Environment and Natural Resources Trust Fund
2018 Request for Proposals (RFP)

Project Title: **ENRTF ID: 039-B**

Defining Minnesota's Environmental Antibiotic and Antibiotic Resistance Footprint

Category: B. Water Resources

Total Project Budget: $ 921,584

Proposed Project Time Period for the Funding Requested: 3 years, July 2018 to June 2021

Summary:

We will quantify and map antibiotic and antibiotic resistance gene contamination in Minnesota waters and soils and identify locations in need of mitigation to protect environmental, human, and animal health.

Name: Randall Singer

Sponsoring Organization: U of MN

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Saint Paul MN 55108

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Web Address

Location

Region: Statewide

County Name: Statewide

City / Township:

Alternate Text for Visual:

Antibiotics, antibiotic resistant bacteria (ARB) and antibiotic resistance genes (ARG) can contaminate Minnesota's natural environment from a diversity of sources. As shown in the image, this project will build a tool for predicting environmental sites within Minnesota that are at risk of being contaminated with antibiotics and ARG. Steps include: 1) estimate the amount of antibiotic used in humans, animals and crops within Minnesota, 2) create a state map depicting areas of highest impact and loading, 3) use this antibiotic 'footprint' to determine sites for quantifying antibiotics and ARG in sediment and soil samples throughout the state, and 4) use the field data to validate and refine a geospatial model to improve its accuracy. Outcomes include: 1) Develop a tool to predict environmental contamination, and 2) Use the model to design risk-based mitigation strategies to protect health.

_____ Funding Priorities	_____ Multiple Benefits	_____ Outcomes	_____ Knowledge Base
_____ Extent of Impact	_____ Innovation	_____ Scientific/Tech Basis	_____ Urgency
_____ Capacity Readiness	_____ Leverage	_____ TOTAL	_____%

PROJECT TITLE: Defining Minnesota's Environmental Antibiotic and Antibiotic Resistance Footprint

I. PROJECT STATEMENT

We will quantify and map antibiotic and antibiotic resistance gene (ARG) contamination in Minnesota waters and soils and then use this information to identify locations in need of mitigation to protect environmental, human, and animal health. The natural environment plays a key role in the emergence and spread of antibiotic resistance (AR). Watersheds, in particular, are recipients of antibiotics, antibiotic-resistant bacteria, and ARG released from human wastewater treatment plants, animal agriculture and aquaculture, crop production, and pharmaceutical manufacturing plants. The overall project goal is to mitigate effects of AR in Minnesota's natural environment on human, animal, and environmental health by:

- Developing an "antibiotic footprint" map of Minnesota's natural environment that predicts areas where antibiotics, resistant bacteria, and ARG are most likely to accumulate
- Quantifying concentrations of antibiotics and ARG at sites variably impacted by anthropogenic activities (ranging from pristine sites to areas with high impact)
- Validating the prediction map with the data collected across the state to develop a risk-based surveillance system that will aid in statewide AR mitigation efforts in the natural environment

We hypothesize that a predictive model developed for the state of Minnesota will identify "hotspots" for antibiotics, resistant bacteria, and ARG accumulation in the natural environment. This project will leverage past ENRTF-funded studies by our team members which have detected antibiotics and ARG in Minnesota lakes and rivers. The proposed work, which will produce tools for predicting areas sensitive to AR and for aiding in mitigation efforts, has never been attempted anywhere in the world and will place Minnesota as a leader in environmental antibiotic and AR detection, prevention, and response.

AR is one of the greatest public health challenges of our time. According to the Centers for Disease Control and Prevention, approximately 2 million people in the U.S. develop antibiotic-resistant infections each year, with more than 23,000 deaths. Our natural environment presents a reservoir for accumulated antibiotics and ARG that must be understood to minimize human health and ecological impact. Resistance genes of concern to human health have already been identified in Minnesota and in other U.S. waters and soil sediments, but it is unclear how these findings relate to modifiable factors (e.g., antibiotic prescribing, waste disposal) and adverse health outcomes. This proposal describes a comprehensive approach to the problem, linking human activity, environmental adulteration, and potential health threats.

