2015 Biennial Report to Council on Inclusion
National Institute of Environmental Health Sciences (NIEHS)

Background/Overview

Among the 27 research institutes and centers that comprise the National Institutes of Health (NIH), the National Institute of Environmental Health Sciences (NIEHS) is the institute most focused on prevention rather than diagnosis or treatment of health issues. The mission of NIEHS is to discover how the environment affects people in order to promote healthier lives. Our vision is to provide global leadership for innovative research that improves public health by preventing disease and disability.

The NIEHS research agenda is based on the concept that all complex diseases have both an environmental and a genetic component, and the Institute focuses on understanding the environmental component and the interaction of environment with genetics. Our research programs cover the effects of environmental exposures throughout the lifespan, from preconception to old age. We fund studies using computational and cell-based models; fish, amphibian, and mammalian models; and epidemiological studies with human subjects. The more we know about environmental exposures and how they affect health outcomes, the greater our ability to create healthy environments by reducing or preventing hazardous exposures. To this end, NIEHS investments are significant and measurable.

The Extramural Division includes review, grants management, program analysis and five program branches with focus on different aspects of the grant portfolio. DERT staff plans, reviews, approves, directs, fiscally administers, and evaluates performance of the Institute's grant, cooperative agreement, and contract programs, all of which support research and training in environmental health science.

The Exposure, Response, and Technology Branch (ERTB) focuses on the development of technologies and infrastructures that can improve our understanding of the complexity of the personal environment and biological response on a systemic level. It stimulates research on emerging areas of fundamental mechanisms of biological response such as the influence of exposures on the translational control of protein synthesis.

The Genes, Environment, and Health (GEH) branch builds on evolving knowledge in the fields of genomics and epigenomics to understand mechanisms that act at the interface of genes and environment to influence gene activity and phenotype. It emphasizes laboratory-based studies in model systems at the cellular, organ, and system level; supports integrative research programs that span basic, clinical, and translational activities; and focuses on the multifactorial etiology of brain behavior disorders.

The Population Health Branch (PHB) focuses on laboratory-based and epidemiologic studies that define and elucidate relationships between exposure during sensitive life stages and disease risk. It also supports research programs that include community-based interventions and prevention; environmental public health research that relates to environmental health disparities and environmental justice; and trans-disciplinary approaches that integrate and span basic, clinical, and translational activities.

The Hazardous Substances Research Branch (HSRB) supports all activities of the Superfund Research Program (SRP), which funds multidisciplinary research that addresses the broad, complex human and environmental health issues surrounding hazardous waste sites. HSRB also coordinates global environmental health and sustainable development activities and enhances collaborations with institutions abroad to understand the effects of, measure, or reduce exposures, primarily in vulnerable populations.

The Worker Education and Training Program (WETP) supports the prevention of work-related harm through the education and training of workers and their communities in environmental health, focusing on safety concerns related to hazardous materials and waste generation, removal, containment, transportation, and emergency response. WETP also supports the National Clearinghouse for Worker Safety and Health Training, which is the primary national source for hazardous waste worker curricula, technical reports, and weekly news on hazardous materials, waste operations, and emergency response.

Strategies for Ensuring Compliance

During review of grant applications and proposals for R&D Contracts, NIEHS review staff applies and strictly follows the NIH's Peer Review regulations (42 C.F.R. 52h) regarding inclusion. These regulations specify that when determining the overall impact reviewers will carefully and conscientiously take into account the effect the project could have on the research field involved and the adequacy of plans to include both sexes/genders, minorities, children, and special populations, as appropriate for the scientific goals of the research. Therefore, reviewers factor their evaluation of the proposed plans for the inclusion of individuals on the basis of their sex/gender, race, ethnicity, and age into their overall evaluation (Overall Impact Priority Score) of a grant application or proposal's scientific and technical merit. Additionally, reviewers are required to prepare written comments, including specific comments describing all inclusion concerns, when Inclusion is rated as unacceptable.

