



Center for Ecogenetics and Environmental Health

University of Washington

4225 Roosevelt Way NE ● Suite 100 ● Seattle, WA 98105-6099
Telephone: (206) 543-4383 ● Fax: (206) 685-4696
Web: <http://depts.washington.edu/ceeh/> ● Campus mail: Box 354695

David L. Eaton, PhD, Director
e-mail: deaton@u.washington.edu
Telephone: 206-685-3785
Fax: 206-685-4696

August 8, 2007

Dr. Dennis Lang
Interim Director
Division of Extramural Research and Training
National Institute of Environmental Health Sciences
Research Triangle Park, NC

By e-mail attachment

Dear Dr. Lang:

As the Director of an NIEHS Core Center, I'm writing to seek some clarification from your office on the 'boundaries' of types of research that are considered to be relevant components of the NIEHS grants portfolio. Specifically, I have identified below seven somewhat 'gray' areas of research for which I (and I believe other Center Directors) could use some guidance from NIEHS:

- 1) **Diet**-- I see 4 'sub-areas' related to diet that may have varying degrees of relevance to the NIEHS mission:
 - a. **Xenobiotic Contaminants of the diet:** It is clear that 'xenobiotic contaminants' of the diet, such as pesticides, metals, mycotoxins, etc, are highly relevant to the NIEHS mission, and constitute areas of research that NIEHS already includes in their portfolio. No need for clarification here. **We agree these are topics that are appropriate for NIEHS.**
 - b. **'Naturally occurring' non-nutritive components of the diet** (e.g., phytochemicals): I also assume that naturally occurring chemical constituents of the diet, such as biologically active phytochemicals (e.g., phytoestrogens, plant components that alter gene expression, etc) are also relevant to the NIEHS mission, since many of these may modulate diseases processes, although it is somewhat less clear to me whether this area of research is considered to be of direct relevance to NIEHS. **These compounds which have been linked to environmental exposure and for which there is a reasonable expectation of a deleterious health effect are appropriate.** This question extends to studies on the mechanism of action / toxicity studies of so-called 'nutraceuticals' (e.g., plant extracts sold as herbal remedies), which for the most part is simply an extension of studies on phytochemicals. Are such studies of interest to NIEHS? **Studies of herbal remedies are not of interest to NIEHS and are considered within the mission of NCCAM.**

- c. **Nutritive components of the diet:** It is not clear to me whether studies focused on understanding the nutrient aspects of diet (e.g., consequences of vitamin deficiency or supplementation; role of folate in disease susceptibility; caloric intake / balances in protein, carbohydrate, lipid metabolism) fall within the realm of NIEHS funding interests. **We believe that they do not.** In NIEHS RFA 06-013 (Biological Response Indicators of Environmental Stress), the following text was included; *“Another example relates to the assessment of gene-specific and global epigenetic changes influenced by dietary exposures. A recent study showed that supplementation with folic acid, vitamin B12, choline, and betaine altered phenotype in agouti (A(vy)) mice through increased DNA methylation at the A(vy) locus. Beginning with animal studies, the effects of dietary supplementation with folic acid and other B vitamins could be assessed with respect to gene-specific epigenetic changes (e.g., alterations in imprinted genes, including IGF2 and CDKN1C), global methylation changes, or histone modification changes”* This language seems to indicate that studies of nutrient components of the diet are of direct relevance to NIEHS. Is that interpretation generally correct? **This language was from a particular initiative written in conjunction with another IC. It should not be interpreted as an area of general interest for NIEHS but rather a “one time” solicitation. We do have a continuing interest in epigenetics as a mechanism of mediating environmental effects and will continue to develop this area of research.**
- d. **Consequences of diet / physical activity** – obesity, diabetes, metabolic syndrome, various types of cancer, etc. I'm sure that studies focused on assessing the impact of dietary contaminants on such diseases is relevant (e.g., studies on the hypothesized roles of arsenic, PCBs and dioxins in diabetes), but I am far less clear whether studies on such things as behavioral aspects dietary choices (food preferences), studies on the role of nutrient components of the diet on such diseases, etc, are of interest to NIEHS. Although NIEHS has sponsored or co-sponsored meetings and symposia on such topics, a search of the NIEHS portfolio showed no grants funded in this area. The NIEHS Exposure Biology GEI program states the following: *A major component will support the development of technology to make precise, quantitative measurements of personal exposure to environmental chemical/biological agents, diet, physical activity, and psychosocial stress* (emphasis added). This clearly suggests a very broad definition of 'environment', but it is not clear to me whether this broad definition is included only for the Exposure Biology GEI program, or can be extrapolated to infer that such studies would be welcome at NIEHS as unsolicited investigator-initiated R01s. **This language was from a particular initiative written in conjunction with three other ICs. It should not be interpreted as an area of general interest for NIEHS but rather a “one time” solicitation that we were coordinating.**

