Resistance of *Culex pipiens pipiens* (Diptera: Culicidae) to Pirmiphos-Methyl and Possible Link to Insecticide Usage in Agriculture and Public Health in Tunisia[1]

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Abstract Mosquito resistance to insecticides remains a growing concern in North Africa. The heavy reliance on insecticides and their recurrent and oftentimes inappropriate application are key sources for resistance, which is a potential threat to the global public health. Four populations of *Culex pipiens pipiens* were sampled from four areas of Tunisia, with the areas characterized by contrasting agricultural activity and usage of insecticides for vector control. Bioassays were performed to determine the level of resistance in each population to pirmiphos-methyl insecticide. Comparison of resistance ratios among the populations suggested a possible link of pirmiphos-methyl resistance with agricultural activity and insecticide usage. Little or no cross-resistance was observed with pirmiphos-methyl and either organophosphates or pyrethroids commonly used in those areas. Detoxification enzymes and target site (acetylcholinesterase) were involved in the observed resistance. Overall, the results of the present study suggest the role of insecticide usage and other activities in the immediate area in impacting the development of insecticide resistance in mosquitoes, with a possible major factor being agricultural activities.

Key Words *Culex pipiens pipiens*, insecticide resistance, agriculture, detoxification enzymes, AChE1, Tunisia

The use of synthetic chemical insecticides remains the most efficient and economic approach in vector control programs and has been shown to be effective in reducing disease transmission (Lengeler 2004, Pluess et al. 2010). However, the success of these control programs is now threatened by the increase in resistance to these insecticides in mosquito populations (World Health Organization 2012). Indeed, the massive use of insecticides in public health has led to the selection of highly adapted resistant natural populations of mosquitoes (Ben Cheikh et al. 1998, Daaboub et al. 2008, Tabbabi et al. 2017a). Several studies suggest that the selection pressure of insecticide resistance is primarily of agricultural origin, threatening the efficacy of vector control interventions (Akogbeto et al. 2006, Antonio-Nkondjio et al. 2008, Diabaté et al. 2002, Nkya et al. 2013, Yadouleton et al. 2009). In Tunisia, the agricultural department utilizes a range of insecticide

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classes sharing the same targets and modes of action as those used for vector control and, therefore, may exert a significant selection pressure on mosquitoes (Nkya et al. 2013). On the other hand, uncontrolled urban growth has been associated with the development of small-scale urban agriculture with uncontrolled use of pesticides (Keiser et al. 2004, Yadouleton et al. 2009).

The two main resistance mechanisms to organophosphates in mosquitoes are enzymatic detoxification (i.e., metabolic resistance) and target site modification (Ben Cheikh et al. 1998, Daaboub et al. 2008, Tabbabi et al. 2017a). The major classes of enzymes involved in metabolic resistance are cytochrome P450 oxidases, esterases, and glutathione-S-transferases. The second common resistance mechanism is the ace1 mutation of the acetylcholinesterase (AChE1). Other resistance mechanisms such as cuticle alteration, altered transport, and sequestration are also likely to occur in resistant mosquito populations.

A positive correlation of resistance to chemical insecticides in mosquitoes with agricultural insecticide usage has been reported by Diabaté et al. (2002), Ranson et al. (2009), Yadouleton et al. (2009), and Matowo et al. (2010). Indeed, many insects, including *Anopheles* mosquitoes in the proximity of intensively managed agricultural areas, have developed resistance, and candidate genes imparting resistance have been identified (Akogbeto et al. 2006, Matowo et al. 2010, Nkya et al. 2014). However, the impact of insect control in agriculture and in public health on resistance to pirmiphos-methyl insecticide in *Culex pipiens pipiens* from Tunisia has not been extensively investigated (Tabbabi et al. 2017a).

Nkya et al. (2013) noted the potential role of agricultural insecticides in the differential development of insecticide resistance in disease vectors, postulating that the use of insecticide classes sharing the same targets and modes of action as those used for vector control may exert a significant selection pressure on the vector populations. Furthermore, human-derived pollutants may affect vector tolerance of insecticides as shown by Poupardin et al. (2008), Riaz et al. (2009), and David et al. (2010). In this context, the ultimate goal of this present study was aimed at investigating the possible impact of the use of chemical products by both agricultural and public health departments on the development of resistance to pirmiphos-methyl insecticide in *C. p. pipiens* populations in Tunisia.

