

**Sponsored Research Proposal, 2006-2007**  
**Maria Bastaki**

**Biological Interactions among Environmental Chemicals**

**Statement of proposed activity**

My goal is to set the ground for developing an independent research direction in Toxicology related to Environmental Health. It is timely for me to resume research activity after two years as a faculty member at the College. This will be accomplished with three parallel efforts:

a) Join in a collaborative effort with new faculty member Clarissa Dirks to set up a functional lab space that was made available to us this year. Clarissa and I have highly compatible research activities that require cell-culture lab space and basic general lab equipment and supplies. We will share most equipment and common reagents and each will obtain more specialized materials as needed.

b) Start using computer-based chemical structure modeling programs and setting up *in vitro* test methods toward my scientific objectives. My research hypothesis is that exposure to multiple chemicals concurrently involves mechanistic and/or metabolic interactions that result in toxicity that differs from the toxicity of each substance alone (additive, synergistic, or antagonistic).

c) Finalize a research proposal for an NSF or NIH AREA grant for funding my research activity in the following years. Additional funding is necessary to sustain my research activity. My summer work will help me strengthen my proposal for grant funding from outside agencies.

**Purpose and scope of the activity**

The purpose of the proposed activity is to take the necessary steps for getting my research agenda off the ground. The goal of my research is to identify environmental chemicals that share common cellular pathways as their targets, and can affect each other's toxicity via biological interactions. Toxicologists in academic and regulatory institutions in the US and the European Union have acknowledged that metabolic interactions among environmental chemicals can occur in humans exposed to multiple agents concurrently, just as interactions among pharmaceutical substances are known to take place and are closely studied and monitored. There is strong support toward better risk assessment and understanding of the impact of environmental hazard exposures on Public Health.

As with the pharmaceutical substances, harmful health effects from exposure to environmental chemicals could be predicted (and perhaps prevented) if a) the toxicity of all environmental chemicals were known and b) it were possible to predict interactions among them. Unlike pharmaceutical substances, however, the biological activities (toxicity) of environmental chemicals are not characterized prior to their release in the market. Biological effects are known for relatively few chemicals only, whereas thousands of chemicals are produced and used annually that have not been tested for toxicity. Interactions among environmental chemicals would potentially explain the observations of adverse health effects that cannot be explained on the basis of single compound toxicity at low levels of exposure. This is critical for the goal of better risk assessment strategies in the field of Environmental Health, and for informed decisions about the safety of existing and new materials released into the environment.

**Interdisciplinary nature of the activity**

Toxicology is interdisciplinary by its own nature. It draws from chemistry, biology, human physiology, and mathematics. I will combine computational methods in addition to toxicology and laboratory research, an approach used very effectively in the Pharmaceutical Industry for the design of new drugs with improved properties. Finally, my research is closely related to US and EU policy priorities about effects of environmental pollution on human health.

**Broad Statement of Professional Agenda:**

The proposed activity will help me resume research in environmental toxicology with a focus on human health. This is a culmination of my background and research experience in pharmacology and

toxicology, as well as in mechanistic cell biology and in environmental health science. Through this project I will be able to develop hypotheses about the implications of exposure to multiple environmental pollutants on human health. I will seek collaborations with scientists in the broader region on relevant epidemiological studies, through which the laboratory hypotheses can be put to test in realistic conditions of human exposure and indicators of health effects (biomarkers). Furthermore, I will contact local policy agencies related to environmental health, to explore the application of scientific information and its implications in public policy. Such interaction is not only at the center of my professional interests but it can also offer unique opportunities of interdisciplinary learning to Evergreen students. Exploring similar interactions with national and international environmental agencies is also conceivable as a future growth route for my professional career, and would open more doors of engagement to our students.

#### **Benefits Expected from the Activity Within the College:**

The proposed research will allow me to offer the unique culmination of my background and my interests toward developing creative interactions with faculty from chemistry, biology, computer programming, and environmental health policy in the form of collaborative research projects within the College. Since there is no other faculty member currently involved in this area of research, I will be able to offer a new range of possibilities to explore in the context of the expertise of my colleagues.

