



U.S. ENVIRONMENTAL PROTECTION AGENCY

OFFICE OF INSPECTOR GENERAL

Improvements to EPA Policies and Guidance Could Enhance Protection of Human Study Subjects

Report No. 14-P-0154

March 31, 2014



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Abbreviations

CAA	Clean Air Act
CAPS	Concentrated Air Particles
CFR	Code of Federal Regulations
CITI	Collaborative IRB Training Initiative
DHRO	Division Human Research Officer
EPA	U.S. Environmental Protection Agency
GAO	Government Accountability Office
HRPO	Human Research Protocol Office
HSRB	Human Studies Review Board
HSRRO	Human Studies Research Review Official
IRB	Institutional Review Board
NAAQS	National Ambient Air Quality Standards
NHEERL	National Health and Environmental Effects Research Laboratory
OHRE	Office of Human Research Ethics
OIG	Office of Inspector General
ORD	Office of Research and Development
PM	Particulate matter
PM _{2.5}	Fine particulate matter
SOP	Standard operating procedure
µg/m ³	Micrograms per cubic meter of air
UNC	University of North Carolina at Chapel Hill

Cover photo: A human subjects air pollution test chamber used during the OMEGACON study in the U.S. EPA Human Studies Facility in Chapel Hill, North Carolina. (EPA OIG photo)

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At a Glance

Why We Did This Review

In response to a congressional request, we conducted this review to determine whether the U.S. Environmental Protection Agency (EPA) followed applicable laws, regulations, policies, procedures and guidance when it exposed human subjects to diesel exhaust emissions or concentrated airborne particles. In particular, we reviewed five studies that the EPA conducted during 2010 and 2011 to determine whether the agency (1) obtained sufficient approval to conduct these studies; (2) obtained adequate informed consent from the human study subjects; and (3) adequately addressed adverse events that occurred during the studies. The EPA's human studies are governed by 40 Code of Federal Regulations (CFR) Part 26, also known as the Common Rule, which establishes minimum standards. The EPA conducts human research studies to better understand the health effects of pollution on humans.

This report addresses the following EPA theme:

- Addressing climate change and improving air quality.

For further information, contact our public affairs office at (202) 566-2391.

The full report is at:
www.epa.gov/oig/reports/2014/20140331-14-P-0154.pdf

Improvements to EPA Policies and Guidance Could Enhance Protection of Human Study Subjects

What We Found

The EPA followed applicable regulations when it exposed 81 human study subjects to concentrated airborne particles or diesel exhaust emissions in five EPA studies conducted during 2010 and 2011. However, we identified improvements that could be made to the EPA's policies and guidance to enhance protection of study subjects.

The EPA can enhance its human studies by improving how it obtains approval for studies; how it communicates risk to people who participate in EPA studies; and how it addresses adverse events in its guidance.

The EPA obtained approval to conduct the five human research studies, including approval from a biomedical Institutional Review Board (IRB) and the EPA Human Studies Research Review Official (HSRRO). However, the EPA's policies and guidance do not address when HSRRO approval is needed for significant study modifications. Developing guidance for when HSRRO must approve significant modifications would ensure their independent review.

The EPA obtained informed consent from the 81 human study subjects before exposing them to pollutants. While the consent forms met the requirements of 40 CFR Part 26, we found that exposure risks were not always consistently represented. Further, the EPA did not include information on long-term cancer risks in its diesel exhaust studies' consent forms. An EPA manager considered these long-term risks minimal for short-term study exposures. We believe presenting consistent information about risks further ensures that study subjects can make the most informed choice about participating in a study.

The EPA addressed six adverse events during its studies, reported them to the IRB, and provided clinical follow-up after the events. While the clinical follow-up appeared to be reasonable, the EPA's policies, guidance and consent forms do not establish the EPA's clinical follow-up responsibilities. According to EPA managers, the agency uses the latest University of North Carolina at Chapel Hill (UNC) IRB's adverse event definitions and reporting timeframes to respond to adverse events. However, the agency's guidance provides different definitions and reporting timeframes and does not state that the EPA has adopted the UNC-IRB definitions and timeframes. Using EPA's guidance, the EPA reported two of the six adverse events later than required and did not report two other events to IRB.

Recommendations and Planned Corrective Actions

We recommend that the EPA establish procedures for obtaining HSRRO approval of significant study modifications, ensure consent forms consistently address pollutant risks, update its guidance to include the EPA's clinical follow-up responsibilities, and address a number of other recommendations. The EPA concurred with all recommendations and provided planned corrective actions and completion dates that meet the intent of the recommendations. All recommendations have been resolved.



