

Final Report

IR-4 HQ Assistance to Register Pesticides for Public Health and Veterinary Use

ARS Cooperative Agreement 58-0208-8-102

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Jerry Baron, Ph.D., IR-4 Project Executive Director (Principal Investigator)

Karl Malamud-Roam, Ph.D., IR-4 Project Public Health Program Manager

Keith Dorschner, Ph.D., IR-4 Entomology Manager

Michael Braverman, Ph.D., IR-4 Biopesticide Program Manager

In June 2008 the IR-4 Project, a publicly funded collaborative pest management research program with headquarters at Rutgers University, entered into a five-year cooperative agreement with USDA-ARS (Cooperative Agreement 58-0208-8-102) with the overall objective of facilitating the registration of conventional and biological pesticides (including repellents, attractants, and toxicants) to protect people and animals from arthropod pests that vector disease, and with a particular focus on enhancing protection of deployed US military personnel from vector-borne diseases. This is the final report for IR-4 activities funded by this Agreement for the five year period June 26, 2008 - June 25, 2013. Many of the activities discussed in this Report are still in progress, and, as anticipated, the agreement has been renewed for a second five-year period. The primary IR-4 activities funded by this agreement and discussed in this report are an integral element of a larger coordinated effort of USDA-ARS and the Department of Defense – the Deployed War-fighter Protection Research Program (DWFP) – established to develop and validate novel methods to protect United States Military deployed abroad from threats posed by disease-carrying insects. The specific expertise and contribution of IR-4 in this effort is broadly defined as regulatory support, and is intended to help transition entomological and chemical research into useful products with U.S. and any other required regulatory approvals for military use anywhere required in the world. In addition, the development and registration of pest control products for applications in civilian public health and/or veterinary medicine come under the terms of this specific agreement.

Background to the Cooperative Agreement

The IR-4 Project was established in 1963 as a publicly funded collaboration between the USDA and the state land grant universities and agricultural experiment stations, with a general goal of improving pest management in small agricultural sectors, where private investment may be unprofitable and insufficient, and the specific mission to facilitate the registration of sustainable pest management technology for specialty crops and minor uses. Traditionally, the IR-4 Project has collected required data and submitted data packages to registrants & EPA for tolerances and registrations for food and ornamental crops. However, the IR-4 scope of work has expanded somewhat over time in response to public needs, and a strategic review of IR-4 in 2008 recognized vector control and other public health uses of pesticides as a minor use market with similar attributes to specialty crop agriculture. This review suggested that providing regulatory support for public health pesticides (PHP's) would be an appropriate role for IR-4, especially given the increasing global significance of vector-borne pathogenic diseases such as West Nile virus, dengue fever, malaria, Lyme disease, etc.

The significance of vector-borne diseases has been increasing in recent decades, both in the U.S. and globally, but the number of available and effective tools to combat these diseases has not kept pace. Despite substantial efforts to develop effective vaccines and therapeutic agents, control of these maladies depends primarily on control of the arthropods that transmit them, and this almost inevitably requires an array of chemical, biochemical, and microbial agents including which act as toxicants, repellents, or attractants, or which otherwise disrupt the disease vectors. Unfortunately, this chemical control "toolbox" has been shrinking, in part because new chemical tools have been scarce, in part because older chemical tools have faced new data requirements to demonstrate their safety, and in part because the small market for these products has limited the opportunity for the manufacturers and registrants of these products to recoup research, development, and regulatory costs for both new and older materials. Addressing this need is the general purpose of this Cooperative Agreement.

A specific reason for IR-4 to begin work with PHP's in 2008 was a request for assistance from the Armed Forces Pest Management Board (AFPMB) and the DWFP to help ensure the availability of effective, safe, and legal tools for protection of deployed US military personnel from vector-borne diseases. The DWFP was initiated in 2004 and by 2008 had determined that effective product development would require regulatory expertise in addition to the research and chemical discovery efforts of collaborating ARS and academic scientists. Thus, the objectives and activities covered in this Report are highly responsive to U.S. military needs.

Goals, Objectives, Scope of Work, and General Approach

Since the Cooperative Agreement was approved, IR-4 has actively and effectively pursued its objectives, initially by establishing a Public Health Pesticides (PHP) Program and by hiring Dr. Karl Malamud-Roam, a PHP expert, to manage it; and then by supporting PHP development efforts by the PHP Program and other IR-4 staff in collaboration with DWFP scientists and with other researchers, product developers, regulators, and vector control practitioners. The activities and products pursued by the IR-4 PHP Program and other IR-4 collaborators have been primarily determined by the explicit objectives of the Cooperative Agreement, as well as by supplemental objectives that have been recognized as critical by IR-4 staff and funders and collaborators. The goals and objectives of the agreement and the PHP Program also define the scope of work of IR-4 involvement with PHP's, and inform the general approach to PHP product development that we have adopted.

