Environment and Natural Resources Trust Fund
2019 Request for Proposals (RFP)

Project Title: **ENRTF ID: 049-B**

Benign Design: Environmental Studies Leading to Sustainable Pharmaceuticals

Category: B. Water Resources

Sub-Category:

Total Project Budget: $ 415,300

Proposed Project Time Period for the Funding Requested: June 30, 2022 (3 yrs)

Summary:

We will identify wastewater treatment and natural processes that prevent the formation of highly toxic byproducts from fluoro-pharmaceuticals. This will lead to improved treatment and rules for better pharmaceutical design.

Name: William Arnold

Sponsoring Organization: U of MN

Title:

Department: Civil, Environmental, and Geo- Engineering

Address: 500 Pillsbury Dr. SE

Minneapolis MN 55455

Telephone Number: (612) 625-8582

Email arnol032@umn.edu

Web Address www.williamarnold.org

Location

Region: Statewide

County Name: Statewide

City / Township:

Alternate Text for Visual:

Fluorinated pharmaceuticals and toxic byproducts could accumulate in Minnesota lakes and rivers

_____ Funding Priorities	_____ Multiple Benefits	_____ Outcomes	_____ Knowledge Base
_____ Extent of Impact	_____ Innovation	_____ Scientific/Tech Basis	_____ Urgency
_____ Capacity Readiness	_____ Leverage	_____ TOTAL	_____%
____ If under $200,000, waive presentation?			

PROJECT TITLE: Benign Design: Environmental studies leading to sustainable pharmaceuticals

I. PROJECT STATEMENT

Many pharmaceuticals contain fluorine in their chemical structures. *There is limited information about how fluorine-containing pharmaceuticals are degraded during wastewater treatment or in the environment, and even less about the products that form.* This is important because one potential breakdown product is the **highly toxic** fluoroacetate while another is the non-toxic fluoride (which is in toothpaste). We need to understand which wastewater treatment and natural processes lead to toxic versus non-toxic breakdown products. Data will be needed for systems such as oxidation ponds in outstate Minnesota as well as in the wastewater treatment plants used in cities. *The objective of this proposal, therefore, is to gain the knowledge necessary to understand both how to best remove fluorinated pharmaceuticals from water and to allow the development of "benign by design" fluorinated chemicals.* Specific goals are to:

- Measure reaction rates and products of fluorinated pharmaceuticals when they are exposed to sunlight,
- Measure reaction rates and products of fluorinated pharmaceuticals in advanced treatment systems,
- Develop environmentally benign fluorinated magnetic resonance imaging (MRI) agents,
- Establish computational tools to predict the reactivity of fluorinated pharmaceuticals, and
- Disseminate the findings to water utilities and the MN Department of Health

There are fewer than 10 natural chemicals that contain fluorine. Because natural fluorinated organic compounds are few, the environmental pathways for processing synthetic fluorinated chemicals may not be as robust as those for other potential water pollutants. The presence of fluorinated chemicals in Minnesota's waters has received substantial attention. These compounds, however, are only a small subset of fluorochemicals used. In particular, a broad range of pharmaceuticals, including antibiotics, steroids, antidepressants, imaging agents, and statins contain fluorine. This could lead to accumulation of specific pharmaceuticals and their fluorinated degradation products in Minnesota's environment. Overall, we lack specific knowledge of
1) the **reaction intermediates and end products of synthetic fluorinated pharmaceuticals** in natural and engineered aquatic environments,
2) the level and type of fluorine incorporation that **maximizes utility and minimizes environmental impact of pharmaceuticals**, and
3) means to **predict the reactivity** and reaction pathways of fluorine-containing species under a variety of conditions.

Modern society requires effective pharmaceuticals, pesticides, and commercial/industrial compounds. The release of such chemicals into the environment is either necessary or inevitable, and having a sustainable society dictates that these chemicals be readily degradable after their desired function is achieved and that any degradation products are benign. This research project will provide critical knowledge that will lead to better wastewater treatment, prevent the accumulation of unanticipated and potentially toxic byproducts in the environment, guide the design of future pharmaceutical compounds, and protect of Minnesota's water resources as well as human and environmental health.

II. PROJECT ACTIVITIES AND OUTCOMES

Activity 1: *Identify toxic and non-toxic fluorinated products formed during wastewater treatment and environmental processing of pharmaceuticals* **ENRTF Budget: $144,300**

The rate at which fluorinated pharmaceuticals are degraded in wastewater oxidation ponds and rivers/lakes via photolysis and in advanced treatment systems for wastewater treatment will be measured. Fluorinated reaction products will be measured. The hypothesis to be tested is that fluorinated pharmaceuticals and imaging agents

break down into fluorinated intermediate and product structures with the potential for environmental persistence and toxicity.

