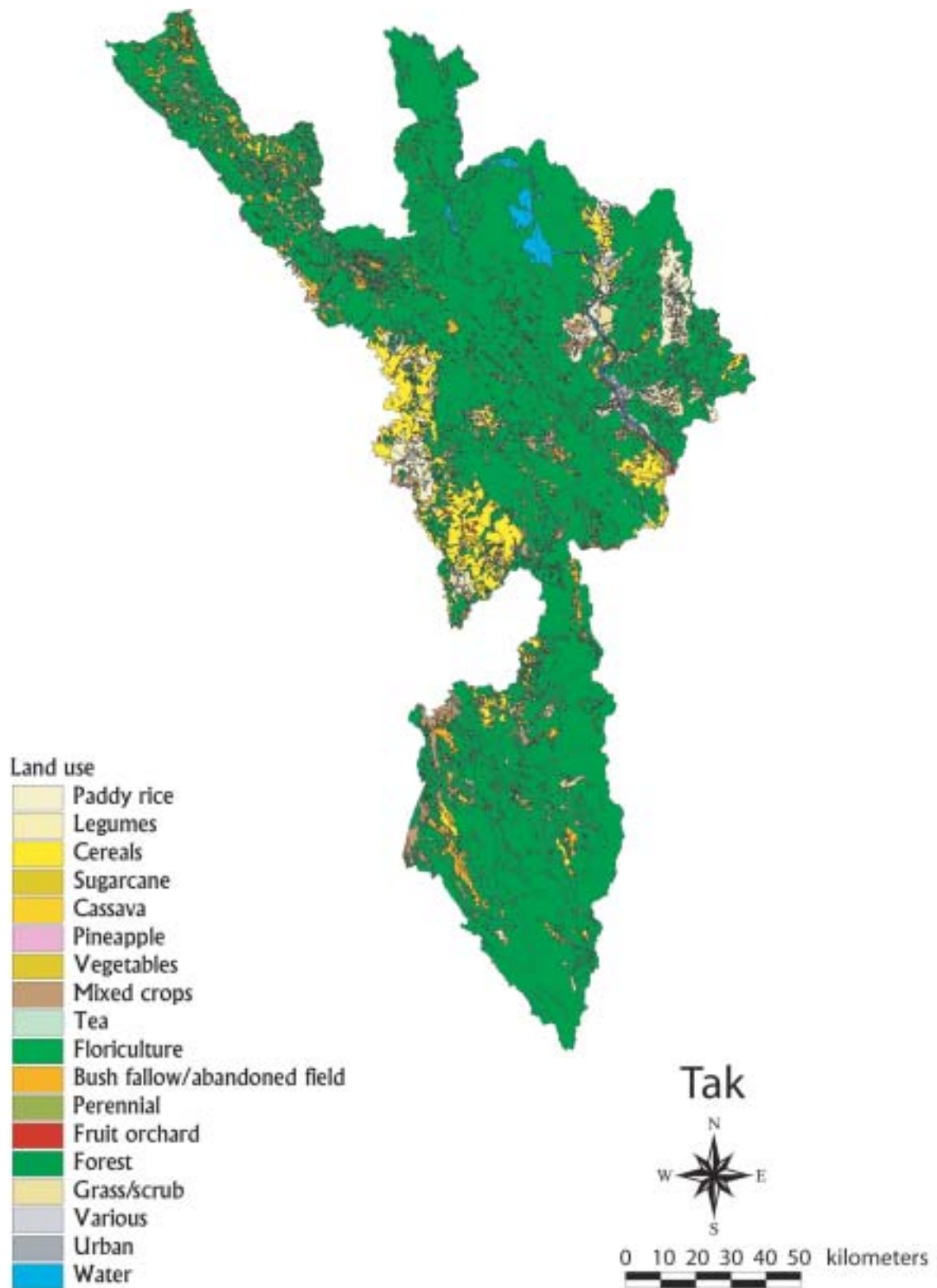
Appendix 2.

Land use in Mae Hong Son.