Goals and Objectives

Vector control practitioners, product developers, funders, and regulators routinely note a common goal of ensuring an adequate “toolbox” of PHP products to allow effective protection of people and domesticated animals from arthropod vectors of disease. Consistent with this broad goal, the overall objective of ARS Cooperative Agreement 58-0208-8-102 has been to register pesticides (including repellents, attractants, and toxicants) for public health and veterinary use. In addition, the Cooperative Agreement explicitly identified several sub-objectives for the IR-4 Project Headquarters (IR-4 HQ):

- IR-4 HQ will attempt to find active ingredients that have registrations for other uses or that are registered abroad and evaluate their utility for public health applications (i.e. identification of materials underutilized vs. public health pests);
- IR-4 will communicate with industry and the U.S. Environmental Protection Agency (EPA) in order to determine what steps are necessary to get registration;
- IR-4 HQ will also participate in managing the registration activities of some of the new, unregistered compounds discovered by USDA Agricultural Research Service (ARS) and the Department of Defense's (DoD) Deployed Warfighter Protection Program (DWFP).

Since the agreement was formalized, staff members from IR-4, ARS, DWFP/AFPMB, and other collaborating institutions have participated in several formal reviews and other forums, and

have identified additional sub-objectives that are critical to achieving the overall objective and that can be realized, at least in part, by IR-4, and these have become fully integrated into the IR-4 PHP Program scope of work:

- Creation and maintenance of a comprehensive inventory and database of materials that can serve as public health pesticides (PHP's), including information on their identification and specification, chemistry, efficacy, risk profile, regulatory status, intellectual property status, and use patterns;
- Consultation and representation of researchers and product developers, and other facilitation and assistance in the registration of potential PHP materials;
- Assistance in efforts to protect the registration of existing PHP's facing new data requirements;
- Evaluation and assistance in efforts to improve, harmonize, and streamline the PHP registration processes, both nationally and internationally; and
- Identification of and collaboration with other efforts to discover, develop, or register PHP's, to help ensure the most efficient collective use of resources.

Scope of Work and General Approach to Product Development Support

The goals and objectives of the IR-4 PHP Program define our scope of work and our approach to supporting product development and regulatory approval. We approach the objectives through a combination of literature review; surveys of users, researchers, users, and regulators; consultation with product developers and project funders and representation of them to regulators; direct conduct of scientific studies; contracting for research and other services; and dissemination of information through papers, reports, the web, conferences, etc. The approach requires close coordination with many collaborators, including funders, researchers, regulators, and product developers, registrants, and users. Prioritizing and coordinating activities with others is critical, given the limited available resources.

A primary objective of the IR-4 PHP Program, assisting the registration of new public health pesticides at the USEPA, is approached through six primary phases of action:

1. Identify PHP candidate materials/products and, working with the military and others in the user community, establish priorities for their development;
2. Identify the regulatory and other steps needed for development and production, leading ultimately to operational use in the field by military and other applicators, and the data needed to complete the regulatory approvals;

3. Collaborate with industry, government, and other personnel to develop the appropriate information and/or data necessary for registration;
4. Prepare and submit Experimental Use Permits, where these are not completed by others, to allow required efficacy and other studies;
5. Where appropriate, design and conduct experiments or contract for studies to generate needed data not available elsewhere; and
6. Submit appropriate information, data, and/or formal submittals to facilitate the regulatory approval of products allowing access to end users.
7. Collaborate with other partners to ensure that non-regulatory requirements are also met in a timely manner.

Subsidiary activities important to the registration of new materials and products include; identification of regulatory activities, including data generation, required to complete experimentation and/or bring the materials and products to the stage where they are operationally available (e.g. the military can add them to their stock list); identification of available information which can be submitted to regulators; identification and solicitation of needed funds from all sources to develop new data; and representation of the military, ARS, and product development partners when appropriate in regulatory negotiations leading to fully usable, registered materials and products.

The approach is similar when currently registered I PHP materials are threatened with cancellation due to cost of development of new data to retain the registration. Due to the limited sales, registrants have reported they cannot economically justify spending the resources to satisfy the data requirements. One key activity over the past five years has been development of an inventory of available PHP tools and the regulatory challenges facing them.

