A. COVER PAGE

Project Title: Preventing Lyme Disease Exposure Among Outdoor Workers	
Grant Number: 5R01OH010791-04	**Project/Grant Period:** 09/01/2015 - 08/31/2019
Reporting Period: 09/01/2018 - 08/31/2019	**Requested Budget Period:** 09/01/2018 - 08/31/2019
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Program Director/Principal Investigator Information: THOMAS N MATHER , BS MS PHD PHD **Phone Number:** 401-874-5616 **Email:** tmather@uri.edu	**Recipient Organization:** UNIVERSITY OF RHODE ISLAND UNIVERSITY OF RHODE ISLAND RESEARCH OFFICE KINGSTON, RI 028810811 **DUNS:** 144017188 **UEI:** CJDNG9D14MW7 **EIN:** 1223011455A1 **RECIPIENT ID:**
Change of Contact PD/PI: NA	
Administrative Official: THEODORE MYATT 70 Lower College Road Kingston, RI 02881 **Phone number:** 401-874-2636 **Email:** tedmyatt@mail.uri.edu	**Signing Official:** FRANCA CIRELLI RESEARCH OFFICE 70 LOWER COLLEGE ROAD, SUITE 2 KINGSTON, RI 028810811 **Phone number:** 401-874-5891 **Email:** franca@uri.edu
Human Subjects: NA	**Vertebrate Animals:** NA
hESC: No	**Inventions/Patents:** No

B. ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Outdoor workers are at high-risk for tick-borne diseases, especially Lyme disease (1-5). They also are at risk for other tick-borne diseases such as anaplasmosis, babesiosis, spotted fever rickettsioses, and ehrlichioses (2-6). NIOSH recommends that at-risk outdoor workers self-apply permethrin to their clothing, but adherence to this effective personal tick bite protection measure is poor (6-8).

Long-lasting permethrin-impregnated (LLPI) clothing can significantly reduce the incidence of tick bites among outdoor workers (9, 10). In a double-blind randomized controlled trial (RCT), funded by our previous NIOSH/CDC grant, we showed that LLPI uniforms reduced the incidence of work-related tick bites among North Carolina forestry, parks, and wildlife workers by more than 80% in the first year of follow-up (9). Almost all of the tick bites in this study were from Lone Star ticks (Amblyomma americanum). In this follow-up study, we ask 3 previously unanswered questions: 1) Do LLPI clothing protect against blacklegged ticks, the vector for Lyme disease, babesiosis and anaplasmosis, as well as against the Lone Star tick? 2) What levels of permethrin and its metabolites are absorbed, and are they potentially toxic? 3) Why did the LLPI clothing in our previous study lose efficacy after a year?

The specific aims of this study are to:

1. Evaluate the effectiveness of LLPI clothing in preventing tick bites among outdoor workers in Lyme endemic areas. Participants will be randomized in a double-blind manner into one of two study arms: 1) Treatment (work clothing factory-impregnated with long-lasting permethrin) and 2) Control (sham-treated clothing). Subjects will be followed for two consecutive tick seasons (March through November) and asked to record all tick bites, collect any attached ticks and report all febrile illnesses or rashes to the study physician. Blood will be drawn at enrollment, after each tick season and in the event of a suspected tick-borne illness. The incidence of tick bites, positive serologies and tick-borne illnesses will be compared between arms for each year of follow-up. The prevalence of infection among ticks removed from subjects will be used to quantify the potential for exposure to tick-borne pathogens.

2. Measure the urine levels of permethrin metabolites in study subjects. Urine samples will be obtained from a random subset of study subjects at 3 time points: prior to the study, after 3 weeks, and after one year of study participation. Urine levels of permethrin metabolites, corrected for creatinine concentration, will be measured by gas chromatography (GC). Levels will be compared between subjects in the two arms and with known benchmarks for toxicity.