Materials and Methods

Specimens from populations of *C. p. pipiens* were collected from four areas in Tunisia, each with different agricultural pest and vector control activities (Table 1). The collected mosquitoes were transported to the laboratory where the identity of the third and fourth instars was confirmed according to the key of Brunhes et al. (1999). A susceptible laboratory strain of *C. p. pipiens* was used as reference to compare the resistance levels to pirimiphos-methyl among the different populations.

Susceptibility of the mosquitoes to the organophosphate pirimiphos-methyl and the carbamate propoxur was determined according to the methods of Raymond et al. (1986). Bioassays were performed with the field populations and/or F1 and F2 laboratory generations. Late 3rd and/or early 4th instars were tested collectively for assessing susceptibility to the insecticide. Five concentrations of pirimiphos-methyl (100, 10, 1, 0.1, 0.01 ppm), providing between 0% and 100% mortality, were used in

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Table 1. Geographic origin of Tunisian populations, breeding site characteristics, and insecticide control.

Site	Locality	Breeding Site	Date of Collection	Mosquito Control (Used Insecticides)[a]	Agricultural Pest Control
1	Kalaa kebira	River	July 2003	Yes (F, Pm, P, D)	None
2	Hajeb Laayoun	River	July 2004	None	Yes
3	Tazarka	River	May 2005	Yes (C, T, Pm, F, P, D)	Yes
4	Sidi khalifa	Water pond	July 2004	None	None

[a] C = chlorpyrifos; D = deltamethrin; F = fenitrithion; P = permethrin; Pm = pirimiphos methyl; T = temephos.

a total volume of 100 ml of water containing 1 ml of ethanol solution of the tested insecticide. The tests were replicated five times per concentration with 20 larvae per replicate. Larval mortality was recorded 24 h after initial exposure. Synergist bioassays were also conducted using S,S,Sributyl phosphorothioate (DEF: 98%, Chem Service, England) and piperonyl butoxide (Pb: 94%, Laboratory Dr. Ehrenstorfer, Germany) by exposing larvae to standard sublethal doses of 0.08 mg/l for DEF and 2.5 mg/l for Pb 4h before the addition of the insecticide using the same methods. Propoxur bioassays included one dose (1 mg/L) and five replicates; all susceptible mosquitoes were killed.

Esterases of high activity were characterized in adults using starch-gel electrophoresis as described by Pasteur et al. (1988). The standard method of Bourguet et al. (1996) was used to study AChE1 polymorphism. The AChE1 activity of homogenates of adult heads in the absence or presence of propoxur was compared. These methods allowed for the identification of only the susceptible (ACHE1S, phenotype [SS]), only the resistant (ACHE1R, phenotype [RR]), or both types (phenotype [RS]) of ACHE1.

Larval mortality was recorded after 24 h of exposure as per Raymond et al. (1986). Data were analyzed using a log-probit program (Raymond et al. 1993) based on Finney (1971).

Results

All samples were resistant to pirimiphos-methyl ($RR > 1$, $P < 0.05$) with a large variation in the tolerance observed (Table 2). Resistance to pirimiphos-methyl in *C. p. pipiens* collected at the various sites with different agricultural pest and mosquito control activities in Tunisia ranged from 7.0 (Site 1) to 62.1 (Site 3) (Table 2). The population subjected to both agricultural and public health insecticide usage (Site 3) exhibited the highest resistance ratio of the median lethal time (RR_{50}) while mosquitoes collected from Site 4, which experienced no insecticide applications, had the lower level of resistance (11.4). Little or no cross-resistance was observed between pirimiphos-methyl and organophosphate and pyrethroid applications at

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Table 2. Resistance to pirimiphos-methyl resistance in *Culex pipiens pipiens* from Tunisia.

	Pirimiphos-methyl		
Population	**LC_{50} in μg/L***	**Slope ± SE**	**RR_{50}***
Slab	2.9 (2.5–3.4)	2.34 ± 0.18	—
1-kalaa Kebira	20 (14–29)	2.52 ±0.34	7.0 (4.7–10.4)
2-Hajeb laayoun	117 (81–168)	2.57** ± 0.39	40.2 (26.5–61.0)
3-Tazarka	181 (166–196)	3.93 ± 0.22	62.1 (50.5–76.4)
4-Sidi khalifa	33 (21–52)	1.48 ± 0.25	11.4 (8.3–15.7)

* 95% confidence interval.