A key question has been the types of chemicals and products that are eligible for support from IR-4. In brief, all materials regulated by FIFRA are eligible, as well as some that are not currently covered by FIFRA data requirements. Thus, conventional pesticides, biopesticides, genetically modified organisms, and genetic materials that can be used as pesticides (e.g. RNAi) are all eligible. Because the military and many other public vector control programs will generally avoid PHP materials unless they are registered by EPA, products designated “Minimal Risk” or 25(b) are eligible for IR-4 support if their efficacy and safety are acceptable. The DWFP definition of PHP includes repellents, attractants, and toxicants, and the IR-4 Scope of Work is even broader, including potentially all chemicals, natural or synthetic, that help control public

health pests, including toxicants, insect growth regulators, repellents, attraction inhibitors, attractants, and other semio-chemicals which influence insect or other arthropod behavior.

The geographic scope of the project and the jurisdiction of different regulators are also important in defining appropriate tasks. The primary goal of the IR-4 PHP Program is obtaining EPA registration for useful vector control products, whether the products will be used within the U.S. or abroad (e.g. for military deployments). This requires not only application of existing regulatory practices to new materials or products but also collaboration with EPA and potentially other regulators to develop practices to allow registration of products useful against pests which do not occur within the U.S., but which may affect military personnel and other U.S. citizens overseas (e.g. *Phlebotomus papatasi* sand flies). This overseas focus also covers pesticide products that are not allowed currently within the U.S., but which may have utility and reasonable safety when used overseas, such as spatial insect repellents for indoor use in tents and other facilities in combat settings or in humanitarian efforts overseas. Regulatory support also is important in jurisdictions other than that of EPA, including specific states & tribal areas within the U.S., such as California which may have additional requirements from those generally required by EPA. Finally, collaboration with regulators outside the U.S. can support the global PHP market, and increase the likelihood that companies can recover the costs of developing new products; examples have included participation in multi-jurisdictional joint reviews, collaboration with the World Health Organization Pesticide Evaluation Scheme (WHOPES) and the Innovative Vector Control Consortium (IVCC) on development support for products of wide interest, and assistance in the development of GLP-like practices appropriate for less-developed countries.

Regardless of the activities, the materials, and the regulators, the IR-4 PHP team recognizes the critical need for communication and collaboration with a wide diversity of stake-holders, and devotes significant efforts to outreach and coordination. Concrete examples include frequent meetings and calls with EPA's Public Health Coordinator and with DWFP and other AFPMB and ARS staff; active participation in relevant workgroups and committees including the PPDC PHP Workgroup, Public Health Pesticide Coalition (PHPC), federal Tick-borne Disease IPM Workgroup, AFPMB, Roll-back Malaria's Vector Control Working Group, etc; and frequent contributions of written materials to newsletters, journals, etc.

Activities and Outcomes – Product/Project Portfolio

Support for the development and registration of specific chemicals, products, and product types constitute the bulk of the work conducted under the cooperative agreement. This includes study protocol development and regulatory data collection; reviewing and commenting on the study designs of others where data may become part of regulatory submittals; serving as a regulatory consultant for scientists and other product developers; direct assistance with regulatory agencies on behalf of potential product registrants, including representation at pre-registration meetings; serving as a liaison between researchers and potential commercial suppliers of chemicals, when there are significant regulatory questions or consequences to these discussions; document preparation and submittals; etc.

IR-4 has used funds provided by the cooperative agreement in support of a wide portfolio of specific products, and there has been considerable variation in the amount of support – both time and direct spending – provided to specific product development projects. This section of the Final Report identifies the products IR-4 has supported and some key partners in each product development project; reports on the degree of effort and direct spending provided, the specific activities undertaken, and the deliverables/milestones reached for each product/project; and discusses the process through which priorities are set and time and other resources allocated between products. For clarity, this section distinguishes between “major” (high-activity) and preliminary or supplemental projects, and also between projects involving new materials and/or new use patterns and those supporting existing materials and uses.

A. Major Projects with New Materials and/or New Use Patterns

Etofenprox All-crop Tolerance.

The first project initiated by the new IR-4 PHP Program was a series of studies in support of wide-area labels for the mosquito adulticide etofenprox, a material with documented efficacy, ease of handling, and a good environmental profile at reasonable cost. IR-4 provided some technical support for some additional efficacy trials. More importantly, the existing registration limited the use in areas where the chemical would not drift over agriculture lands. This made application in many areas impracticable. To remove this restriction, IR-4 conducted residue studies to determine the amount of residues remaining on the crop. Here, IR-4 was solely responsible for the residue quantification and magnitude of the residue studies that were required for the use of this material over agricultural (food crops and animal feed) areas. The magnitude of the residue study was novel both in the requirement to characterize and model

the behavior of ultra-low-volume (ULV) droplets, and in the need to ensure they hit small test plots when applied from moving aircraft. This required development of a new experimental protocol and negotiation with EPA; development and validation of tools to calculate the appropriate flight offsets for different aircraft, droplet size, elevations, and wind conditions; production of three crops over two seasons in two states; and precise measurement of the applications and the resulting residues collected and measured. This study has now been completed, and the petitions submitted to EPA.