In Minnesota, human, animal, and environmental health professionals have joined as the Minnesota One Health Antibiotic Stewardship Collaborative (http://www.health.state.mn.us/onehealthabx/), with a mission of promoting appropriate antibiotic use to reduce impacts of antibiotic-resistant pathogens on human, animal, and environmental health. As pledged in the *Minnesota Antibiotic Stewardship Five-Year Strategic Plan*, one goal of this nationally unique Collaborative is to understand the "footprint" of our collective antibiotic use on the natural environment and human health. Collaborative engagement ensures the benefits of sector-specific insight during project execution as well as dissemination of results to hundreds of stakeholders statewide.

II. PROJECT ACTIVITIES AND OUTCOMES

Activity 1: Geospatial modeling of Minnesota's "antibiotic footprint" **Budget: $ 358,936**

Antibiotic use in Minnesota's medical and agricultural sectors will be mapped to create an environmental "antibiotic footprint". Data regarding the persistence and spread of antibiotic chemicals in the environment will be added to this dynamic map. This activity will inform environmental sampling in Activities 2 and 3, and after validation with the collected data, will serve as the basis for a functional risk-based surveillance tool.

Outcome	Completion Date
1. Estimation and mapping of antibiotic usage in Minnesota	6/30/19

2. Map-based modeling of the environmental fate of antibiotic compounds released from human and animal sources ("antibiotic footprint")	12/31/19
3. Comparison of model-predicted environmental "hotspots" of antibiotics and ARG with data collected during field sampling (Activities 2 and 3)	6/30/20
4. Use of "antibiotic footprint" to develop a risk-based surveillance tool and to identify opportunities for risk mitigation in medical, agricultural, and disposal sectors.	6/30/21

Activity 2: Measure antibiotic concentrations in Minnesota's environment **Budget: $ 219,040**

Widely used in medicine and agriculture, antibiotic chemicals accumulate in Minnesota's waters and soils. We will modify a method (developed by past ENTRF funding) to measure 30 antibiotic compounds in lake sediment for use on soil and water. High and low-risk sampling sites will be chosen based on Activity 1 mapping.

Outcome	Completion Date
1. Collection of soil and water samples	10/31/19
2. Antibiotic quantification in water samples	6/30/20
3. Antibiotic quantification in soil samples	6/30/21

Activity 3: Quantify antibiotic resistance genes in Minnesota's environment **Budget: $ 343,608**

Antibiotic use in human and animal health is likely associated with environmental AR and ARG. Past ENTRF funding led to methods to quantify 40 ARG in environmental samples. Sampling sites will be based on Activity 1.

Outcome	Completion Date
1. Collect soil, water, and sediment samples for quantification of ARG	8/31/20
2. DNA extraction/purification	12/31/20
3. Quantify ARG via a novel microfluidic method developed at UMN	5/1/21

III. PROJECT STRATEGY

A. Project Team/Partners The project team will be led by Randall Singer (University of Minnesota; Dept. of Veterinary Biomedical Sciences), Timothy LaPara (UMN; Dept. of Civil, Environmental, and Geo-Engineering), William Arnold (UMN; CEGE), Amanda Beaudoin (MN Dept. of Health; Executive Office), and Kristine Wammer (Univ. of St. Thomas; Dept. of Chemistry). Dr. Singer is an expert on AR in humans and animals and the use of antibiotics in animal agriculture. Dr. LaPara is an expert on bacteria and ARG in the environment, particularly in areas affected by municipal wastewater discharges. Dr. Arnold is an expert on environmental fate of pharmaceutical compounds, including antibiotics. Dr. Beaudoin is an expert on antibiotic use and resistance in humans and animals and directs the One Health Antibiotic Stewardship Collaborative. Dr. Wammer is an expert in environmental chemistry and antibiotic resistance in the environment. The team has ongoing, productive relationships with partners from government agencies, medical and agricultural industry, and academia throughout Minnesota.