#### **Benefits to students' education and curricular development**

From within the MES program, I introduce students to concepts of Environmental Toxicology, an area new to MES and the undergraduate curriculum. My proposed research activity and cell culture laboratory will support a) hands-on student training in computational and *in vitro* toxicology that can lead a student into graduate research; b) interdisciplinary education tools combining chemistry, biology, computer modeling and connection between science and public policy; c) engage them in collaborative research (e.g. graduate theses), which will help in writing educational grants; d) extending the scope of toxicity assessment to other species to investigate the effects of environmental pollutants to wild life.

#### **Benefits Expected from the Activity Outside the College:**

As a result of the proposed activity I will be on a good start to establish my own independent research direction toward the application of pharmacology/toxicology in the areas of Environmental Health and Environmental Policy and maintain a productive presence in my field. I will be able a) to contribute presentations to scientific conferences and peer review publications that are beneficial to the image of the college as an active intellectual environment; b) to use preliminary data to apply successfully for additional external funding; c) to engage in collaborative research with scientists outside of the College; d) to establish interactions with public policy agencies locally and beyond.

#### **Detailed Project Plan:**

I plan to combine computational and classic toxicology approaches to evaluate the toxicity of chemicals that have never been tested and examine the potential for interactions among them.

My hypothesis is that exposure to multiple chemicals concurrently can lead to biological and/or metabolic interactions that in turn have health effects not anticipated from the toxicity of single substances. Three categories of substances could result in interactions:

- a) Those with shared molecular targets of action based on structural similarities;
- b) Those with molecular targets of action that belong in the same or related cellular pathways;
- c) Those that are substrates for the same enzyme of metabolic biotransformation.

Based on this, my overall research plan will take the following steps. During the summer of 2007, I will be able to work on steps 1-2 and begin step 3:

1. Set up a mammalian cell culture area and adjacent general lab appropriate for *in vitro* cell-based toxicity assays. Progress has been made in establishing a mammalian cell culture laboratory space

with the hiring of a new faculty member, Clarissa Dirks, with compatible research interests. I will set up the cell cultures for my project and purchase necessary supplies to do so.

2. Search of literature and online toxicity databases for chemicals that have been tested positive for at least one of the following activities: a) mammalian cell transformation *in vitro*, b) DNA damage and repair, and c) mammalian cell mutagenesis.

Initially, I will focus on genotoxic chemicals (carcinogens) since the computer models work better for them and there are standardized laboratory methods for their evaluation. I will take advantage of computational methods that are used in Quantitative Structure Activity Relationships (QSAR) for the efficient screening of large number of chemicals that lack toxicity testing (a time-consuming, resource and labor intensive, and expensive endeavor). I will use existing molecular modeling software, such as:

- i. TOPKAT, for toxicity assessment, (has ADME<sup>1</sup>/Toxicity info with 16 toxicological endpoints) (<http://www.accelrys.com/products/topkat/index.html>)
- ii. Accord, for chemical info database management (<http://www.accelrys.com/products/accord/>)
- iii. MedChem, for exploring the medically active properties of environmental chemicals: (<http://www.accelrys.com/products/medchem/>)

3. Determine if there are interactions among them: Test combinations of two of these chemicals *in vitro* using standard protocols adopted by the EU (<http://ecb.jrc.it/testing-methods/>) in order to maintain a standardized process of chemical assessment under the REACH policy (<http://ecb.jrc.it/REACH/>). During the summer I will set up the assays to have them operational for future work.

4. Assess the available information about the metabolic transformation of the selected chemicals and identify key metabolic enzymes.

5. Apply the pharmaceutical design approach by using the enzymes identified in step 4 as baits to interrogate chemical structure databases for substances that would be likely substrates, but for which there is no toxicity information. I will limit the number of chemicals to those of higher priority in the agenda of the US-EPA and/or European Union REACH program.

6. Repeat the laboratory tests in step 3 with each of the chemicals identified in step 5 alone and in combinations, starting with two chemicals at a time and at two dose combinations.