Subsequent to the data submittal from the first phase of studies, EPA notified IR-4 that the measured residues indicated potential risks from the dietary exposure, and required development of another series of novel studies by IR-4:

- Cumulative residues following applications on over 200 possible spray patterns, to define possible label restrictions to limit peak residue while still allowing multiple mosquito control applications;
- Ground vs. aerial application peak ground deposition (using a new physical model of drift deposition, and a literature review of empirical observations of both application types);
- Estimates of crops potentially exposed to drift from etofenprox or any other mosquito adulticide.

Negotiations are currently ongoing with EPA and registrants that are likely to result in all-crop tolerances for aerial applications of the product for mosquito control, to be followed by magnitude of the residue and foliar dissipation studies for ground applications, to allow extension of the tolerance to all application methods, and to reduce the allowable tolerance and free room in the risk cup.

Pyriproxyfen vs. *Aedes albopictus*

The second major project was provision of regulatory support for a series of experiments by the U.S. Navy Entomology Center of Excellence (NECE) in Jacksonville, FL and the Rutgers University Center for Vector Biology, which use of the IGR (Insect Growth Regulator) pyriproxyfen to manage the container breeding mosquito *Aedes albopictus* in NJ and FL. Initially, negotiations with regulators allowed phases of the work to take place in 2010 under the minimal risk experiment provisions of FIFRA. Subsequently, as the experiments scaled up in scope and added new application technologies and formulations, IR-4 obtained Experimental Use Permits (EUP's) from the USEPA and the states of NJ and FL for NECE and Rutgers. This required the

first-ever preparation and submission of an EUP application on behalf of the AFPMB, obtaining EPA recognition of AFPMB as a pesticide “Company” and the Rutgers Center for Vector Biology as a registered Pesticide Producing Establishment, negotiation with the commercial registrant to provide no-cost access to toxicological data, establishment of a mechanism for producing Confidential Statements of Formulation and Material Safety Data Sheets for novel pesticide formulations, and other procedural steps which will greatly expedite future experiments with this and other materials. Much of the large-scale experimental work with the initial formulations and application methods has been completed, but new formulations and autodissemination stations are being developed at Rutgers, which may require additional EUP’s.

Attractive Toxic Sugar Baits (ATSB)

The IR-4 PHP Program has served as the regulatory consultant and representative for companies proposing to register and market this novel technology for mosquito control that has been largely funded by DWFP development funds. Specific IR-4 activities have included development of criteria for selecting an AI, development of a matrix to summarize existing data on the technology in order to clarify needed efficacy data, development of proposals for data collection for pollinator safety and phytotoxicity for a product class new to EPA, and representation of the developers and registrants with regulators.

Volatile Repellents & Toxicants (“Spatial Repellents”)

A major project for IR-4 and DWFP involves support for the U.S. registration of volatile materials which could result in the development of labels, possibly for military use only, for the use of indoors-use spatially active insect repellents and toxicants. While many of these products, which rely on heat, fans, or other mechanisms to maintain a critical level of repellents in the air, are allowed overseas, U.S. registrations have not been allowed for indoor use. To date, negotiations with EPA and the military have identified the critical regulatory data needs; IR-4 has produced tables allowing comparison of candidate AI’s; and discussions with registrants have identified likely strategies for regulatory submittals. A hope for the coming year is to at least initiate a formal submittal to EPA for a new label allowing military personnel to use these devices outside the U.S., but under the cover of a full U.S. registration. Discussions with AFPMB staff are ongoing regarding which of the available products should be first presented for EPA consideration, and it is expected that IR-4 will participate in formal preregistration meetings and submittals on behalf of the AFPMB partners by the end of 2013.

A related area of significant DWFP innovation has been the development of volatile repellent products, using both existing and novel chemicals, which can be applied as patches or otherwise on the outside of uniforms. By avoiding direct treatment of the uniform fabric and the use of novel formulation technologies, the researchers propose use of relatively high doses of volatile repellents, allowing greater protection of hands, faces, and other exposed skin, without undue risk to the user. IR-4 initiated a series of pre-registration negotiations on the data requirements for the product(s), and has negotiated with project developers and primary material registrants regarding active ingredient (A.I.) selection and product formulation. In the coming years, we hope to move at least to the stage of field trials approved by all needed regulators; clarification of the best A.I., the supplier, and the intellectual property needs for the products, including any data compensation.