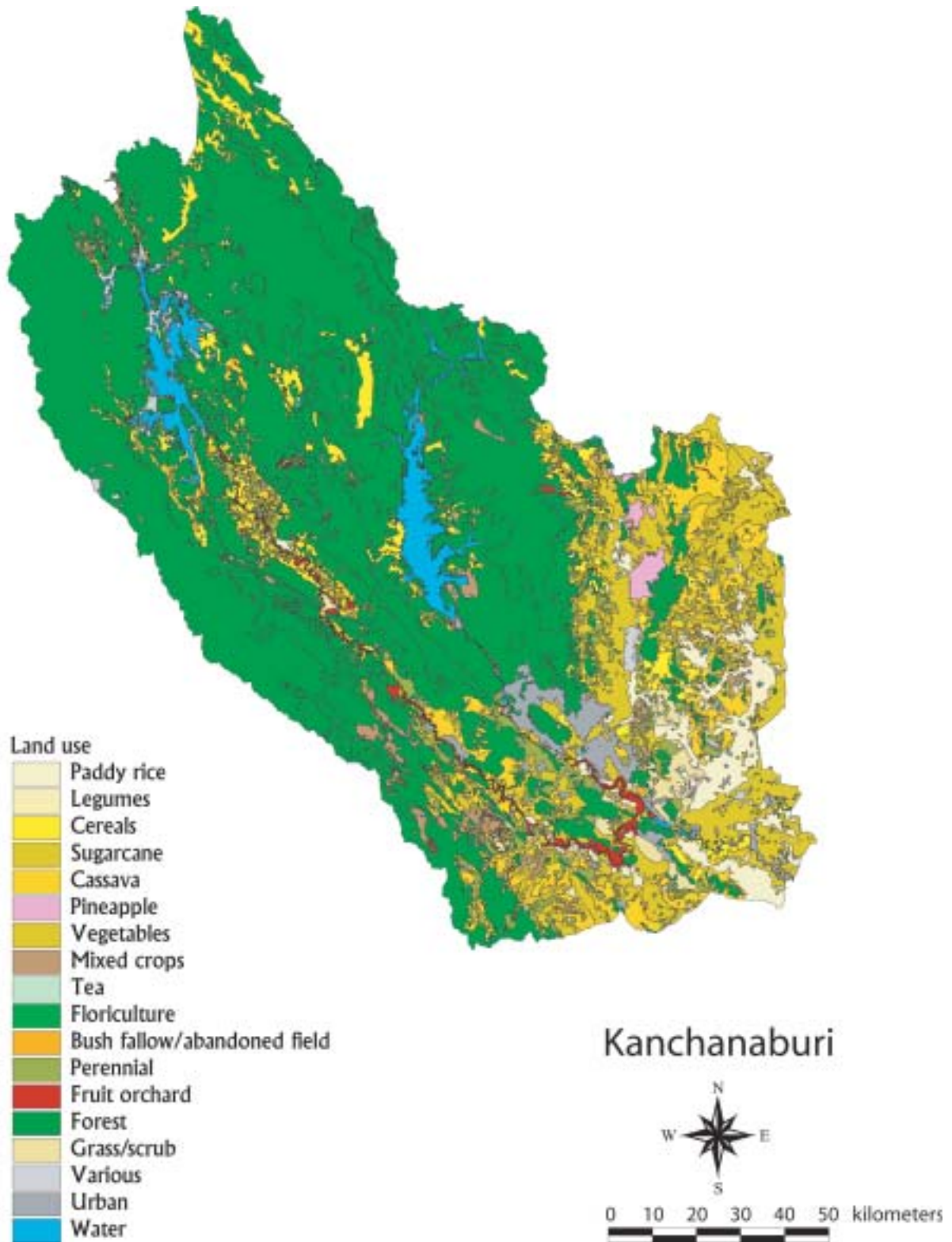
Appendix 3.

Land use in Tak.



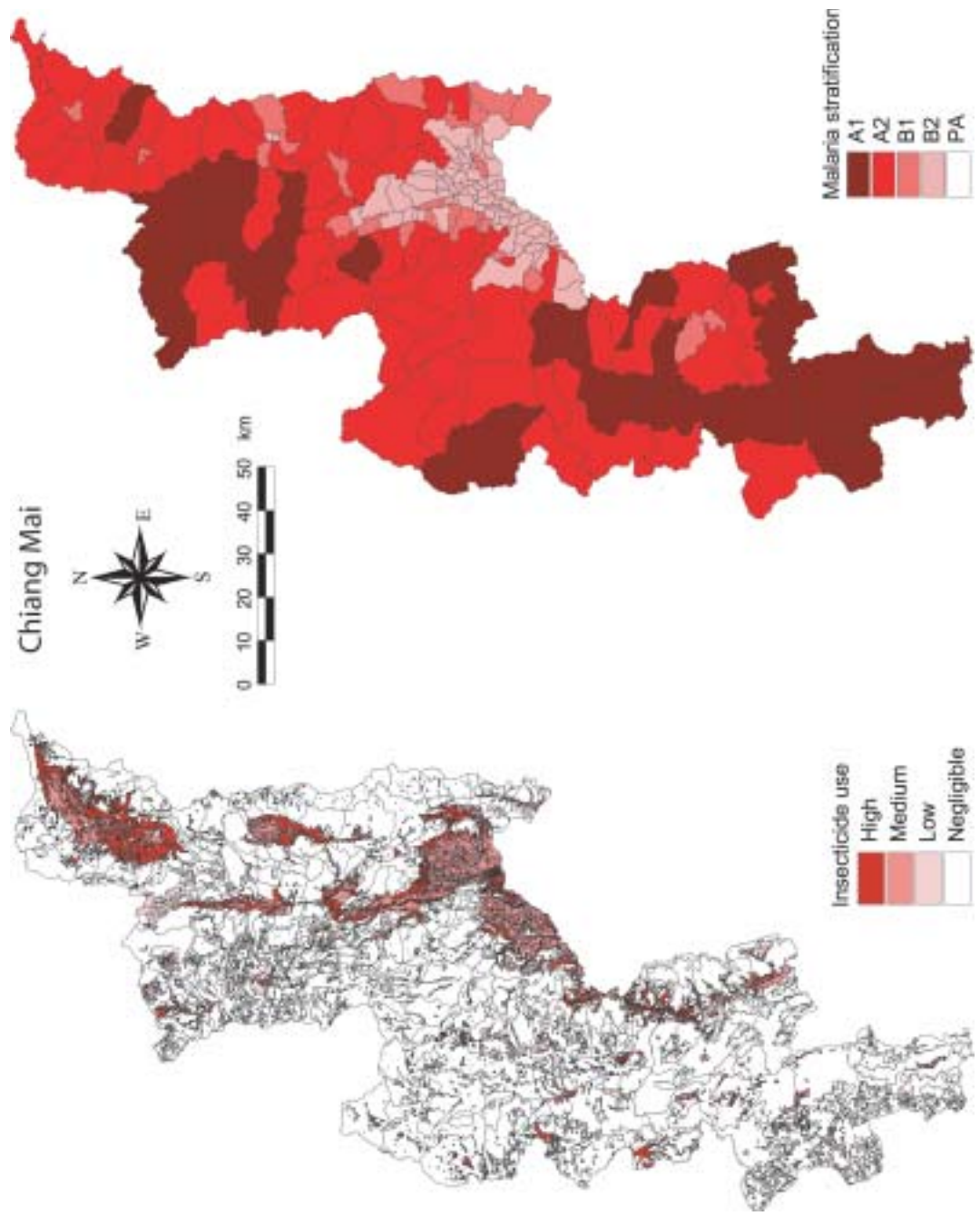
Appendix 4.