2) Tobacco

I was under the impression from discussions and / or public comments from Dr. Schwartz that NIEHS was explicitly not interested in funding tobacco-related research. However, the same RFA referenced above (NIEHS RFA 06-013; Biological Response Indicators of Environmental Stress) contains the following text in regards to the development of biomarkers: *“For example, by using lung tissue and blood samples in a gene expression array, a signature of genetic response to the chemicals in cigarette smoke can be defined and compared to results in non-smokers. If a defined panel of genes is identified with exposure and these genes are not expressed in non-smokers, then this marker defines components of the genetic response to cigarette smoke exposure. This marker should be compared to traditional measures of cigarette smoke: smoker/non-smoker status, frequency of use, recentness of exposure,*

(gathered by questionnaire) and cotinine level to determine if the marker categorizes smokers and non-smokers adequately.” This language clearly suggests that NIEHS is interested in funding studies related to consequences of tobacco use. But perhaps only in limited context, e.g., develop of biomarkers? Is NIEHS interested in funding tobacco-related research e.g., potential role of nicotine as a human teratogen? **This language was from a particular initiative written in conjunction with another IC. It should not be interpreted as an area of general interest for NIEHS but rather a “one time” solicitation. In general we can say that we are not interested in primary tobacco use and its consequences. There is plenty of research old and new focused on this topic and funded by other ICs. We do have an interest in environmental exposure to secondary tobacco smoke and health effects. Young children growing up in homes where there is tobacco use is of particular concern and interest to NIEHS.**

3) Alcohol

Much the same as the tobacco question above- Since there is a specific institute with a focus on alcohol research (NIAAA), I assume that studies on the consequences of alcohol intake and abuse are not considered pertinent to the NIEHS mission. But what about studies looking at, for example, ‘gene environment interactions’ with alcohol (e.g., studies looking at whether polymorphisms in ALDH2 are important in disease risk), or studies examining how alcohol might interact with or otherwise alter response to other xenobiotics? (e.g., modulation of aflatoxin B1 hepatocarcinogenesis by alcohol intake). **We have an interest in alcohol use as a potential co-factor in disease processes but only when considered along with a more traditional environmental stressor.**

4) Pharmaceuticals

I have been under the impression that NIEHS is not interested in funding studies that examine the adverse consequences of pharmaceutical agents (drug toxicology), even though this is probably one of the most important ‘environmental’ sources of exposure and disease. For example, we were told explicitly that NIEHS was not interested in considering whether long-term pharmaceutical use might be a risk factor for chronic neurodegenerative diseases. But what about studies of pharmaceutical agents that might reveal genetic polymorphisms that have broad implications beyond clinical use, or studies that utilize pharmaceutical agents as probes to evaluate mechanisms of action (e.g., use of acetaminophen to explore fundamental mechanisms of hepatotoxicity)? While we would have interest in using pharmaceutical agents as probes to evaluate mechanisms of action, the enthusiasm for this type of research would be substantially enhanced if the research was directly connected to environmental toxins/toxicants. Thus, the emphasis should be on the toxin/toxicant to biological target relationship and the pharmaceutical agent is used as a means of understanding this relationship.

5) Physical agents (ionizing radiation –**yes, along with UV**), thermal stress/heat shock – **yes**, EMF, noise, etc - **No**).