B. Project Impact and Long-Term Strategy Our project will define relationships between essential activities (e.g., healthcare, wastewater treatment, animal agriculture) and the maintenance and proliferation of AR in Minnesota's natural environment. The long-term goal is to develop scientific and risk-based guidance in human, animal, and environmental health for the mitigation of AR in the natural environment. The "footprint" methodology will also be useful to explore other biologically active chemicals in Minnesota's environment, such as hormones and endocrine disruptors. Results will be shared at local conferences, in open-access scientific publications, by publically available final report, and through the national reach of the Minnesota One Health Antibiotic Stewardship Collaborative.

C. Timeline Requirements The project will be completed over 3 years. Sample collection, chemical analysis, and microbiological analysis take time and will require detailed quality assurance and quality control.

2018 Detailed Project Budget

Project Title: Defining Minnesota's Environmental Antibiotic and Antibiotic Resistance Footprint

IV. TOTAL ENRTF REQUEST BUDGET *3* years

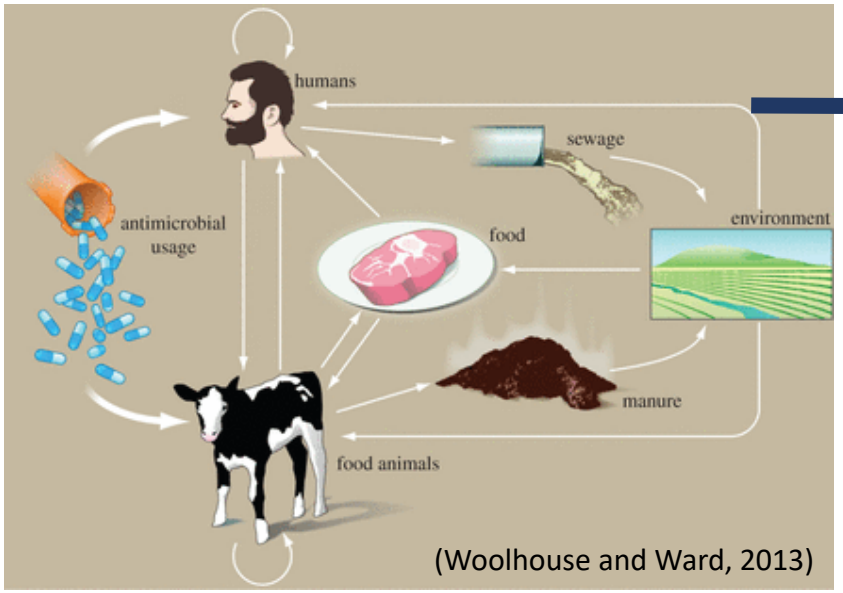
BUDGET ITEM	AMOUNT
Personnel:	
Randall Singer, Project Manager (including 33.5% fringe); 5% FTE years 1-3	$ 33,134
William Arnold, co-Project Manager (including 33.5% fringe); 5% FTE years 1-3	$ 31,822
Timothy LaPara, co-Project Manager (including 33.5% fringe); 5% FTE years 1-3	$ 26,938
Kristine Wammer, co-Project Manager (93% salary, 7% fringe benefits). 8% FTE years 1-3	$ 20,876
Graduate student research assistant in Veterinary Medicine/UMN, data collection and analysis (61% salary, 39% fringe benefits) 50% FTE for years 1, 2 and 3	$ 153,622
Geospatial analyst in Vet Med (82% salary, 18% fringe). 75% FTE to develop and validate the geospatial models for years 1, 2 and 3	$ 162,180
Graduate student research assistant in CEGE/UMN, sample collection, extraction, and analysis (58% salary, 42% fringe benefits) 50% FTE for year 2 and year 3	$ 93,519
Post-doctoral research associate in CEGE/UMN, sample collection, extraction, and analysis (82% salary, 18% fringe benefits) 100% FTE for year 2 and year 3	$ 126,918
Undergraduates at CEGE/UMN to help with sample collection and processing (paid hourly)	$ 42,560
Undergraduates at UST to help with sample collection and processing (paid hourly)	$ 51,515
Professional/Technical/Service Contracts:	$ -
Analytical instrument time at UST	$ 3,000
Analytical instrument time at UMN/Cancer Center	$ 42,500
Analytical instrument time at UMN/UMGC	$ 20,000
Equipment/Tools/Supplies:	
Supplies for sample collection, DNA extraction, and qPCR at UMN	$ 30,000
Supplies for sample collection, DNA extraction, and qPCR at UST	$ 18,000
Supplies for sample collection, extraction, and quantification of antibiotics at UMN	$ 23,000
Travel:	
Travel to collect water and soil samples (vehicle rental, meals, and hotel)	$ 22,500
Travel to attend in-state conferences to disseminate results	$ 6,500
Additional Budget Items:	
Open access publication charges	$ 13,000
TOTAL ENVIRONMENT AND NATURAL RESOURCES TRUST FUND $ REQUEST =	$ 921,584