B. Major Projects with Existing Materials / Products

Retreatment of Pre-treated Fabrics and Non-destructive Evaluation of Pyrethroids on Fabrics

Durable insecticide- or repellent-treated fabrics, fabricated into bednets, clothing, and other products, comprise a significant portion of the global toolbox for prevention of vector-borne diseases, but they face a number of major challenges which IR-4 is working to address. The spread of insect resistance to pyrethroids, which are by far the most common treatment chemicals, will likely require multi-constituent treatments, and IR-4 support for these is discussed elsewhere.

An equally severe problem is the failure of the insecticide treatments as fabrics age and are exposed to sunlight, washing, and abrasion; unfortunately, the treatment chemicals have no detectible smell or visual cue, and until now it has been impossible to tell which treated fabric products are still effective without destroying the products (e.g. by using traditional analytical chemical extractions). This is particularly challenging for the military, which requires that millions of individual uniforms protect adequately against insect biting when worn in the field. IR-4 has very actively participated in workgroups intended to resolve these problems, and is developing novel approaches to non-destructive evaluation of pyrethroids on military uniforms, nets, and other fabrics. Specific IR-4 activities include

- Development of a revised risk assessment for long-term use of treated fabrics vs. dermal absorption of permethrin and subsequent cancer risk;
- Identification of the extent of retreatment that could be allowed without exceeding published health risk thresholds, and that retreatment was a viable option when pesticide levels decayed to approximately 10% of the initial treatment rate;
- Identification and evaluation of possible strategies for non-destructive measurement of permethrin on military uniforms, including x-ray fluorescence, UV fluorescence, and IR reflectance;
- Theoretical and empirical demonstration, for the first time, that reflected IR scanners can measure permethrin on fabrics in general and on military uniforms in particular, at relevant concentrations, and preliminary definition of the limits of detection and limits of quantitation for this unique technology;
- Initiation of evaluation of whether this technology might work for evaluation of other pesticides on other fabrics, including mosquito nets, at high sensitivity and low cost;
- Theoretical demonstration that UV fluorescence scanners may also be a cost-effective tool for non-destructive sampling, and collaboration with an instrument designer on possible prototype development.

Retention of Registration for Resmethrin, Temephos, etc.

IR-4 review of public documents identified a set of vector control products facing regulatory and data requirements for EPA Reregistration and Registration Review, which could result in their loss from the toolbox. Discussions with AFPMB, EPA, the American Mosquito Control Association (AMCA), the federal Public Health Pesticides Consortium, and other vector control experts have indicated that the loss of registration of some of these products, which do not have comparable replacements, would have significant negative consequences for the military and/or other vector control personnel. Given the limited number of effective vector control tools, regulatory support for these products has been an intense-activity area for the IR-4 PHP Program. Since the IR-4 PHP Program was initiated, all products based on temephos, resmethrin, the allethrin, Lagenidium, and potentially other PHP AI's have faced cancellation, as well as many of the military-used products based on malathion, all due to expensive new data requirements for materials with relatively small markets and a low return on investment for commercial manufacturers. IR-4 has collaborated closely with EPA, the registrants, and military and other pesticide users to prepare, present, and negotiate a low-cost data submittal package for resmethrin is helping prepare a similar package for temephos, based largely on minor use waivers arguments and "bridging" arguments from data on similar materials.

We have also worked with these stake-holders on reducing the reregistration data costs for malathion products, and potentially other useful materials, by helping negotiate an agreement that EPA will accept non-GLP, pre-existing data on product efficacy where it is available and of high quality. IR-4 initiated a discussion on whether the existing EPA Guidelines for efficacy studies with mosquitocides should be revisited, but instead collaborated with EPA on their broader new Product Performance Rule, which will govern interpretation on these and many other sets of Guidelines, to help ensure that it allows and encourages a comprehensive vector control toolbox.

Military medical entomologists have indicated that a loss of temephos registration would be difficult to accept, and therefore IR-4 has been forming a formal task force to develop the minimum required data on product metabolism to prolong the registration of this material.