Land use in Kanchanaburi.



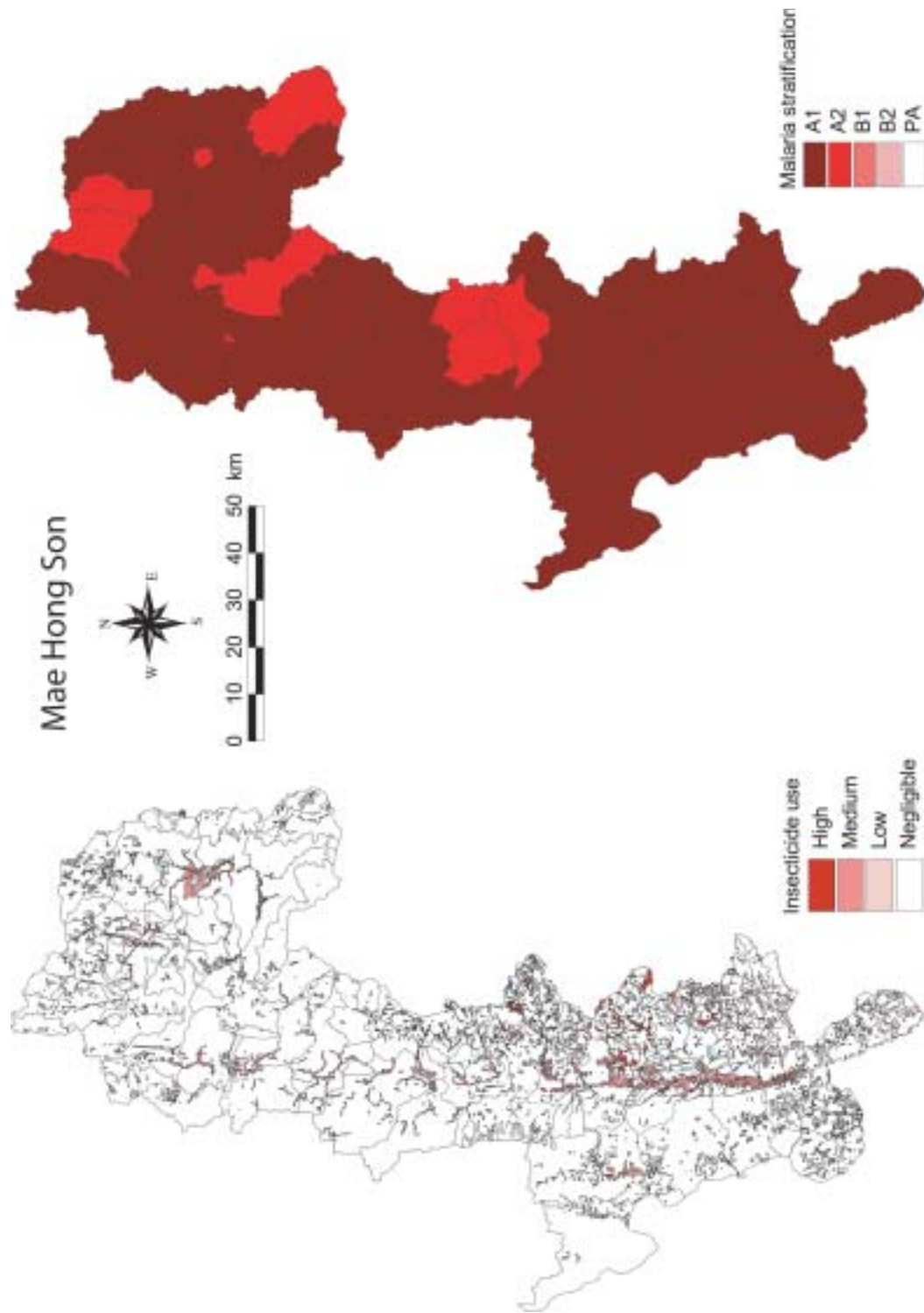
Appendix 5.