**Dates and Length of Request:** The proposed work will take place during July and August of 2007. Since the activity is not feasible without funds for supplies, I am requesting support in the form of seed money as described in the Faculty Handbook. Sufficient funding for supplies necessary for setting up lab methods is estimated approximately at \$5,000-\$6,000 (including software licenses). Further funding will be sought from extramural sources.

**Letters of Support:** Letters of support from Lin Nelson and Lydia McKinstry are submitted separately.

**Current Curriculum Vita:** Attached.

**Other Sources of Funding:** I am not currently funded by any grant. However, I will be submitting a research proposal for additional grant funding from NSF or NIH AREA grants during 2007.

Respectfully,

Maria Bastaki

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<sup>1</sup> Absorption Distribution Metabolism and Excretion

# EVERGREEN

THE EVERGREEN STATE COLLEGE  
OLYMPIA, WASHINGTON

October 16, 2006

Sponsored Research Review Committee  
The Evergreen State College

Dear Review Committee:

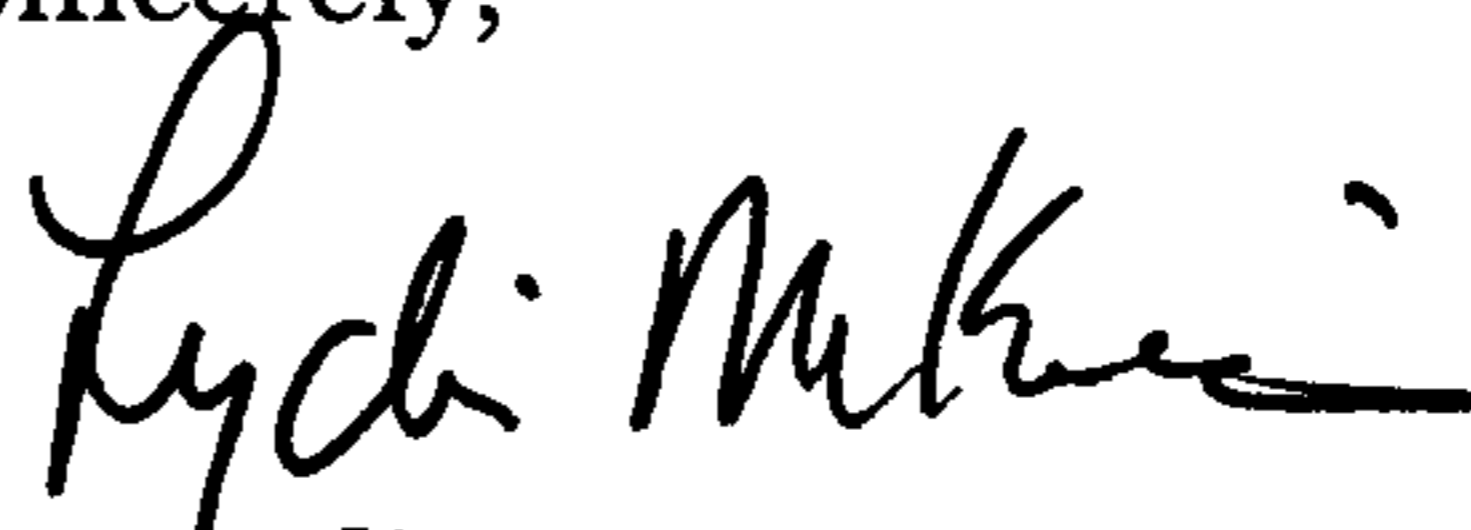
It is with great enthusiasm that I recommend your approval and funding of the Sponsored Research grant proposal submitted by Dr. Maria Bastaki. Maria joined the Evergreen faculty in Fall of 2005 and is currently teaching in the Master of Environmental Studies (MES) program. In the last year I have come to know Maria well, and have learned to value her as a colleague. She is a person of great integrity and we share similar philosophies about education and faculty development. In fact, I look forward to the opportunity of teaching with Maria next year (2007-08) in an interdisciplinary program with Glenn Landram called Money, Molecules and Meds.