When evaluating inclusion on the basis of sex/gender, race and ethnicity, reviewers are required to comment on the following four items: planned distribution of subjects; description and rationale of subject selection; rationale for exclusion; and description of outreach programs for recruitment. Reviewers are also required to address if the grant application or proposal adequately describe plans for the inclusion/exclusion of children (individuals under the age of 21, as per NIH's definition of children). The human subjects, gender, minority and inclusion codes are set by the reviewers at the review meeting. However, at the time of review, the SRO is responsible for making the final determination as to the accuracy of the codes, and corrects any code, as necessary.

Should there be a bar-to-funding for a human subject's issue, the Grants Management Specialist (GMS) will generate a request for information to the Principal Investigator, who will provide a response to the GMS through their Institutional Signing Official. The GMS forwards the information to the Program Officer (PO) who checks for completeness and writes a statement that he/she has reviewed and concurs with the PIs response and then forwards to the designated official for concurrence. The designated official reviews the information and forwards to GMS, copying the Program Officer (PO), with concurrence.*The GMS compiles the packet and forwards to the Human Subjects Protection Assessment System for review and processing. *If anyone in the chain does not concur, the process goes back to the GMS and begins again with request for additional information to PI with guidance as to what the remaining issues are seen to be.

Staff in the Office of Extramural Policy (OEP) will evaluate the information in the request; request clarification if necessary; change the human subject code in the NIH database after OEP concurs with the resolution of the HS concerns; and send an e-mail to the program official and grants management specialist summarizing the action and any human subject restriction terms that must be placed on the award.

The next two tables show the level of compliance in NIEHS extramural grant applications during scientific review and the bars-to-funding issued on applications that were subsequently selected for award. NIEHS policy is to delay awards until bars-to-funding are resolved. However, should there be insufficient time remaining in the fiscal year to remove the bars-to-funding, NIH allows issuance of a restricted award. It is NIEHS policy that no human subjects work may begin until all bars-to-funding are resolved and any restrictions are lifted.

Table 1. Level of Compliance with Inclusion Policy in New Extramural Grant Applications as Assessed During Scientific Peer Review

Fiscal Year		2013	2014
Total Number of Applications Reviewed	(#)	1526	1294
Number of Applications with Human Subjects	(#)	505	581
Number (percent) of Applications approved by IRG as	(#)	498	565
submitted	(%)	98.61%	97.25%
Number (percent) of Applications with unacceptable minority-	(#)	0	5
only inclusion	(%)	0.00%	0.01%
Number (percent) of Applications with unacceptable	(#)	1	1
sex/gender-only inclusion	(%)	0.00%	0.00%
Number (percent) of Applications with both unacceptable	(#)	6	10
minority AND sex/gender inclusion	(%)	0.02%	0.02%
Total Number (percent) of Applications with unacceptable	(#)	6	15
minority inclusion	(%)	0.02%	0.03%
Total Number (percent) of Applications with unacceptable	(#)	7	11
sex/gender inclusion	(%)	0.01%	0.02%
Total Number (percent) of unacceptable Applications as	(#)	7	16
submitted	(%)	0.01%	0.03%

Table 2. Extramural Research Awards: Bars-to-Funding and Resolutions for NIEHS

	2013	2014
Total Number of Awards	284	320
Number of Awards Involving Human Subjects	84	87
	29.6%	27.2%
Number (%) of Awards Involving Human Subjects that met the Inclusion Requirements as Submitted	84	86
	100.0%	98.9%
Number (%) of Awards where *Minority-Only* Bar-To-Funding was Removed by Program Staff	0	1
	0.0%	1.1%
Number of Awards where *Sex/Gender-Only* Bar-To-Funding was Removed by Program Staff	0	0
	0.0%	0.0%
Number (%) of Awards where both Minority AND Sex/Gender Bar-To-Funding was Removed by Program Staff	0	0
	0.0%	0.0%
Total Number (%) of Awards where Bar-To-Funding was Removed	0	1
	0.0%	1.1%