Insecticide intensity and malaria stratification areas in Chiang Mai. Malaria stratification categories are A1=Perennial transmission; A2=Periodic transmission; B1=High-risk non-transmission; B2=Low-risk non-transmission; and PA=Pre-integration Area.



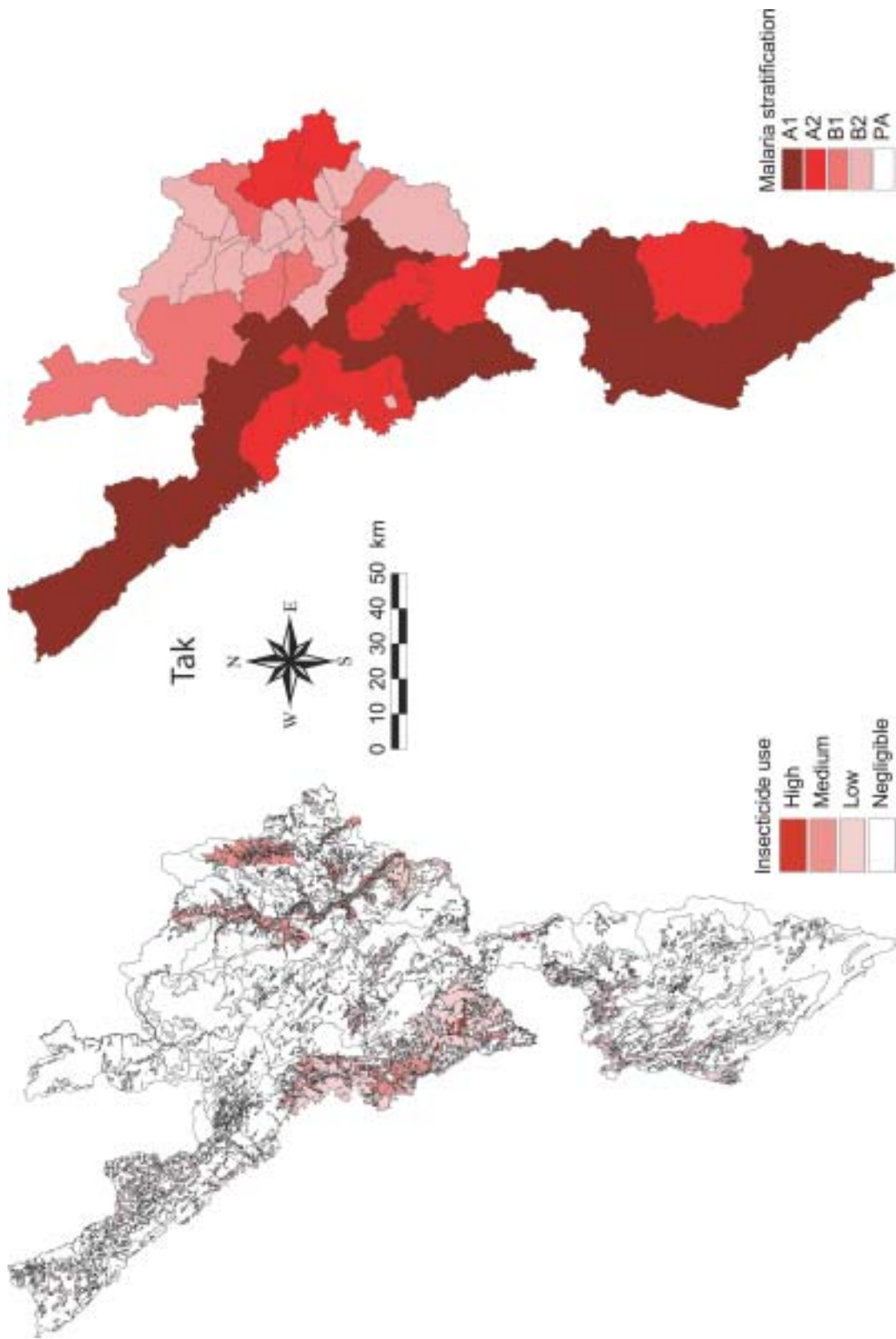
Appendix 6.

Insecticide intensity and malaria stratification areas in Mae Hong Son. Malaria stratification categories are A1=Perennial transmission; A2=Periodic transmission; B1=High-risk non-transmission; B2=Low-risk non-transmission; and PA=Pre-integration Area.