Strategic Planning for Currently Registered Chemicals and Products

While neither resmethrin nor temephos is a high volume product for the military at the moment, it has seemed appropriate to support the general principles that 1) a complete tool box is essential to protect against future contingencies, including deployments and possible changing conditions at home, as well as current needs; and 2) vector control products should be removed from service only when there is evidence of unreasonable harm or risk associated with their use, not solely because of a lack of funding to demonstrate their safety in light of new testing requirements. To help structure the response of military and other vector control staff when future data requirements are imposed on existing chemical control tools, the IR-4 PHP Program initiated a process similar to the development of an USDA Pest Management Strategic Plan. Here, support was provided by USDA's Office of Pest Management Policy, EPA, CDC, AMCA, and a number of military vector control experts. After recent discussions with the EPA Pesticide Reevaluation Division and the Environmental Fate and Effects Division, IR-4 activities are continuing in five areas:

- Completion of an updated report, effective June 2013, of the regulatory status of all PHP's active in the U.S. (attached as an appendix to this report);
- Development with AMCA, CDC, and other vector control personnel of a questionnaire on mosquito adulticide use practices;
- Evaluation and preliminary development of a survey tool adding geographic specificity to the use patterns, to better calibrate models of endangered species exposure to mosquitocides;

- Provision of workshops on mosquitocide drift and deposition for EFED staff, to allow more fruitful discussion of possibly useful and needed label changes to limit potential impacts while allowing effective vector control; and
- Discussions with EFED on the possible use of probabilistic methods for Tier II evaluations of cumulative foliar deposition of mosquitocides following repeated applications under varying wind conditions.

C. Preliminary / Supplemental Activities with New Materials and/or Use Patterns

The IR-4 PHP Program has provided preliminary regulatory support for a number of new materials or products developed through DWFP or identified by AFPMB staff as military priorities, both through facilitating general policy level negotiations with EPA and other regulators, and through discussions and preliminary submittals on specific potential pesticide products. While regulatory progress on some of the new products has been slow due to incomplete intellectual property, formulation, or other product development requirements, significant initial regulatory steps have been taken, and a number of projects could see the initiation or expansion of formal regulatory processes during the next funding cycle.

Lethal Ovitrap

A vector control priority identified by AFPMB staff has been the development and registration of effective tools against container-breeding mosquitoes such as *Aedes aegypti* and *Aedes albopictus*. In addition to the work on the IGR Pyriproxyfen discussed above, the IR-4 PHP Program has been actively involved in efforts to develop some form of lethal ovitrap to work against these vectors. To date, negotiations with the patent holders, the licensee, and regulators helped identify regulatory needs and some key fabrication issues, and helped facilitate experimental use during a dengue outbreak in Florida. Objectives for the future could include EUP's and regulatory submittals. The licensee of the Army-patented lethal ovitrap has outside consultant assistance with regulatory work at this time, but IR-4 can assist again in the future as needed.

Rodent Feed-through Pesticides vs. Sandflies

Another vector control priority identified in meetings with AFPMB staff is effective control tools against sand flies, and IR-4 has assisted on a number of projects by DWFP and other researchers

in this area. One possibility is the use of novaluron, imidacloprid, or another insecticide as a rodent pass-through against sand flies. Although several years of experimental work have taken place on this concept since the initiation of the DWFP, none of the work to date has required an EUP. As these projects scale up their experiments, IR-4 has been negotiating with researchers and EPA regarding EUP's for field work, including both components overseas and some potentially within the U.S., and we are able to help as requested.

U.S. Registration of Aqueous Adulticide Formulations

IR-4 has been approached by Bayer for regulatory support for registration of an aqueous deltamethrin formulation for area-wide control, which could be useful against mosquitoes as well as sand flies. In addition, IR-4 has had preliminary discussions with Cheminova about regulatory support for a pending aqueous formulation of malathion for PHP use.

Nets Treated with Novel or Multiple Insecticides and/or Repellents

A high priority vector control need identified in discussions with AFPMB staff is effective tools against pyrethroid-resistant mosquitoes, especially in areas with malaria transmission.

The IR-4 PHP Program has led an effort to review the potential utility of nets treated with multiple insecticides and/or repellents as a strategy to improve product efficacy and manage pesticide resistance. As an initial step, IR-4 PHP staff is translating several relevant reports and other documents from French and is negotiating with authors and publishers to provide these to interested parties, including the AFPMB Literature Retrieval System. In addition, IR-4 has extensively assisted the Innovative Vector Control Consortium (IVCC) with development of Quality Assurance mechanisms for evaluating field efficacy of novel products to address this need. Other specific product concepts which have been discussed with AFPMB staff and which may need regulatory support in coming years from IR-4 include the use of nets or other fabrics treated with pirimiphos-methyl, novel pyrethroids, Chlorfenapyr, and/or low-mammalian-toxicity carbamate-like molecules. Finally, we have initiated discussions with researchers at the Rutgers Center for Vector-borne Diseases about potential collaboration on novel approaches to researching the behavior of mosquitoes encountering insecticide-treated nets.