Staff Training on the Utilization of the Population Tracking System

A staff member of the Population Health Branch, Division of Extramural Research and Training, has been the designated person responsible for monitoring inclusion of all studies supported by the NIEHS Extramural Division and for submitting and approving data in the NIH Population Tracking System, from 1995 through FY2014. She received training on the Population Tracking System and also participates in annual training on human subject's and bioethics-related issues through the NIH Staff Training in Extramural Programs (STEP) as well as other seminars and training classes. She has represented the Institute on the Inclusion Operating Procedures Working Group, and its predecessor committee since 1996 and the Human Subjects Protection Liaison Committee since its inception. She has had an active role in the development of the new Inclusion Monitoring System that came online at the start of FY2015 and serves as co-chair of the IOPW training subcommittee. She has taken training on the new Inclusion Management System (IMS) and, over the past year, has held several staff training sessions on the new process and more recently on the new system.

Additional Staff Training

All NIEHS extramural program officers, grants management and review officers are required to take NIH training on research on human subjects and inclusion. Every year NIH offers an 8-week course related to human subjects research and protections. A number of DERT staff members have completed the course. In addition NIH offers one or more seminars related to human subject's inclusion as well as current NIH policy updates. All professional staff members are expected to attend those sessions relevant to their position. As NIEHS is not located in Bethesda, NIEHS staff is not able to attend in person. However, we arrange to watch specific training opportunities via videocast and webinars in a group and all staff has access to the training on their individual computers. Most training is available in an archive should staff be unable to participate during the originally scheduled time. Examples of training activities related to human subjects (HS) and inclusion in which NIEHS staff has participated over the two past years include the Inclusion Policy Training: Warning Curves Ahead: Clinical Research – Inclusion and You – A Scientific Forum; Part I - HS protections: What you always wanted to know about Regulation-NIH; Part II - HS Protections Training by OHRP/OER for NIH Extramural Staff; Bioethics – Why we Should Care; and Annual NIH Research Integrity 2013 Training – Research Misconduct in the Clinical Setting.

It should be noted that NIEHS has supported very few studies that are classified as Phase III Clinical trials. Nevertheless, staff is expected, and required, to be familiar with and enforce all requirements for research involving human subjects as defined by NIH/DHHS, including Phase III trials.

Analysis and Interpretation of Data

Congress mandates the collection of race, ethnicity and sex of participants in studies that use human subjects. Since 2002, investigators have been required to ask subjects to identify ethnicity and race in a two question format: ethnicity first, followed by identification of race. Although the PI is expected to collect race and ethnicity data appropriate for their particular study, they must be able to report the data in the required NIH categories. Ethnicity is broken out as either Hispanic or Not Hispanic. Race must be broken out as American Indian/Alaska Native; Asian; Black or African American; Hawaiian/Pacific Islander; or White. Subjects may identify one or more race, and if they do so are reported as "More than one race." Any participant may decline to report their race, ethnicity, or sex, in which case they are reported as "Unknown/not reported" in that category. As of FY2007, all NIEHS extramural protocols have been reported using the 2002 format.

Cumulative Enrollment in Extramural Research

Tables 3 and 4 below provide information on the distribution of cumulative enrollment in extramural research protocols by race, ethnicity and sex/gender for fiscal years 2013 and 2014.

Table 3. Total of All Subjects Reported in FY2013, Using the 1977 OMB Standards

Number of Protocols with Enrollment Data = 161

	American Indian/ Alaska Native	Asian	Black/ African American	Hawaii/ Pacific Islander	White	More Than One Race	Un-known/ Not Report	Total	Not Hispanic	Hispanic	Un-known/ Not Report	Total
Female	622	21,818	8,977	89	23,090	1,389	3,252	59,237	48,271	9,373	1,593	59,237
Male	443	13,506	4,779	57	20,790	1,237	1,944	42,756	35,115	6,554	1,087	42,756
Unknown	1	3	48	0	71	13	72	208	69	68	71	208
Total	1,066	35,327	13,804	146	43,951	2,639	5,268	102,201	83,455	15,995	2,751	102,201