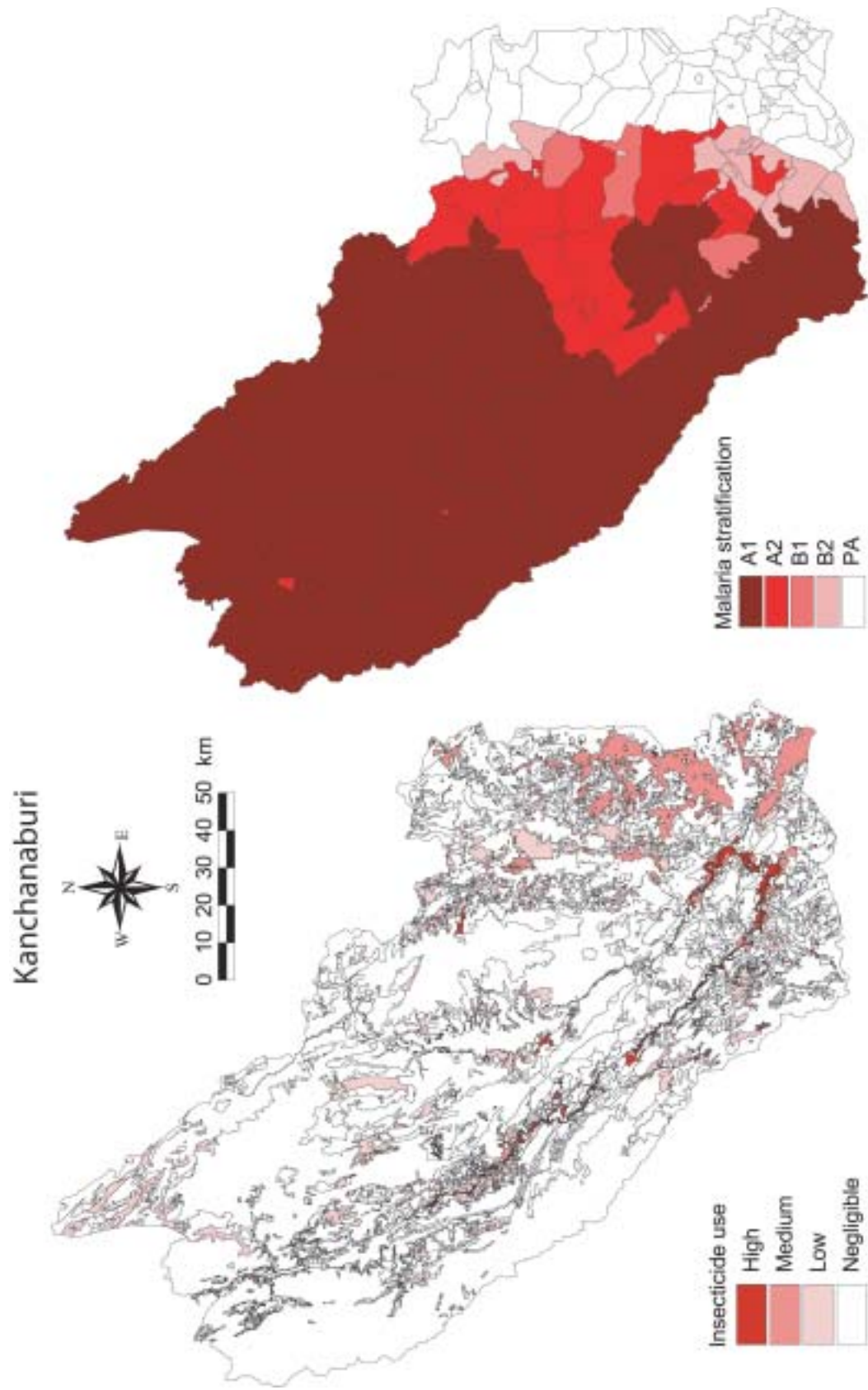
Appendix 7.

Insecticide intensity and malaria stratification areas in Tak. Malaria stratification categories are A1=Perennial transmission; A2=Periodic transmission; B1=High-risk non-transmission; B2=Low-risk non-transmission; and PA=Pre-integration Area.