I believe that NIEHS has funded or at least expressed interest in funding EMF studies in the past, but also have the impression that NIEHS is not explicitly interested in studies on ionizing radiation. I’m even less clear on other aspects of physical agents. **We do have an interest in physical agents (particulate matter, nanomaterials, combustion products, diesel exhaust for example).** For example, one of my Center Investigators has been studying the role of induced hyperthermia on the development of SIDS, and has some very interesting biomarker data with heat shock proteins

suggesting that bundling up babies with blankets could actually be causing hyperthermia that might contribute to SIDs. But I'm not clear if such research would be of interest to NIEHS. **(It would not).**

6) Occupational Exposures

I assume that NIEHS is generally not interested in funding studies that are directly addressing occupational health issues, since that is largely the purview of NIOSH. However, studies on occupationally exposed populations often provides the only useful human data for public health risks that might occur from lower level environmental exposures, such as community pesticide exposures or drinking water contaminants. It is not clear to me how NIEHS views funding studies of occupationally-exposed individuals or populations. What types of occupational studies (if any) are considered relevant to NIEHS, and what are clearly not? **It depends on the exposure, but certain exposures are more easily studied in workplace due to the level of exposure and the concentration of adverse health effects. For example we fund studies of pesticide exposure in farm workers and benzene exposure of Chinese shoe factory workers. Genetic susceptibility studies and studies focusing on disease pathogenesis in these settings are also of interest to us.**

7) Microbial organisms

- a. Illness-causing 'contaminant' organisms (e.g. *salmonella*, *giardia*, *e. coli*, etc.)
Historically, even though food- and water-borne illness from microbial contamination has been in the purview of traditional 'environmental health', it has not, to my knowledge, been an area that NIEHS has focused. Is that true? **That is true, research on microbial pathogenesis is funded primarily by NIAID.**
- b. Disease-causing organisms (e.g., viruses and other infectious, transmissible organisms). This clearly seems out of the realm of NIEHS mission, except perhaps in areas where other environmental factors of interest to the Institute interact. For example, studies that identified the strong interaction between hepatitis B virus infection and the mycotoxin aflatoxin B1 in causing liver cancer were funded by NIEHS. It would be useful to know if NIEHS explicitly encourages research in the area of xenobiotic-infectious agent interactions (for lack of a better term). It is likely that subtle biological effects of many xenobiotics could alter how people respond to infectious agents. Some clear directions from the Institute in this area would be helpful. **Again, infection as a co-factor for environmental stressors is of interest. Example, the interaction between infectious agents and environmental stressors as co-factors in disease etiology or severity.**

Perhaps there is a place on NIEHS's website that already addresses this and can help investigators and NIEHS Center Directors determine whether specific areas of research are of relevance to NIEHS-- but I was not able to find it if it exists. Of course, a phone call to specific program officers is always useful, but some explicit guidance on some of these somewhat 'fringe' areas would be most helpful. The primary reason for this request is that I, like the other 23 NIEHS Core Centers, have a pilot projects program that is designed to help investigators collect preliminary data for full NIH grant proposals. Obviously, since these are NIEHS funds, we expect that the projects that we fund are relevant to the mission of NIEHS. I frequently get calls from UW faculty wanting to know if their potential project is relevant to the mission of NIEHS, and it is pretty difficult for me to answer that, based on the NIEHS Mission statement or the new Strategic Plan (which I participated in developing). Throughout the strategic plan it talks about 'environmental exposures', but, as indicated above, exactly what constitutes relevant 'environmental exposures' is pretty wide open to interpretation. I have had lots of investigators conduct 'gene-environment' interactions in which the environmental component is a drug, a physical agent, tobacco, alcohol,

social factor, some component of the diet, etc., and for which I am not sure that an R01 grant would actually be picked up by NIEHS even if it scored well.

My apologies for the length of this letter. I do think that a 'FAQ' section on the NIEHS web site that could directly address questions such as this would be most useful to NIEHS Center Directors as well as a large number of potential grantees who are unclear as to how 'environmental exposures' are defined by the Institute, and whether their particular idea is likely to be of interest to the NIEHS.

Thanks very much,



David L. Eaton, Ph.D.
Professor and Director, UW Center for Ecogenetics and Environmental Health;
Associate Vice Provost for Research

Other comments:

- 1) **Exposure to "model toxicants" – H₂O₂ to induce oxidative stress would seem appropriate**
- 2) **Studies of key metabolic pathways known or suspected to be involved in environmental stress responses but not including a specific exposure would depend on the grantee making a compelling case**