V. OTHER FUNDS

SOURCE OF FUNDS	AMOUNT	Status
Other Non-State $ To Be Applied To Project During Project Period:	N/A	N/A
Other State $ To Be Applied To Project During Project Period:	N/A	N/A
In-kind Services To Be Applied To Project During Project Period:		*Secured*
Unrecovered F&A associated with research from U of MN (54%)	$ 497,655	
The project manager and co-project managers will put forth in-kind effort	$ 161,715	
Past and Current ENRTF Appropriation:	$ 1,916,000	*Completed*
$302,000 - ENTRF for ML 2007-5L "Pharmaceutical and microbiological pollution in Minnesota's surface waters" (LaPara and Arnold)	$ 1,916	
$254,000 - ENTRF for ML 2010-5F "Evaluation of dioxins in Minnesota lakes" (Arnold)		
$190,000 - ENTRF for ML 2011-5E "Assessment of Minnesota River antibiotic concentrations" (Wammer, LaPara, and Stoll)		
$203,000 - ENTRF for ML 2013-5H "Antibiotics in Minnesota waters - Phase II Mississippi River" (Wammer, LaPara, and Stoll)		
$380,000 - ENTRF for ML 2014-3C "Triclosan impacts on wastewater treatment" (LaPara and Donato)		
$300,000 - ENTRF for ML 2014-3E "Antibiotics and antibiotic resistance genes in Minnesota lakes" (Arnold and LaPara)		
$287,000 - ENTRF for ML 2016-4D "Assessing techniques for eliminating contaminants to protect native fish and mussels" (Wammer, Martinovic-Weigelt, Stoll, Schroeder)		
Other Funding History:	N/A	N/A

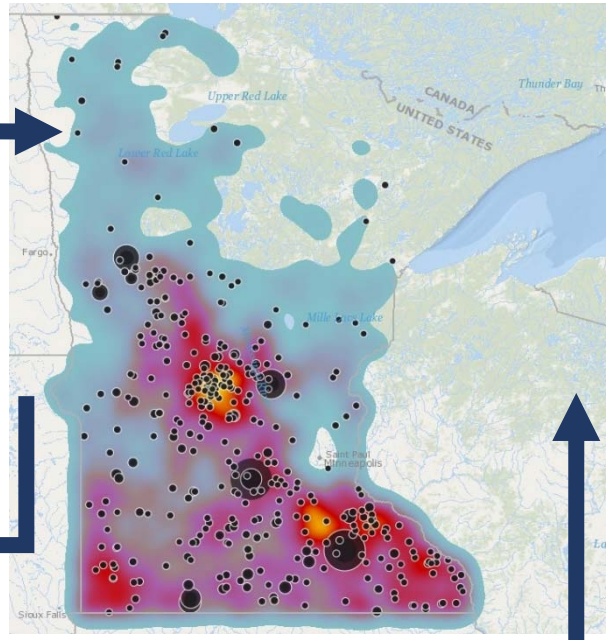
Mitigation of Antibiotic and Antibiotic Resistance Gene Pollution Requires Understanding the Sources of Contamination in Minnesota's Natural Environment