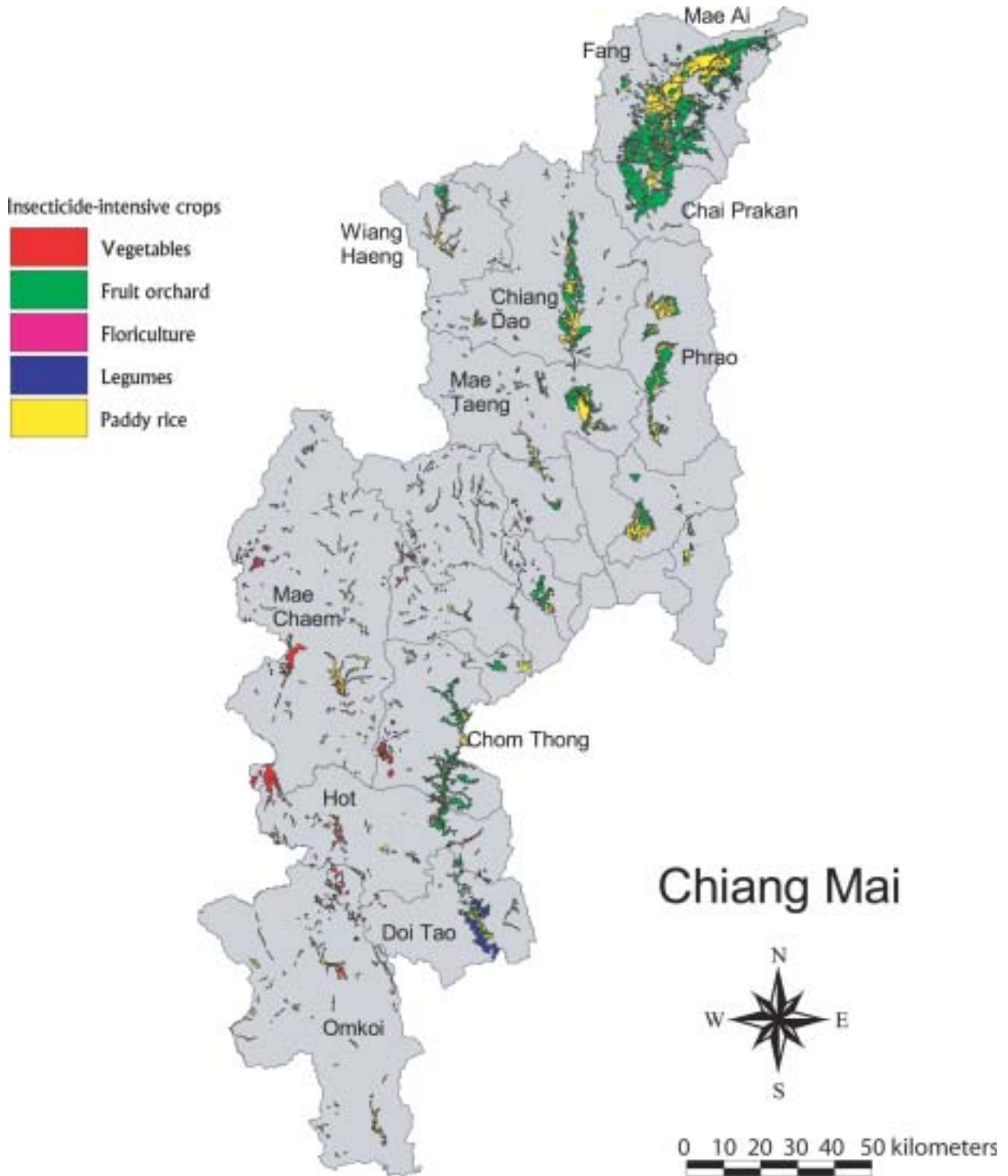
Appendix 8.

Insecticide intensity and malaria stratification areas in Kanchanaburi. Malaria stratification categories are A1=Perennial transmission; A2=Periodic transmission; B1=High-risk non-transmission; B2=Low-risk non-transmission; and PA=Pre-integration Area.



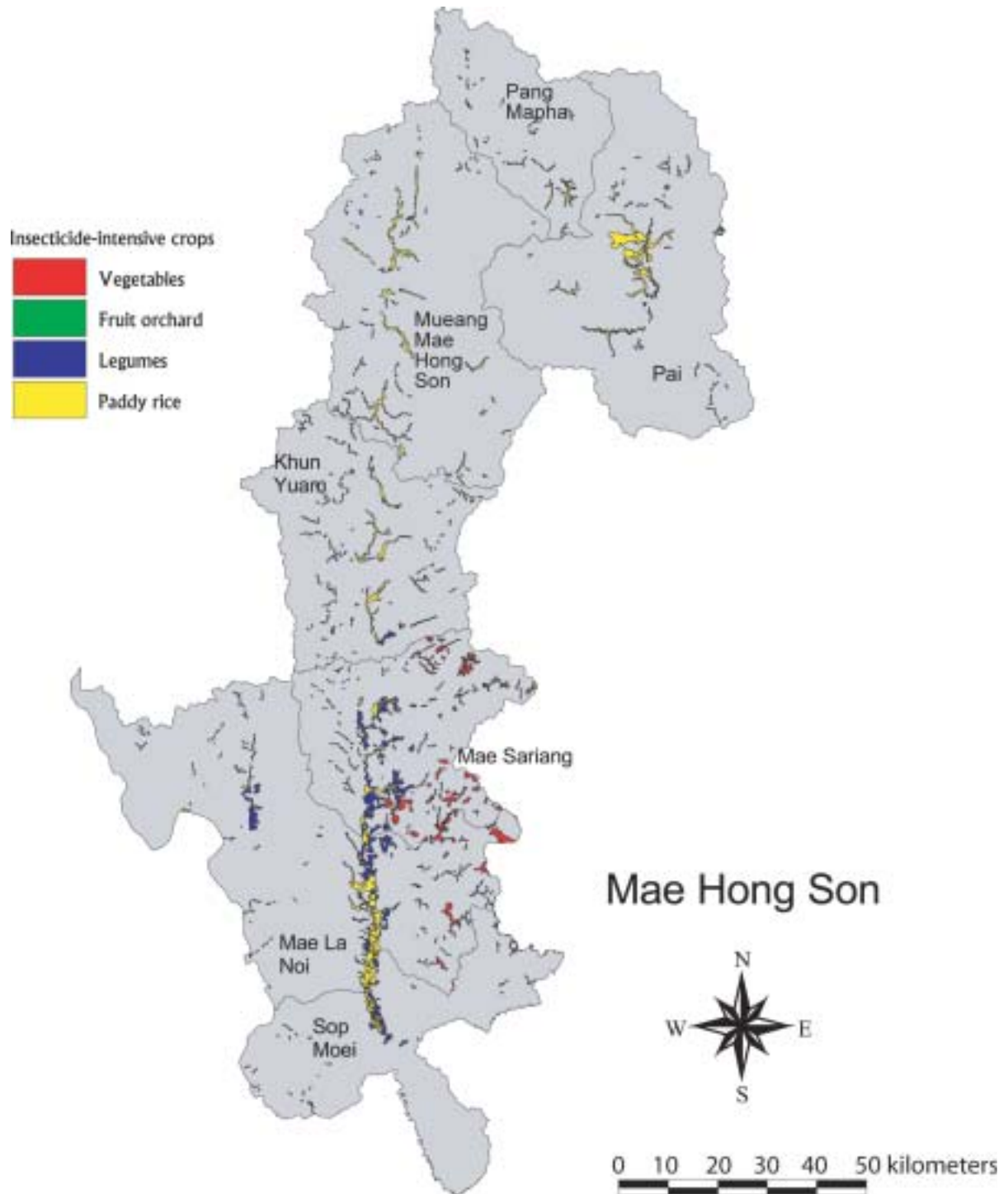
Appendix 9.