** Parallelism test positive but without probability; RR_{50} = resistance ratio at LC_{50} (RR_{50} = LC_{50} of the population considered / LC_{50} of slab).

Site 1 (7.0), which did not differ significantly from the level of resistance found at Site 4 where no insecticidal inputs occurred.

The pirimiphos-methyl resistant populations were highly resistant to propoxur, thus indicating involvement of an insensitive AChE1 target site. Investigation of AChE1 polymorphism detected three phenotypes including only the susceptible (ACHE1S, phenotype [SS]), only the resistant (ACHE1R, phenotype [RR]), or both types (phenotype [RS]) of ACHE1. The highest frequencies of AChE1 resistant phenotypes (100%) and susceptible phenotypes (56%) were recorded in the most-resistant (Site 3) and a susceptible (Site 4) population.

Resistance to pirimiphos-methyl was not significantly affected by prior exposure to either DEF (Table 3) or Pb (Table 4) in populations tested ($P < 0.05$), suggesting the presence of another mechanism such as altered target site sensitivity (AChE1) and, thus, confirmed our results cited in the previous paragraph. However, biochemical studies indicated high activity of five esterases in the resistant population as compared to the susceptible. The esterase C1 is encoded by the *Est-1* locus while the other four esterases are encoded by the *Ester* super locus: A1, A2-B2, A4-B4 (or A5-B5, which has the same electrophoretic mobility), and B12. Several esterases were detected in mosquitoes from all sites, with the only exception being Site 2.

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Table 3. Effect of DEF synergist on Pirimiphos-methyl toxicity in *Culex pipiens pipiens* from Tunisia.

	Pirimiphos-methyl + DEF				
Population	**LC_{50} in µg/L***	**Slope ± SE**	**RR_{50}***	**SR_{50}***	**RSR**
Slab	0.30 (0.16–0.56)	1.7 ±0.42	—	9.79 (6.16–15.5)	—
1-kalaa Kebira	5.7 (3.9–8.3)	1.96** ± 0.3	19.3 (11.9–31.4)	3.56 (2.33–5.43)	0.36
2-Hajeb laayoun	4.7 (4.0–5.3)	2,2 ± 0,2	15.7 (10.2–24.4)	24.9 (16.9–36.8)	2.6
3-Tazarka	122 (110–136)	4.48 ±0.37	411 (251–673)	1.48 (1.15–1.90)	0.15
4-Sidi khalifa	29 —	2.64 ±0.90	97.9 (36.7–260)	1.14 (0.44–2.98)	0.12

* 95% confidence interval (CI).

** The log dose-probit mortality response is parallel to that of S-Lab; RR_{50} = resistance ratio at lethal concentration (LC_{50}) ($RR_{50} = LC_{50}$ of the population considered / LC_{50} of slab); SR_{50} = synergism ratio (LC_{50} observed in absence of synergist / LC_{50} observed in presence of synergist). RR and SR considered significant ($P < 0.05$) if their 95% CI did not include the value 1; RSR = relative synergism ratio (RR for insecticide alone / RR for insecticide plus synergist).

Discussion

Mosquito larval ecology is important in determining larval densities and species assemblage. This, in turn, influences vector potential and disease transmission in an area. Therefore, understanding larval habitat ecology is important in designing vector disease control programs. Vanek et al. (2006) postulated that preferred mosquito larval habitats in Tanzania are associated with agricultural production areas. Furthermore, Nkya et al. (2013) suggested that agricultural pollutants play a significant role in exerting selection pressure for development of insecticide resistance in mosquitoes, including *C. p. pipiens*. However, other studies implicate insecticide usage for vector control as the primary cause of resistance development in mosquito populations (Balkew et al. 2010, Marcombe et al. 2012, N'Guessan et al. 2007, Protopopoff et al. 2008).

Our results reported herein show different levels of resistance to pirimiphos-methyl at different areas of Tunisia. The population subjected to both agricultural and public health insecticide usage exhibited the highest resistance ratio of the

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Table 4. Effect of piperonyl butoxide (Pb) synergist on Pirimiphos-methyl toxicity in *Culex pipiens pipiens* from Tunisia.