1. Estimate amount of antibiotics used in humans, animals and crops and resistance gene prevalence



(Woolhouse and Ward, 2013)

2. Build geospatial model predicting areas of highest impact and loading



3. Use geospatial model to identify sites where mitigation is needed

4. Use data collected in this project to validate model

Outcomes

- Develop a tool to predict environmental contamination with antibiotics and resistance genes
- Propose risk-based mitigation strategies
- Protect environmental, human, and animal health

Project Manager Qualifications and Organization Description

Randall Singer
McKnight Land-Grant Professor and Resident Fellow of the Institute on the Environment
Department of Veterinary and Biomedical Sciences, University of Minnesota

B.A., Animal Physiology and Ecology, 1991, University of California, San Diego, CA
D.V.M., Veterinary Medicine, 1995, University of California, Davis, CA
M.P.V.M., Epidemiology, 1995, University of California, Davis, CA
Ph.D., Epidemiology, 1999, University of California, Davis, CA

Dr. Randall Singer will be responsible for overall project coordination. He will lead the geospatial modeling, a subject about which he has been researching and teaching for 20 years. He will coordinate the sampling activities of the project with the other project managers. He has led several large field studies requiring extensive coordination of sampling activities. Dr. Singer has been studying antibiotic resistance for 20 years; he has focused on the environmental dissemination of antibiotic resistance for 15 years. For the past several years he has been developing an approach for building a geospatial model to predict the environmental loading of antibiotics and antibiotic resistance and how to relate these predictions to environmental health impacts. In 2000 he was awarded the Presidential Early Career Award for Scientists and Engineers by President Clinton for his work on antibiotic resistance. Between 2006 and 2010 he served on the U.S. Delegation to the CODEX Task Force on Antimicrobial Resistance and has spoken twice to the U.S. House of Representatives on this topic. He currently serves as a voting member of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria and organized a full symposium for this Council on antibiotic resistance in the environment.

William Arnold (Distinguished McKnight University and Joseph T. and Rose S. Ling Professor, Civil, Environmental and Geo-Engineering) is an expert in chemical fate, transport, and treatment. He has been studying the fate of pharmaceutical and pesticide compounds, including antibiotics, in aquatic environments for 17 years. He is a Resident Fellow of the University of Minnesota Institute on the Environment, an Associate Fellow of the Minnesota Supercomputing Institute, and a member of the graduate faculty in Water Resources Science.

Timothy LaPara (Professor, Civil, Environmental and Geo-Engineering) is an expert in waste treatment and the environmental dissemination of antibiotic resistance genes. He has been studying antibiotic resistance in waste streams for more than 15 years.

Kristine Wammer (Associate Professor, Chemistry, University of St. Thomas) is an expert on chemical and microbiological processes affecting transformations of organic contaminants in the aquatic environment. She has been studying fate and effects of pharmaceuticals, including antibiotics, in natural waters for the past 14 years.

Amanda Beaudoin (Director of One Health Antibiotic Stewardship, Minnesota Department of Health) is an expert in the prevention and control of antibiotic-resistant pathogen transmission in healthcare settings and in the discipline of antibiotic stewardship. Dr. Beaudoin has worked on international antibiotic resistance issues as a Centers for Disease Control and Prevention employee and, as of August 2016, is a Minnesota state employee, leading the statewide One Health Antibiotic Stewardship Collaborative, engaging stakeholders from human, animal, and environmental health.

Organization Description
The University of Minnesota is one of the largest, most comprehensive, and most prestigious public universities in the United States (http://www1.umn.edu/twincities/01_about.php). The laboratories and offices of the PI and co-PIs contain all of the necessary fixed and moveable equipment and facilities needed for the proposed studies.