3. Measure the loss over time of knockdown activity against ticks and of permethrin in LLPI clothing. In order to understand why LLPI clothing lost effectiveness after 1 year, we will compare new uniforms with uniforms from workers after 1 and 2 years of wear and measure knockdown capacity against Ixodes scapularis and Amblyomma americanum ticks. After knockdown capacity is measured, we will assess fabric permethrin concentrations by GC.

The results of this study have implications for a large number of people working in many different occupations; there are >400,000 forest and conservation workers, recreation workers, and loggers in the US and >1.5 million vegetation management and utility line workers (http://www.bls.gov/), many of whom are at high risk for tick-borne diseases. This study should determine definitively whether LLPI uniforms effectively and safely protect a wide range of at-risk outdoor workers from tick-borne diseases.

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File Uploaded : Final Progress Report for RPPR.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

NOTHING TO REPORT

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

Through publications and tick-bite prevention safety videos on YouTube

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Not Applicable

PROGRESS REPORT

Specific Aim 1. Evaluate the effectiveness of LLPI clothing in preventing tick bites among outdoor workers in Lyme endemic areas.

Mitchell, C, M Dyer, F Lin, N Bowman, T Mather, S Meshnick. 2020. Protective effectiveness of long-lasting permethrin impregnated clothing against tick bites in an endemic Lyme Disease setting: A randomized control trial among outdoor workers. **J Med Entomol** 57:1532-1538 doi.org/10.1093/jme/tjaa061

Summary. A 2-year randomized, placebo-controlled, double-blinded trial that included 82 outdoor workers in Rhode Island and southern Massachusetts showed that factory-impregnated clothing significantly reduced tick bites by 65% in the first study year and by 50% in the second year for a two-year protective effect of 58%. No significant difference in other tick bite prevention method utilization occurred between treatment and control groups, and no treatment-related adverse outcomes were reported. Conclusions: Factory permethrin impregnation of clothing is safe and effective for the prevention of tick bites among outdoor workers whose primary exposure is to blacklegged ticks in the northeastern United States.

Additionally, we produced 4 tick safety videos available to the community on YouTube targeting outdoor workers; these videos were developed initially as part of our participant recruitment plan but going forward are intended to build interest and confidence in taking TickSmart actions to prevent tick bites, including the regular practice of wearing long-lasting permethrin treated clothes.

- Video 1 (https://www.kollaborate.tv/link?id=58b459f7d8c8c);
- Video 2 (https://www.kollaborate.tv/link?id=58b4594a82802);
- Video 3 (https://www.kollaborate.tv/link?id=58b45887d28e8);
- Video 4 (https://www.youtube.com/watch?v=cRpaYjGW0zY);

(NOTE: video links broke during pandemic and video files need to be updated and re-posted—still in progress)

Specific Aims 2 & 3. Measure the urine levels of permethrin metabolites in study subjects, and loss of permethrin in LLPI clothing and knockdown activity against ticks over time

Sullivan, KM, A Poffley, S Funkhouser, J Driver, J Ross, M Ospina, AM Calafat, CB Beard, A White, J Balanay, S Richards, M Dyer, TN Mather, S Meshnick. 2019. Bioabsorption and effectiveness of long-lasting permethrin-treated uniforms over three months among North Carolina outdoor workers. **Parasites Vectors** 12:52-61.

Summary. In a pilot study, we recruited 13 state and county park employees from North Carolina to wear LLPI uniforms for three months during the summer. We collected spot urine samples for biomonitoring of permethrin metabolites at one week, one month and three months after first use of the LLPI uniform. Following three months of wear, we collected pants and socks and analyzed them for permethrin content and mortality to ticks and mosquitoes. Bioactive amounts of permethrin remained in all clothing swatches tested, although there was great variability. Tick mortality was high, with 78% of pant and 88% of sock swatches having mean knockdown percentages ≥ 85%. In contrast, mosquito mortality was low. Over the study period, the absorbed dosage of permethrin averaged < 4 µg/kg/d of body weight based on measurements of three metabolites. LLPI clothing retained permethrin and bioactivity against ticks after three months of use in real-world conditions. The estimated absorbed dosage of permethrin was well below the U.S. EPA level of concern, suggesting that LLPI clothing can be used safely by outdoor workers for tick bite prevention.