	Pirimiphos-methyl + Pb				
Population	**LC_{50} in μg/L***	**Slope ± SE**	**RR_{50}***	**SR_{50}***	**RSR**
Slab	0.40 (0.31–0.55)	1.47 ± 0.18	—	7.2 (5.7–9.1)	—
1-kalaa Kebira	18 (10–30)	1.54 ± 0.25	45.1 (31.2–65.4)	1.1 (0.72–1.7)	0.16
2-Hajeb laayoun	4.7 (1.3–17)	1.87** ± 0.68	11.8 (6.6–20.9)	24.7 (12.8–47.4)	3.4
3-Tazarka	184 (113–299)	4.68 ± 1.03	457 (256–816)	0.98 (0.56–1.7)	0.13
4-Sidi khalifa	15 (10–20)	2.11 ± 0.34	39.6 (28.2–55.5)	2.0 (1.3–3.2)	0.29

* 95% confidence interval (CI).

** The log dose-probit mortality response is parallel to that of S-Lab; RR_{50} = resistance ratio at lethal concentration $(LC)_{50}$ ($RR_{50} = LC_{50}$ of the population considered / LC_{50} of Slab); SR_{50} = synergism ratio (LC_{50} observed in absence of synergist / LC_{50} observed in presence of synergist). RR and SR considered significant ($P < 0.05$) if their 95% CI did not include the value 1; RSR = relative synergism ratio (RR for insecticide alone / RR for insecticide plus synergist).

median lethal time. On the other hand, little or no cross-resistance was observed between pirimiphos-methyl and both organophosphate and pyrethroid. These results imply that the use of insecticides in agricultural and vector pest management are linked to development of insecticide resistance in *C. p. pipiens* populations in Tunisia despite examination of only four populations. Our findings corroborate those of Diabaté et al. (2002), Ranson et al. (2009), Matowo et al. (2010), and Yadouleton et al. (2011), which tie observed pyrethroid resistance to agricultural insecticide applications. Indeed, most insecticides used in agriculture have the same targets as those used for vector control and can, therefore, select for resistance mechanisms in mosquitoes breeding in areas of intense agricultural production activities (Antonio-Nkondjio et al. 2008, 2011, Diabaté et al. 2002, Yadouleton et al. 2009).

Most studies on the impact of agricultural practices on the development of insecticide resistance have been focused on *Anopheles* mosquitoes in Africa. These studies reported important levels of resistance to dichlorodiphenyltrichloroethane, permethrin, and deltamethrin, which were linked to intensive application of

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insecticide against crops and livestock pests as well as for the control of disease vectors in the same locality (Diabaté et al. 2002, Dongus et al. 2009, Overgaard 2006, Ranson et al. 2009). Other studies have shown that urban pollutants can affect mosquito detoxification systems, leading to an enhanced tolerance to insecticides (Djouaka et al. 2008, Jones et al. 2012, Poupardin et al. 2008, 2012, Riaz et al. 2009, Suwanchaichinda and Brattsten 2011), which may explain the low level of resistance detected at Sites 1 and 4 with little to no previous chemical inputs.

The loss of insecticide efficacy may, thus, lead to partial operational failure of vector control and probably to increased disease transmission. Vector control in the field of public health and its complex implications require the coordination of all parties involved and various other sectors. The use of insecticides by both agricultural and public health departments in Tunisia should be planned so as to reduce the potential development of resistance in *C. p. pipiens* populations (Tabbabi and Daaboub 2017).

Many mechanisms, including mutations in the target proteins (target-site insensitivity), a lower penetration or sequestration of the insecticide, or an increased biodegradation of the insecticide due to enhanced detoxification activities (metabolic resistance), are involved in insecticide resistance in mosquito vectors. Resistance to pirimiphos-methyl (organophosphate) is mainly associated to an insensitive AChE1 target site and metabolic resistance mechanisms (Ben Cheikh et al. 1998, Tabbabi et al. 2017a, Weill et al. 2003). These mechanisms also confer resistance to the carbamate propoxur.

Our results demonstrate that the resistance to pirimiphos-methyl insecticide was associated with the increase in detoxification enzymes and the presence of an insensitive AChE1 site. Although bioassays of synergists did not identify the detoxification mechanism in the all studied samples, direct analyses of the detoxifying enzymes using starch electrophoresis indicated that they were present in these mosquitoes. This disagreement between the two methods may be explained by the insensitivity of enzymes to some synergists. Reduced sensitivity of AChE1 and detoxification enzymes has been reported as an important mechanism of organophosphate resistance in many arthropod species, including mosquitoes (Ben Cheikh et al. 1998, Tabbabi et al. 2017b, Weill et al. 2003).

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