Outcome	Completion Date
1. Reaction rates of fluorinated pharmaceuticals wastewater and river water in sunlight	January 30, 2021
2. Reaction rates of fluorinated pharmaceuticals under advanced treatment conditions	October 31, 2021
3. Reaction product identification	January 30, 2022

Activity 2: *Synthesis of new polyfluorinated MRI agents that breakdown during wastewater treatment or in the environment* **ENRTF Budget: $ 128,000**

Potential new MRI reagents with superior sensitivity and minimal environmental persistence will be synthesized. All synthesized compounds will be tested under the reaction conditions of Activity 1. Current clinical trials are using perfluorochemicals which will be environmentally persistent, and our work will provide critical knowledge about how to make fluorinated structures that are medical useful yet environmentally benign.

Outcome	Completion Date
1. Development of environmentally friendly MRI reagents	December 31, 2021
2. Evaluation of sunlight and advanced treatment of MRI reagents	June 30, 2022

Activity 3: *Assess the parameters that dictate reaction rates and products of pharmaceuticals containing fluorine* **ENRTF Budget: $ 143,000**

While it is known that many fluorinated compounds are unreactive, a better understanding of how reactions of fluorinated pharmaceuticals occur under a variety of conditions is needed. We will develop computational methods to predict how fluorinated compounds breakdown under water treatment conditions and in sunlight. The theoretical results will be tested during the experiments performed in Activities 1 and 2. This will facilitate prediction of which compounds may accumulate in the environment and which are likely to be degraded.

Outcome	Completion Date
1. Modeling of reactive states/energies of reactions	October 31, 2021
2. Development of tools to predict reactivity of fluorinated pharmaceuticals	June 30, 2022

III. PROJECT PARTNERS: The project team will be led by William Arnold University of Minnesota; Dept. of Civil, Environmental, and Geo- Engineering) collaborating with William Pomerantz and Christopher Cramer (Dept. of Chemistry, UMN) . Dr. Arnold has expertise in the environmental analysis, fate, and transport of organic contaminants and has been studying the fate of pharmaceuticals in the environment for 20 years. Dr. Pomerantz is an expert in the development of new fluorinated molecules, and Dr. Cramer's expertise is in theoretical chemistry and predicting the environmental fate of pollutants. Two graduate students and an undergraduate students will conduct the research activities. Their duties will include collecting water samples, performing experiments, data analysis, and presenting the results at in-state scientific conferences.

IV. LONG-TERM- IMPLEMENTATION AND FUNDING: The long-term goal of the project is to prevent wastewater treatment plants, whether they be oxidation ponds in out-state Minnesota or advances treatment plants in cities, from becoming hotspots of fluorochemical contamination. This project will provide information about specific chemicals that could be problematic, **wastewater treatment techniques that result in non-toxic (fluorinated) reaction products,** and means to new fluorochemicals that are of medical use but environmentally benign. The proposed study will help to safeguard Minnesota's lakes and rivers and human and animal health.

V. TIME LINE REQUIREMENTS: The proposed project will be completed in a three-year period.

2019 Proposal Budget Spreadsheet

Project Title: Benign Design: Environmental studies leading to sustainable fluorochemicals

IV. TOTAL ENRTF REQUEST BUDGET 3 years

BUDGET ITEM (See "Guidance on Allowable Expenses")	**AMOUNT**
Personnel: William Arnold, Project Manager (75% salary, 25% fringe benefits). 4% FTE for years 1 - 3. Overall project coordination, lead Task 1 studies, co-lead Task 3. $34,500 William Pomerantz, co-Project Manager (75% salary, 25% fringe benefits). 4% FTE for years 1 - 3. Lead Task 2, co-lead Tasks 1 and 3. $20,000 Christopher Cramer, co-Project Manager (75% salary, 25% fringe benefits). 2% FTE for years 1 -3. Lead Task 3. $22,400 Graduate student Research assistant 1, Perform environment fate studies for Task 1, perform computations in Task 3 (55% salary, 45% fringe benefits) 50% FTE for years 1 &2, 25% for Year 3. $124,100 Graduate student Research assistant 2, Synthesize new MRI regents in for Task 2, perform computations in Task 3 (55% salary, 45% fringe benefits) 25% FTE for year 1, 50% for Years 2&3. $124,100 Undergraduate researcher. Assist with laboratory experiments. 10 hrs per week during academic year, 40 hours per week in summer. (100% salary) $25,200	$ 350,300
Equipment/Tools/Supplies: Supplies (chemical standards, chemical reagents for fate and synthesis experiments, necessary glassware, solvents, consumable supplies, laboratory notebooks, software licenses; instrument operation $27,000 total). Analytical time for identification of breakdown products using NMR (700 samples, $10 per sample; $7,000) and mass spectrometry (700 samples $30 per sample; $21,000).	$ 55,000
Travel: University vehicle rental and hotel stays to collect water samples. Presenation of results at local conferences. Will be reimbursed via the University of Minnesota plan.	$ 4,000
Additional Budget Items: Publication charges to make published journal articles (2-3) immediately available via open access to maximize data availability and dissemination	$ 6,000
TOTAL ENVIRONMENT AND NATURAL RESOURCES TRUST FUND $ REQUEST =	$ 415,300