Richards, S.L., J. Driver, M.C. Dyer, T.N. Mather, S. Funkhouser, C. Mitchell, J. Balanay, A. White, S. Meshnick. 2022. Assessing durability and safety of permethrin impregnated uniforms used by outdoor workers to prevent tick bites after one year of use. **J Med Entomol**. 59:615-622.

Summary: Long lasting permethrin-impregnated (LLPI) clothing can retain permethrin and repel ticks for up to three months and without exceeding EPA-approved safe levels in human blood. However, little is known about longer term effects of wearing LLPI clothing. Here, permethrin content was measured in new forester pants soon after initial impregnation (Insect Shield®) and again one year later after being repeatedly worn by foresters in the field. Urine samples were collected from foresters for biomonitoring of permethrin metabolites at multiple time intervals (pre-use, one month, three to four months and one-year post-use). Lethality against ticks was measured in clothing after one year of wear by foresters. Furthermore, to test potential variability in permethrin impregnation of different batches of clothing, separate sets of clothing were anonymously sent to Insect Shield® for permethrin treatment over a period of three months and permethrin was quantified by investigators. Results showed that, after one year of wear, 33% of participants' pants had no measurable permethrin and permethrin content and tick mortality varied significantly ($P < 0.05$) between participants' clothing. Only two of the participants' clothing resulted in > 60% tick mortality after one year of wear. Significant differences ($P < 0.05$) were observed in 3-PBA and trans-DCCA, but not cis-DCCA metabolites in participants over the four measured time points and were higher than baseline levels in the United States population. This study provides practical information on the safety (measured by urinary metabolites) over time of LLPI clothing. It also provides snapshots (pre-washing and after one year of wear) of effectiveness of LLPI clothing as personal protective equipment against ticks for outdoor workers.

C. PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

Yes

Publications Reported for this Reporting Period

Public Access Compliance	Citation
N/A: Not NIH Funded	Sullivan KM, Poffley A, Funkhouser S, Driver J, Ross J, Ospina M, Calafat AM, Beard CB, White A, Balanay JA, Richards S, Dyer M, Mather TN, Meshnick S. Bioabsorption and effectiveness of long-lasting permethrin-treated uniforms over three months among North Carolina outdoor workers. Parasites & vectors. 2019 January 23;12(1):52. PubMed PMID: 30674346; PubMed Central PMCID: PMC6343280; DOI: 10.1186/s13071-019-3314-1.
N/A: Not NIH Funded	Sullivan KM, Poffley A, Funkhouser S, Driver J, Ross J, Ospina M, Calafat AM, Beard CB, White A, Balanay JA, Richards S, Dyer M, Mather TN, Meshnick S. Bioabsorption and effectiveness of long-lasting permethrin-treated uniforms over three months among North Carolina outdoor workers. Parasites & vectors. 2019 January 23;12(1):52. PubMed PMID: 30674346; PubMed Central PMCID: PMC6343280; DOI: 10.1186/s13071-019-3314-1.
N/A: Not NIH Funded	Mitchell C, Dyer M, Lin FC, Bowman N, Mather T, Meshnick S. Protective Effectiveness of Long-Lasting Permethrin Impregnated Clothing Against Tick Bites in an Endemic Lyme Disease Setting: A Randomized Control Trial Among Outdoor Workers. Journal of medical entomology. 2020 September 7;57(5):1532-1538. PubMed PMID: 32277701; DOI: 10.1093/jme/tjaa061.
N/A: Not NIH Funded	Mitchell C, Dyer M, Lin FC, Bowman N, Mather T, Meshnick S. Protective Effectiveness of Long-Lasting Permethrin Impregnated Clothing Against Tick Bites in an Endemic Lyme Disease Setting: A Randomized Control Trial Among Outdoor Workers. Journal of medical entomology. 2020 September 7;57(5):1532-1538. PubMed PMID: 32277701; DOI: 10.1093/jme/tjaa061.
N/A: Not NIH Funded	Richards SL, Driver J, Dyer MC, Mather TN, Funkhouser S, Mitchell C, Anne Balanay J, White A, Meshnick S. Assessing Durability and Safety of Permethrin Impregnated Uniforms Used by Outdoor Workers to Prevent Tick Bites after One Year of Use. Journal of medical entomology. 2022 March 16;59(2):615-622. PubMed PMID: 34958094; PubMed Central PMCID: PMC9272190; DOI: 10.1093/jme/tjab216.
N/A: Not NIH Funded	Richards SL, Driver J, Dyer MC, Mather TN, Funkhouser S, Mitchell C, Anne Balanay J, White A, Meshnick S. Assessing Durability and Safety of Permethrin Impregnated Uniforms Used by Outdoor Workers to Prevent Tick Bites after One Year of Use. Journal of medical entomology. 2022 March 16;59(2):615-622. PubMed PMID: 34958094; PubMed Central PMCID: PMC9272190; DOI: 10.1093/jme/tjab216.

