PROJECT REPORT:

Project Title: In-Vitro Inhibition of Chlorophacinone Metabolism in Resistant Meadow Voles Using FIFRA 25B Inert Ingredients

Research Agency: National Wildlife Research Center

Principal Investigator: Katherine Horak

Budget: $42,865.00

Background:

Voles cause significant damage to agricultural crops in California; both chlorophacinone and zinc phosphide are registered for use to control vole populations. Problems with bait shyness to zinc phosphide have led to the reliance on chlorophacinone. Because of its continued use, there are now populations of voles that are resistant to chlorophacinone. Without a solution to the resistance that can be enacted quickly, growers face the problem of no efficacious way to control vole populations and decrease damage.

Interesting compounds from the EPA FIFRA 25b list of inert ingredients will be screened for inhibition of chlorophacinone metabolism. These compounds are attractive because they can be added to chlorophacinone bait formulations without significant re-registration requirements, giving growers a novel tool to combat chlorophacinone resistance in a timely manner.

California meadow voles cause significant damage to agricultural crops although chlorophacinone has been used to control their populations for over two decades. Complaints from growers about the efficacy of chlorophacinone for the control of meadow voles have prompted scientists to examine the developments of possible resistance in vole populations. In a VPCRAC funded study 50% of meadow voles from Castroville, CA survived a lethal dose of chlorophacinone (Salmon Final Report 2006). Although zinc phosphide has been approved for the control of voles in artichoke fields concerns over bait acceptance have limited its use, causing growers to continue to use chlorophacinone as the mainstay for control of voles. The development of resistance to chlorophacinone has severely limited control of damage to agriculture crops and must be addressed.

The liver is responsible for most of the metabolism and detoxification of compounds in the body; these reactions are carried out by cytochrome p450 enzymes. Some cytochrome p450 enzymes can be induced by the compounds that are ingested which allow the organism to adapt to changes in its environment (Dennison *et. al.* 2005). Changes in metabolism have been linked to resistance to both warfarin and bromadiolone (Ishizuka *et. al.* 2007, Markussen *et. al.* 2008, Lasseur *et. al.* 1999). Previous VPCRAC funded studies have shown that resistant meadow voles metabolize 42% of chlorophacinone while susceptible voles only metabolize 2% (Horak unpublished data). From this it follows that if the metabolism of resistant voles can be inhibited it is possible

to render them susceptible again. *In-vitro* experiments using cytochrome p450 experiments shown that inhibitors such as ketoconazole and fluvoxamine significantly inhibit metabolism (10% and 29% respectively), however transitioning these compounds produced as human pharmaceuticals into agricultural rodenticides would prove difficult and costly.

It is well documented that some natural products have inhibitory properties to cytochrome p450 enzymes. These include grapefruit and pomegranate juices (Chan *et. al.* 1998, Faria *et. al.* 2007, Farkas *et. al.* 2007). However, neither of these juices is specifically on the FIFRA inert products list (EPA Inert Ingredients Eligible for FIFRA 25b Pesticide Products). Thus, approval for the addition of these products to current chlorophacinone formulations may require additional data. Moreover, these findings suggest that a closer examination of the FIFRA 25b list could elucidate other compounds that inhibit the cytochrome p450 enzymes involved in chlorophacinone resistance in California meadow voles. Finding an inhibitor on the FIFRA 25b list would make it possible to add that compound to current formulations using chlorophacinone without re-registration. This would not only save large amounts of money, it would save time, a valuable commodity to growers. Not having to go through re-registration would mean that these inhibitors could be added to formulations as soon as they are determined to be efficacious, giving growers a solution to the problem of chlorophacinone quickly.

This research is designed to identify important additives for chlorophacinone baits that increase efficacy among anticoagulant-resistant populations. The search for these additives will be limited to the list of EPA approved inert ingredients to ensure rapid and inexpensive approval for use to control pest species.

Objectives:

In-vitro cytochrome p450 enzymes experiments will be used to determine compounds from the FIFRA 25b inert ingredient list that inhibit the metabolism of chlorophacinone.

Progress To Date:

Last Updated:

01/22/2011