Maria has successfully completed her first year of teaching at Evergreen and is now eager to develop a research program that emphasizes collaborative, hands-on learning in toxicology for both undergraduate and graduate level students. Maria believes that the best educators are those who stay active in their field of research. Her proposed research plan in toxicology and environmental health is highly interdisciplinary and would surely lead to many opportunities for collaborative teaching and learning. Moreover, our students currently do not have opportunities to do research in toxicology and Maria's unique expertise in this field is a much needed and desired addition to research programs at Evergreen.

Establishing a student-focused research program requires a considerable time investment, which can be difficult to do while teaching in a full time program, such as MES. Maria intends to set up a laboratory and lay the groundwork of this research in the summer of 2007, when she is free from teaching commitments. A Sponsored Research award will support Maria's effort to accomplish her goal at this critical early stage of her career and would be a worthwhile investment for the college. It is my belief that Maria will develop an active research program involving undergraduate and Masters level students which will surely lead to successful collaborations with scientists in the local business community as well as funding from external agencies.

Maria is an asset to the Evergreen community and is very deserving of this opportunity to develop here. Therefore, I give Dr. Maria Bastaki my highest recommendation for a Sponsored Research Grant, and hope you will consider her application favorably. Please do not hesitate to contact me with any additional questions or concerns.

Sincerely,



Dr. Lydia McKinstry  
Member of the Faculty

THE EVERGREEN STATE COLLEGE



THE EVERGREEN STATE COLLEGE

OCT 16 2006

OFFICE OF THE ACADEMIC  
VICE PRESIDENT AND PROVOST

October 15, 2006

RE: Maria Bastaki's Sponsored Research Proposal  
TO: Sponsored Research Review Committee  
FROM: Lin Nelson

Dear Sponsored Research Review Committee:

I am writing to enthusiastically support Maria Bastaki's proposal.

As a new faculty member, Maria is working hard to develop the foundation for significant work here in both the MES and undergraduate programs. As a participant in the committee that hired Maria, I know that we all very much want her to be able to establish and strengthen her work in a way that is professionally gratifying and supports student learning.

Not being one of the science faculty, I'll leave that feature of the assessment to my colleagues. As a social scientist in Environmental Studies, I'll limit my comments to the broad context for what Maria is proposing.

Maria's proposed work will enhance our capacity to offer students opportunities in analyzing risks to human health. Environmental Health is a burgeoning field, with complex connections between the fields of toxicology, pharmacology, epidemiology, statistics, chemistry, public health practice and public policy. Here in Washington State, the interest in human health impacts of chemical exposures has grown measurably over the past several years. As a state very much dependent on the agricultural sector, we face more and more cases of pesticide exposure and unexplained patterns of illness among farmworkers. There is heightened attention to the complexities of indoor air pollution, whether for workers at Boeing or children in our public schools. Many a legislative hearing or agency taskforce is taken up with the challenge of deciphering chemical exposures and shaping both preventive and remedial pathways.

Both the Washington State Departments of Health and Ecology are increasingly focused on emergent policies and research regarding PBTs – Persistent, Bioaccumulative Toxics. Many of the discussions at the policy level reveal the difficulties faced by public health practitioners in trying to identify and track the impacts of multiple, synergistic exposures. Currently, the approach tends toward a chemical-by-chemical approach. But the need for expanding the knowledge base around multiple, interactive exposures is very clear.

And so, Maria's proposal is strong not only on its own merits – that is in terms of the significant knowledge to be gained regarding complex chemical exposures. It is also timely and strategic in the context of state environmental health policy, legislation, agency practices and on-the-ground challenges faced in our county health departments and clinical services.

Therefore, I urge my colleagues on the Committee to give Maria's proposal very serious consideration. I think her work will be very helpful to our immediate and primary teaching mission and it could help connect students and the college with the serious challenges being taken up by Environmental Health practitioners and advocates here in the region.

Sincerely, 

Lin Nelson