Table 4. Total of All Subjects Reported in FY2014, Using the 1977 OMB Standards

Number of Protocols with Enrollment Data = 169

	American Indian/ Alaska Native	Asian	Black/ African American	Hawaii/ Pacific Islander	White	More Than One Race	Un-known/ Not Report	Total	Not Hispanic	Hispanic	Un-known/ Not Report	Total
Female	927	22,569	11,228	69	24,272	2,227	1,951	63,243	53,527	8,920	796	63,243
Male	738	13,708	4,294	40	16,131	2,380	1,343	38,634	30,947	7,165	522	38,634
Unknown	0	1	31	0	60	20	47	159	73	29	57	159
Total	1,665	36,278	15,553	109	40,463	4,627	3,341	102,036	84,547	16,114	1,375	102,036

In 2013 (Table 2), NIEHS funded 284 studies of which 84 involve human subjects with a combined total of 102,201 participants (Table 3). Of these 59,237 (57.96%) were female; 42,756 (41.84%) were male; and 208 (0.20%) chose not to identify their gender. Of the total number of subjects, participants self-identified in the following percentages for race: 1.04% American Indian/Alaska Native, 24.57 Asian, 13.51% Black/African American, 43.00% White, 2.58% More Than One Race, with 5.15% choosing not to identify their race. Ethnicity breakdown was 81.56% Not Hispanic, 15.65% Hispanic with 2.69% choosing not to identify their ethnicity.

In 2014 (Table 2), NIEHS funded 320 studies of which 87 involved human subjects with a combined total of 102,036 participants (Table 4). Of these 63,243 (61.98%) were female; 38,634 (37.86%) were male; and 159 (0.16%) chose not to identify their gender. Of the total number of subjects, participants self-identified in the following percentages for race: 1.63% American Indian/Alaska Native; 35.65% Asian; 15.24% Black/African American; 39.66% White; 4.53% More Than One Race; with 3.27% electing not to identify their race. Ethnicity breakdown was 82.86% Not Hispanic; 15.79% Hispanic, with 1.35% not identifying their ethnicity.

In 2013 and 2014, Asians made up a significant portion of the subject population. This is not unusual for NIEHS. In 2012 we had a total enrollment of 119,423 subjects in 156 protocols of which 56,402 (47.26%) were Asian. The large percentage of Asians was due to two studies, a large Phase III cook stove study in Nepal and a study on arsenic and manganese in Bangladesh. The Nepal study has ended and accounts for the decrease in the number of Asians and the overall decrease in overall research participants. The current percentage of Asians is due to the single cohort in Bangladesh. This study has a total of 30,039 subjects enrolled in both 2013 and 2014 and accounts for over 82% of the participants reporting as Asian.

The numbers of participants reporting as unknown/not reported for ethnicity and race shows ongoing improvement. NIEHS staff continues to work with principal investigators (PI) in an effort to educate them on the importance of gender and race/ethnicity reporting and to minimize discrepancies due to reporting errors. Staff questions a PI when a high number of unknowns are reported to confirm the PI is using the

appropriate two-question format in requesting that information. However, subjects self-report for gender, ethnicity and race. As long as investigators are using the two question format to obtain the information, and are accurately reporting ethnicity and race as provided to them, the requirement to NIH is fulfilled.

Phase III Clinical Trials

As seen in Table 5 below, NIEHS supported no Phase III clinical trials in 2013 or 2014. We supported two grants with Phase III trials that began in 2008 and ended in 2012. An intervention study in Nepal looked at the effect of biomass cook stoves on acute respiratory illness and respiratory health of newborns and children up to 36 months of age before and after replacement with a stove that is more efficient and vented to the exterior. This is the primary study and includes more detailed evaluation than the second piece which includes the respiratory health of the intervention on family members living in the same house as the children. Because the study population is 100% Asian there was no plan to analyze by race. The sample was sufficiently large that analysis by gender was planned. However, as the grant ended, it is unknown whether this analysis was ever completed.