Novel Topical Repellents

DWFP-funded and CDC researchers have identified a number of promising new repellents, including nootkatone, callicarpenal, chromene derivative 131-1, etc., effective against mosquitoes, ticks, and/or other arthropod vectors. While IR-4 has provided regulatory

consultations to the developers, it is not clear at this time which of any of these will require regulatory support from IR-4 to be available for military use and/or civilian applications, but we have the capacity to assist as needed with any of these biopesticide materials or novel synthetic repellents. We have provided limited regulatory support for several developers of novel products, primarily types of biopesticides, to control bed bugs, which, though not true vectors of pathogenic diseases, could be significant pests in military facilities as well as in civilian sites.

Genetic Strategies for Vector Control

A set of projects with huge long-term potential for control of many vectors has focused on the development and registration of RNAi-based pesticides or other highly selective products. RNAi products are distinct from either the conventional or biopesticides typically registered by EPA and will require a novel regulatory regime to evaluate their safety. IR-4 previously introduced RNAi technology to EPA as a tool for fighting a virus in honey bees, but a determination was made at the time that FDA had jurisdiction over that application. Recently, DWFP and USDA approached IR-4 for possible representation to EPA of some regulatory actions covering this novel approach to highly selective pest control, and we have had extensive discussions with EPA staff, as well as several teams developing tools based on this technology against a range of pests. We expect that coming years will see the development of basic regulatory paradigms and protocols for this class of material, negotiation of specific EUP's, and, eventually, full registration of these products. It is not clear at the moment what IR-4's specific roles will be, but we are available for any DWFP needs in this realm and have staff experienced in presenting RNAi to EPA.

In this area of long-term development of highly selective control technologies, IR-4 has also provided regulatory consultations for developers of mosquito control technologies based on reproductive incompatibility associated with infestation by *Wolbachia* bacteria, on GM (genetically modified) mosquitoes that show mating failures (RIDL), and on GM mosquitoes that resist infestation by malaria plasmodia.

New Uses for Existing Materials

The recent IR-4 and AFPMB review identified several areas where the military could benefit from expanded labeling or other regulatory changes for existing chemical control tools. Specific areas in which IR-4 has supported registrants in regulatory actions include

- Regulatory support for the Florida Flybaiter trap system, which was developed largely with DWFP funding;
- Regulatory support for a proposal to introduce etofenprox as a fabric treatment, potentially including on uniforms, for military uses; and
- Extensive review with AFPMB and APHIS staff of possible solutions to the need for improved aircraft disinsection technologies and products acceptable to EPA.

While specific roles for IR-4 have not been identified to date on several other PHP needs, we have discussed and are able to help as needed with regulatory support and, depending on funding, possible data collection in support of the following activities:

- military use of spinosad larvicides;
- military use of DUET (prallethrin + sumithrin) vs. adult mosquitoes and/or sand flies;
- military use of Agnique monomolecular film vs. larval mosquitoes;
- alternative topical repellents, including materials currently on the 25b list but requiring formal registration for military use; and
- next-generation “carbamate-like” products with novel toxicity patterns and possible exclusion from the n-methyl-carbamate risk cup.

Activities and Outcomes – Program Development

In addition to activities that have directly supported specific product development, the IR-4 Project made substantial progress towards the objectives of the cooperative agreement in several broad areas of program development, capacity-building for partners, database development / data management, communications, and priority setting.

The IR-4 Public Health Pesticides Program

The funding from ARS and DWFP was instrumental in allowing IR-4 to initiate a Public Health Pesticides Program to complement existing food, ornamental, and biopesticide programs. IR-4 hired, Dr. Karl Malamud-Roam, who began as PHP Program Manager in September 2009. IR-4 also hired a Research Assistant to support the PHP Manager. In addition, while the IR-4 PHP Program has had primary responsibility for implementation of the tasks in the cooperative agreement, IR-4 has provided professional staff collaborators from other Programs as well as support staff and facilities to provide the institutional basis for PHP product development and registration support.