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

NOTHING TO REPORT

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period? No

If yes, has this information been previously provided to the PHS or to the official responsible for patent matters at the grantee organization? No

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Category	Explanation
Audio or video	Links to 4 tick prevention education videos (reported previously) were broken during pandemic. We are currently working with videographer to re-establish these final products with new links and to host them on our TickEncounter YouTube page.

D. PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
TMATHER	Y	Mather, Thomas N	BS,MS,PHD,PHD	PD/PI	0.0	0.0	1.0			NA
STEVE_MESHNICK	Y	Meshnick, Steven Richard	AB,PHD,MD	PD/PI	0.0	0.0	1.5			NA
	N	Dyer, Megan	MS	Study Manager	12.0	0.0	0.0			NA
	N	Richards, Stephanie	PhD	Co-Investigator	0.0	0.0	1.0			NA

Glossary of acronyms:
S/K - Senior/Key
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RS - Reentry Supplement
DS - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Not Applicable

D.2.b New Senior/Key Personnel

Not Applicable

D.2.c Changes in Other Support

Not Applicable

D.2.d New Other Significant Contributors

Not Applicable

D.2.e Multi-PI (MPI) Leadership Plan

Not Applicable

E. IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?

Not Applicable

E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?

Tick-bite prevention education was provided to all participants and organizations from which participants were recruited.
The randomized case-control format of the trial helped demonstrate the benefit to users of wearing long-lasting permethrin treated clothing to prevent tick-bites.
The studies provided documented support for employers and employees of outdoor worker professions to offer long-lasting permethrin treated clothing as personal protective equipment (PPE).
The study to assess longevity of permethrin activity in clothing provides new guidance on the need for annual re-charge of treatment to provide optimum protection against tick-bites.
Tick-bite prevention education videos were very popular (thousands of views) on social media channels.

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

Not Applicable

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?

NOTHING TO REPORT

G. SPECIAL REPORTING REQUIREMENTS SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

Not Applicable

G.4.b Inclusion Enrollment Data

NOTHING TO REPORT

G.4.c ClinicalTrials.gov

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

NOT APPLICABLE

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT
No foreign component
G.10 ESTIMATED UNOBLIGATED BALANCE
Not Applicable
G.11 PROGRAM INCOME
Not Applicable
G.12 F&A COSTS
Not Applicable

I. OUTCOMES

I.1 What were the outcomes of the award?

This study provided documentation and support for adding long-lasting permethrin treated clothing to the list of personal protective equipment for outdoor workers potentially exposed to disease-carrying ticks. Studies examined the short- (3 months) and longer-term (1 year) human exposure risk of wearing long-lasting permethrin treated clothing. Studies also demonstrated the loss of tick repellent efficacy after one year of use, and provides justification for renewing treatment each year clothing will be used.