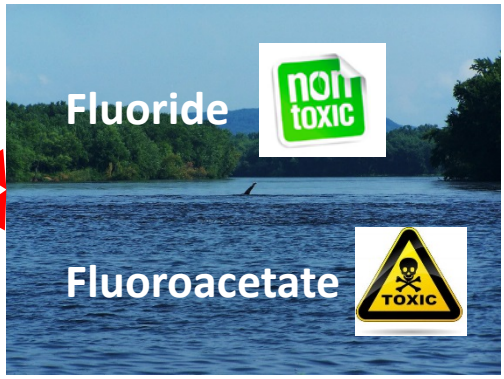
V. OTHER FUNDS *(This entire section must be filled out. Do not delete rows. Indicate "N/A" if row is not applicable.)*

SOURCE OF FUNDS	**AMOUNT**	**Status**
Other Non-State $ To Be Applied To Project During Project Period: N/A	$ -	
Other State $ To Be Applied To Project During Project Period: N/A	$ -	
In-kind Services To Be Applied To Project During Project Period: Because the project is overhead free, laboratory space, electricty, and other facilities/adminstrative costs (54% of direct costs excluding permanent equipment and graduate student tuition benefits) are provided in-kind.	$ 178,500	*secured*
Past and Current ENRTF Appropriation: N/A	$ -	
Other Funding History: N/A	$ -	

Fluorinated pharmaceuticals and toxic byproducts in Minnesota lakes and rivers

Oxidation ponds

Antibiotics, statins, etc often contain fluorine



Advanced treatment

Outcomes:

1. Assess toxic byproduct formation
2. Identify wastewater treatment processes that lead to non-toxic products
3. Improve outstate and urban wastewater treatment
4. Develop rules for environmentally benign design of new compounds

Project Manager Qualifications and Organization Description

William A. Arnold
Distinguished McKnight University and Joseph T. and Rose S. Ling Professor and Associate Head
Department of Civil, Environmental, and Geo- Engineering, University of Minnesota

B.S., Chemical Engineering, 1994, Massachusetts Institute of Technology, Cambridge, MA.
M.S., Chemical Engineering, 1995, Yale University, New Haven, CT.
Ph.D., Environmental Engineering, 1999, The Johns Hopkins University, Baltimore, MD.
Dr. William Arnold will be responsible for overall project coordination and supervision and design of the field sampling and reactivity studies. He has been studying the fate of pharmaceutical and pesticide compounds in aquatic environments for seventeen years. As part of these studies, he has determined the transformation rates and identified reaction products of numerous compounds. He has published over twenty peer-reviewed papers on pesticide and pharmaceutical fate since 2003, and he is the co-author of a textbook on water chemistry published in 2011. Dr. Arnold is a 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.

William C. K. Pomerantz
Land Grand McKnight Assistant Professor, Department of Chemistry

B.S. Chemistry 2002, Ithaca College, Ithaca, NY
Ph.D., Chemistry, 2008, University of Wisconsin-Madison, Madison Wisconsin
Dr. Pomerantz will be responsible for guiding the synthesis of new fluorinated molecules as medical contrast agents. He will also assist in the analysis of fluorinated degradation products. He has developed sensitive spectroscopic methods for the characterization of fluorinated bioactive molecules. Over the last six years, he has published 19 peer-reviewed manuscripts pertaining to the synthesis of new fluorinated materials, fluorinated medical contrast agents, and spectroscopic analysis of fluorinated molecules. His research is also covered in a book chapter describing his work on applied biophysics for drug discovery. Dr. Pomerantz is a member of the University of Minnesota's Masonic Cancer Center and Institute of Engineering and Medicine, and graduate faculty in the Department of Medicinal Chemistry.

Christopher J. Cramer
Distinguished McKnight and University Teaching Professor, Department of Chemistry
Associate Dean for Academic Affairs, College of Science and Engineering

A.B., Chemistry and Mathematics, 1983, Washington University, St. Louis, MO.
Ph.D., Chemistry, 1988, University of Illinois, Urbana, IL.
Dr. Christopher Cramer will be responsible for modeling degradation paths of fluorinated pharmaceuticals in the environment. He has been instrumental in developing models for predicting environmental fates of contaminants and has been active in this area for twenty-five years. He has published many peer-reviewed papers on the environmental fates of pesticides, pharmaceuticals, and chemical weapons agents, and he is the co-author of a textbook on computational chemistry first published in 2002. Dr. Cramer is a Fellow of the University of Minnesota Supercomputing Institute, and the American Chemical Society.

Organization Description
The University of Minnesota is one of the largest, most comprehensive, and most prestigious public universities in the United States (http://twin-cities.umn.edu/about-us). The laboratories and offices of the PI contain the necessary fixed and moveable equipment and facilities needed for the proposed studies.