The second study looked at the effect of indoor particulate matter air pollution generated by wood stoves on asthmatic children in rural Montana. It was a small three-arm study: placebo control, air filters and replacement of stove with an EPA rated stove. The population in rural Montana is primarily white so again racial analysis was not planned. Analysis by gender was to take place, but the sample size (planned total n=108) was not expected to be sufficiently large to yield significant results. In 2012 the PI reported information on caregivers, so that piece was newly added. Data was still being collected at the time the grant ended.

Clinical Research by Sex/Gender

As shown in Table 5 below, in 2013 NIEHS supported 35 protocols that reported women only and 9 that reported men only. There was one study that reported only men and unknown for sex. In 2014, there were 44 protocols reporting women only and 11 that reported men only. In 2014 neither the female or male single sex studies reported any subjects that did not report sex/gender.

NIEHS continues to have more females than males represented in research studies. While the overall number of male only studies increased over 2011 and 2012 levels, the average number of men participating in research studies decreased from approximately 45% in 2011 and 2012 to 41.84% in 2013 to 37.86% in 2014. The data on single sex studies is deceptive though. The majority of female only studies are a result of mother/child epidemiology studies with the mothers reported separately from the children. Some of these studies include a population of children either all female or all male depending on the focus of the research. The decision to report the mothers and children separately was made to increase the accuracy of the reporting of the children; however that decision artificially increases the number of single sex studies.

Table 5. FY2013 and FY2014 - Summary of all NIEHS Extramural Research: Total Number of Protocols and Enrollment by Sex/ Gender

	2013			2014	
	Phase III Trials	Other Clinical Research		Phase III Trials	Other Clinical Research
Protocols reporting women only	0	35		0	44
Protocols reporting men only	0	9		0	11
Protocols reporting both women and men	0	107		4	104
Protocols reporting both men and unkown	0	1		0	0
Protocols reporting both women and unknown	0	0		0	0
Protocols reporting both women, men and unknown	0	9		0	10
Early stage studies where gender enrollment data has not yet been submitted	0	114		0	111

NIH requires reporting of foreign studies separately from domestic (U.S.) studies. As show in Table 6 below, in 2013 73.9% of NIEHS studies were performed within the United States and its territories. The other 26.1% were performed in foreign countries. In 2014, Table 7 below, 71.6% of studies were domestic and 28.4% were performed in foreign locations. Some of the foreign countries in which these studies were performed include China, Bangladesh, Nepal, Korea, Israel, Sri Lanka, Canada, Mexico, Uruguay, Ecuador, Jamaica, Honduras, Peru, Russia, Poland, Italy, Denmark, Greenland, the Faroe Islands, the Seychelles, Ghana, Rwanda, Congo, Egypt, South Africa, and Malawi.

Table 6. FY2013 - Summary of all NIEHS Extramural Clinical Research including Phase III Trials Reported: Total Number of Protocols and Enrollment by Domestic versus Foreign Protocols

PROTOCOLS REPORTED	Total All Clinical Studies*	Domestic	Percent Domestic (%)	Foreign	Percent Foreign (%)
Protocols with Enrollment	161	119	73.9%	42	26.1%
Percent of Total Protocols (%)	58.5%	59.2%		56.8%	
Protocols with zero enrollment. Enrollment data has not yet been submitted	114	82	71.9%	32	28.1%
Percent of Total Protocols (%)	41.5%	40.8%		43.2%	
Total Number of Protocols	275	201	73.1%	74	26.9%

Table 7. FY2014 - Summary of all NIEHS Extramural Clinical Research including Phase III Trials Reported: Total Number of Protocols and Enrollment by Domestic versus Foreign Protocols

PROTOCOLS REPORTED	Total All Clinical Studies*	Domestic	Percent Domestic (%)	Foreign	Percent Foreign (%)
Protocols with Enrollment	169	121	71.6%	48	28.4%
Percent of Total Protocols (%)	60.4%	61.1%		58.5%	
Protocols with zero enrollment. Enrollment data has not yet been submitted	111	77	69.4%	34	30.6%
Percent of Total Protocols (%)	39.6%	38.9%		41.5%	
Total Number of Protocols	280	198	70.7%	82	29.3%

Intramural Research Data

Data for intramural projects/contracts are submitted through the NIH Clinical Center database and are not a part of the extramural process. These data are not discussed here, but are included for information purposes in Tables 8 through 12 below.