Areas of potential risk of insecticide resistance in malaria mosquitoes due to agricultural insecticides and districts in Chiang Mai.



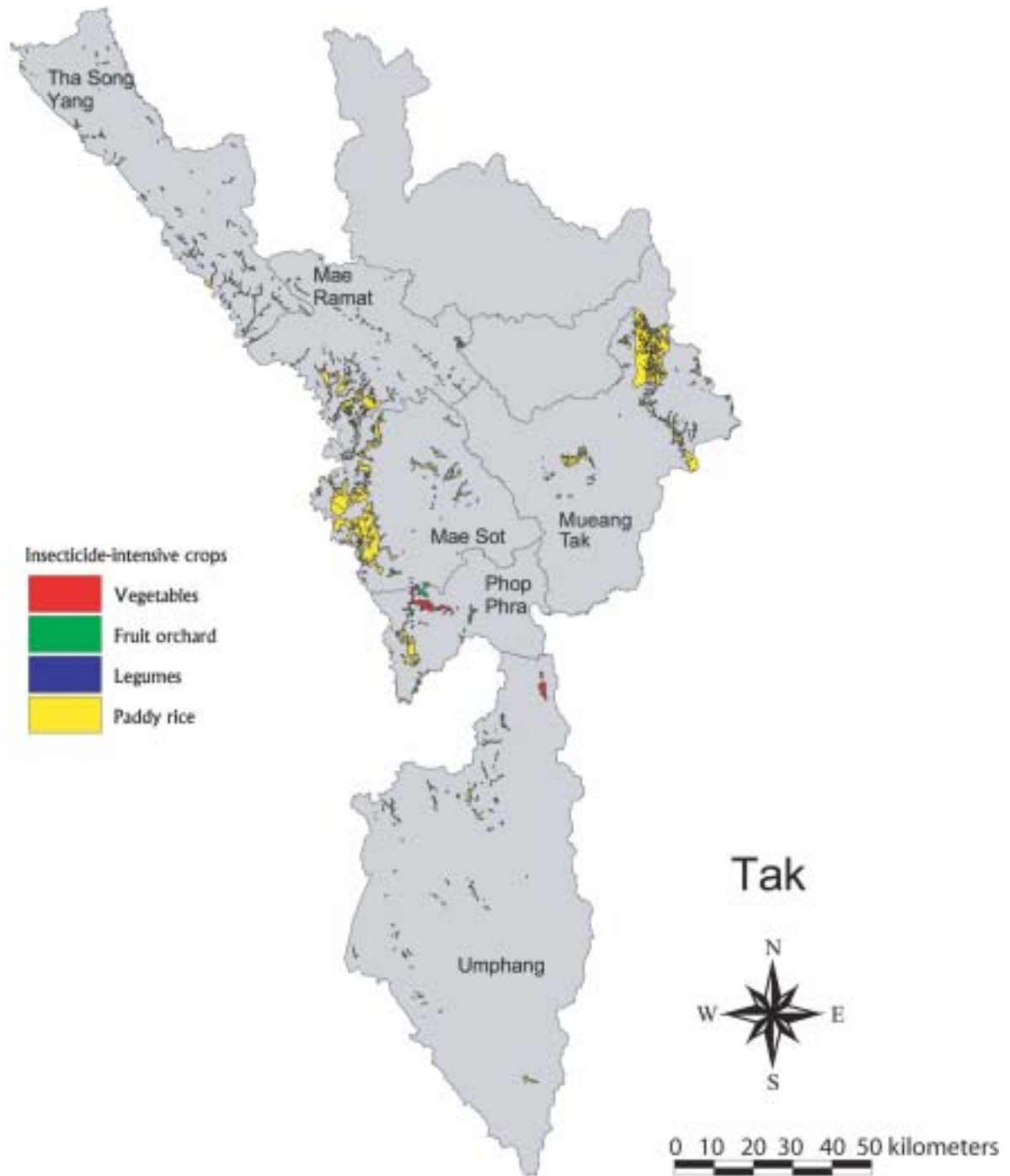
Appendix 10.