Major general purpose activities of the IR-4 PHP Program have included

- Development of a portfolio of potential product development projects and collaboration with DWFP and other representatives of the vector control user community, EPA staff, and registrants to establish action priorities.
- Initiation and facilitation of a series of meetings with DoD personnel, EPA, and IR-4 to investigate the policy implications of military pesticide registration needs, leading to formation of an interagency workgroup to ensure appropriate follow-up.
- Development of a PHP project management database, flowcharts, and a checklist of necessary and required tasks to achieve registration and availability of PHP products to the military and civilian stakeholders.
- Development of a comprehensive inventory and a unique searchable database of PHP materials (<http://ir4.rutgers.edu/PublicHealth/publichealthDB.cfm>), with detailed information on product identification and specification, efficacy vs. public health pests, and regulatory status, among other attributes. This database complements other databases on vectors and vector control tools.
- Active interaction, including initiation of meetings, with the major PHP registrants, user groups, and NGO's (e.g. Gates Foundation, WHO) to identify needs and opportunities for new products, and to identify gaps in the data required for regulatory support of existing PHP products.

Communications, Collaboration, and Capacity Building

The IR-4 PHP Program has in the last five years become an active and well-respected participant in many U.S. and international vector control technical work groups, with a strong commitment to information exchange within the limits of business confidentiality, collaboration in improving vector control methods, and building the capacity of partners. Specific examples of IR-4 PHP activities and accomplishments in this realm include

- Establishing an EPA Company Number for the Armed Forces Pest Management Board, allowing direct submittal of regulatory requests of interest to the military;
- Successfully petitioning EPA that submittals from the AFPMB will be exempt from PRIA regulatory review fees;
- Established a mechanism by which IR-4 could formally act as Agent for the AFPMB or other military entities or their research or commercial partners when this is required;

- Established the Rutgers Center for Vector Biology as an EPA-recognized Pesticide Producing Establishment, allowing for production of novel pesticide products for experimental purposes;
- Lectured on project management and pesticide innovation practices in annual reviews and other meetings of DWFP participating scientists;
- Actively participated in meetings with the ARS Office of Technology Transfer to help clarify the best methods of intellectual property protection for DWFP collaborators and other ARS PHP developers;
- Consulted extensively with the Innovative Vector Control Consortium on GLP methods in international studies, and provided >100 examples of SOP's for data collection, analysis, and management in pesticide studies;
- Led a series of workshops on mosquitocide drift and deposition for EPA;
- Collaborated in Roll Back Malaria Vector Control Working Group (VCWG) work streams, including preparation of a review on larval mosquito control for malaria management;
- Collaborated with the Stockholm Convention staff on evaluation of alternatives to DDT;
- Wrote and disseminated a report for USAID on multi-component treated nets for protection from pyrethroid-resistant mosquitoes.

The PHP Database(s) and Inventory

The IR-4 PHP Program has developed and disseminated a comprehensive [Inventory of Public Health Pesticides](#) with global scope and an associated online PHP Database, with detailed information on over 600 current or potential PHP's. These print and digital documents focus on identification and specification of materials active against mosquitoes, ticks, and other key public health pests; compilation of data on efficacy of both existing and potentially useful materials; and a review of the regulatory status of these materials in the U.S. and elsewhere.

Product / Project Prioritization

The IR-4 PHP staff has undertaken a series of actions to help set priorities both for IR-4 action, and also to help guide the priority-setting of collaborating entities. Defining high activity priorities within the realm of potential materials and activities requires frequent collaboration with military staff, both inside and outside DWFP, and other vector control experts, to identify 1) key unmet public health and veterinary needs; 2) product use patterns where existing strategies are relatively ineffective or at risk (e.g. from resistance development); and 3) opportunities in which success is most likely in a reasonable time period.

IR-4 has been a key facilitator and participant in ongoing focused discussions and work group documents seeking to define the priorities of the U.S. military in vector control research and development, including formal participation in the recently formed Vector Control Integrated Product Development (IPD) Team.

For the larger audience of vector control practitioners, the IR-4 PHP Program has led an effort to define a long-term plan for provision and retention of an adequate toolbox of materials with EPA registration for chemical control of mosquitoes, as EPA implements requirements for new data requirements for pesticides. Specific actions include

- Compilation and maintenance of a unique database on the current regulatory status of all pesticides registered for use vs. mosquitoes, ticks, sand flies, fleas, and bed bugs in the U.S., including the timing of data call-in's (DCI's) under EPA's registration review process;
- Developed a White Paper, based on USDA Guidelines for Pest Management Strategic Plans, for mosquito control in the U.S., defining the scope and significance of the pest problem;
- Led initial workshops with American Mosquito Control Association, AFPMB, CDC, and others to articulate common priorities for research, education, and regulatory assistance on mosquitocides.

In addition, IR-4 PHP staff have been actively involved in crafting the National Strategy document for community-based control of tick-borne diseases, working with EPA, CDC, and others, including helping organize two national conferences on the topic.