Table 8. New Form: Total of All Subjects Reported in FY2013, Using the 1977 OMB Standards

Number of Protocols with Enrollment Data = 60

	American Indian/ Alaska Native	Asian	Black/ African American	Hawaiia/n Pacific Islander	White	More Than One Race	Un-known/ Not Report	Total	Not Hispanic	Hispanic	Un-known / Not Report	Total
Female	357	38,301	10,830	62	139,218	904	4,990	194,662	187,483	5,477	1,702	194,662
Male	418	30,948	6,246	56	23,170	863	4,335	66,036	61,461	3,546	1,029	66,036
Unknown	0	0	1	0	407	0	90	498	439	19	40	498
Total	775	69,249	17,077	118	162,795	1,767	9,415	261,196	249,383	9,042	2,771	261,196

Table 9. New Form: Total of All Subjects Reported in FY2014, Using the 1977 OMB Standards

Number of Protocols with Enrollment Data = 59

	American Indian/ Alaska Native	Asian	Black/ African American	Hawaiian/ Pacific Islander	White	More Than One Race	Un-known/ Not Report	Total	Not Hispanic	Hispanic	Un-known / Not Report	Total
Female	390	3,165	11,518	63	140,576	957	5,211	161,880	154,399	5,647	1,834	161,880
Male	501	3,819	7,344	62	26,357	1,011	5,022	44,116	38,679	4,283	1,154	44,116
Unknown	0	0	1	0	407	0	140	548	439	20	89	548
Total	891	6,984	18,863	125	167,340	1,968	10,373	206,544	193,517	9,950	3,077	206,544

Table 10. FY2013 and FY2014 - Summary of all NIEHS Intramural Research: Total Number of Protocols and Enrollment by Sex/ Gender

	2013			2014	
	Phase III Trials	Other Clinical Research		Phase III Trials	Other Clinical Research
Protocols reporting women only	0	15		0	15
Protocols reporting men only	0	2		0	2
Protocols reporting both women and men	0	38		4	37
Protocols reporting both men and unkown	0	0		0	0
Protocols reporting both women and unknown	0	0		0	0
Protocols reporting both women, men and unknown	0	5		0	5
Early stage studies where gender enrollment data has not yet been submitted	0	6		0	6

Table 11. FY2013 - Summary of all NIEHS Intramural Clinical Research including Phase III Trials Reported: Total Number of Protocols and Enrollment by Domestic versus Foreign Protocols

PROTOCOLS REPORTED	Total All Clinical Studies*	Domestic	Percent Domestic (%)	Foreign	Percent Foreign (%)
Protocols with Enrollment	60	52	86.7%	8	13.3%
Percent of Total Protocols (%)	90.9%	89.7%		0.0%	
Protocols with zero enrollment. Enrollment data has not yet been submitted	6	6	100.0%	0	0.0%
Percent of Total Protocols (%)	9.1%	10.3%		0.0%	
Total Number of Protocols	66	58	87.9%	8	12.1%

Table 12. FY2014 - Summary of all NIEHS Intramural Clinical Research including Phase III Trials Reported: Total Number of Protocols and Enrollment by Domestic versus Foreign Protocols

PROTOCOLS REPORTED	Total All Clinical Studies*	Domestic	Percent Domestic (%)	Foreign	Percent Foreign (%)
Protocols with Enrollment	59	51	86.4%	8	13.6%
Percent of Total Protocols (%)	90.8%	89.5%		100.0%	
Protocols with zero enrollment. Enrollment data has not yet been submitted	6	6	100.0%	0	0.0%
Percent of Total Protocols (%)	9.2%	10.5%		0.0%	
Total Number of Protocols	65	57	87.7%	8	12.3%