Areas of potential risk of insecticide resistance in malaria mosquitoes due to agricultural insecticides and districts in Mae Hong Son.



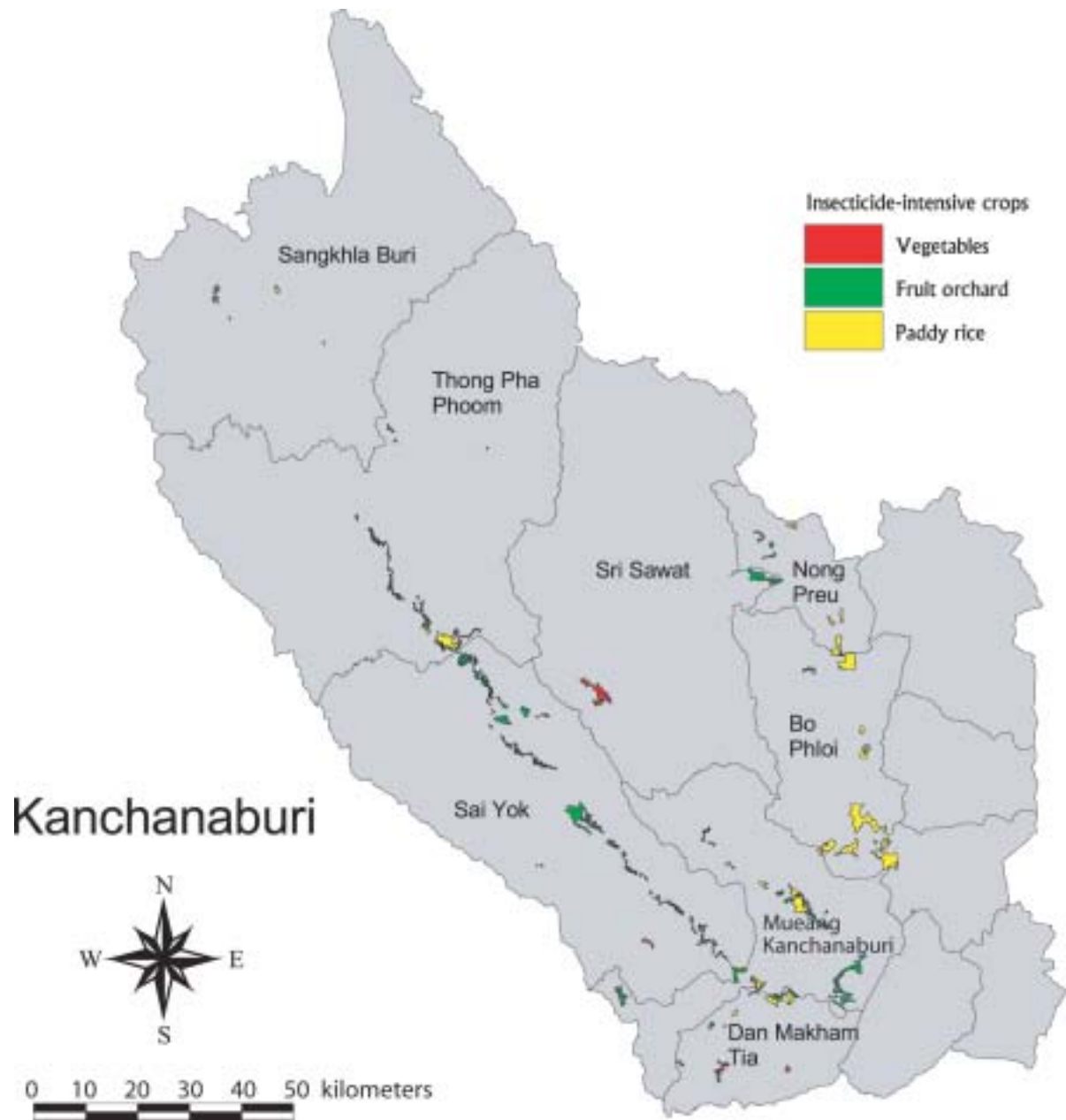
Appendix 11.

Areas of potential risk of insecticide resistance in malaria mosquitoes due to agricultural insecticides and districts in Tak.



Appendix 12.

Areas of potential risk of insecticide resistance in malaria mosquitoes due to agricultural insecticides and districts in Kanchanaburi.



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