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

THE INSPECTOR GENERAL

March 31, 2014

MEMORANDUM

SUBJECT: Improvements to EPA Policies and Guidance Could Enhance Protection of
Human Study Subjects
Report No. 14-P-0154

FROM: Arthur A. Elkins Jr.

A handwritten signature in black ink, appearing to read "Arthur A. Elkins Jr.", is placed to the right of the "FROM:" line.

TO: Lek Kadeli, Acting Assistant Administrator
Office of Research and Development

This is our report on the subject evaluation conducted by the Office of Inspector General (OIG) of the U.S. Environmental Protection Agency (EPA). This report contains findings that describe the problems the OIG has identified and corrective actions the OIG recommends. This report represents the opinion of the OIG and does not necessarily represent the final EPA position. Final determinations on matters in this report will be made by EPA managers in accordance with established audit resolution procedures.

The EPA office having primary responsibility over the issues evaluated in this report is the Office of Research and Development's National Health and Environmental Effects Research Laboratory.

Action Required

The agency agreed with all recommendations and provided planned corrective actions and completion dates that meet the intent of these recommendations. Therefore, the agency is not required to provide a written response for these recommendations. Recommendation 2 is closed and no further action is required. For the remaining recommendations, which are in an open status, please update the EPA's Management Audit Tracking System as you complete the planned corrective actions. Please notify my staff if there is a significant change in the agreed-to corrective actions. Should you choose to provide a response to this final report, we will post your response on the OIG's public website, along with our memorandum commenting on your response. You should provide your response as an Adobe PDF file that complies with the accessibility requirements of Section 508 of the Rehabilitation Act of 1973, as amended.

We will post this report to our website at <http://www.epa.gov/oig>.

If you or your staff have any questions regarding this report, please contact Carolyn Copper, Assistant Inspector General for Program Evaluation, at (202) 566-0829 or copper.carolyn@epa.gov; or Rick Beusse, Director, Air Evaluations, at (919) 541-5747 or beusse.rick@epa.gov.

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Chapter 1

Introduction

Purpose

In response to a congressional request, the Office of Inspector General (OIG) conducted a review of the U.S. Environmental Protection Agency's (EPA's) research involving human subjects to determine whether the EPA followed applicable laws, regulations, policies, procedures and guidance when it exposed human subjects to concentrated airborne particles or diesel exhaust emissions. Our specific objectives were to determine whether the EPA, in conducting five studies¹ that exposed human subjects to diesel exhaust emissions or Concentrated Air Particles (CAPS) during 2010 and 2011:

- 1) Obtained sufficient approval to expose subjects to specific levels of diesel exhaust emissions or concentrated airborne particles;
- 2) Obtained adequate informed consent from human study subjects before exposing them to diesel exhaust emissions or concentrated airborne particles; and
- 3) Adequately addressed any adverse events that occurred, including:
 - (a) Notifying the University of North Carolina at Chapel Hill's (UNC's) Institutional Review Board (IRB), the Human Studies Review Board (HSRB) and the EPA Human Subjects Research Review Official (HSRRO);
 - (b) Revising consent forms as needed; and
 - (c) Providing clinical follow-up in accordance with the approved protocol.

Background

What Is Human Subjects Research?

According to the EPA, any project that collects data from or about humans may constitute human subjects research. As such, it would be subject to EPA-issued regulations regarding the protection of human subjects under Title 40, Part 26 of the Code of Federal Regulations (CFR). Under these regulations, the EPA defines "human subject" as a "living individual about whom an investigator conducting

¹ The studies were entitled XCON, KINGCON, OMEGACON, DEPOZ and LAMARCK.

research obtains 1) data through intervention or interaction with the individual, or 2) identifiable private information.” *Interventions* include physical procedures or manipulations of the subject or the subject’s environment by which data are gathered. *Interaction* includes communication or interpersonal contact between investigator and subject. Research is defined as a “systematic investigation... designed to develop or contribute to generalizable knowledge.”

The EPA has been conducting controlled exposure studies for about 40 years. In controlled exposure studies, human subjects are intentionally exposed to pollutants under controlled conditions. These studies allow investigators to isolate and explain health events related to such exposures. According to National Health and Environmental Effects Research Laboratory (NHEERL) guidance, the studies can also help estimate “safe threshold exposures for humans.” The EPA is among 15 federal agencies² that have adopted rules governing the protection of human subjects used in this and other types of human subjects research.

Why Does the EPA Conduct Research Involving Human Subjects?

The Clean Air Act (CAA) authorizes the EPA Administrator to establish a national research and development program for the prevention and control of air pollution. According to the CAA, the Administrator shall conduct a research program on the short-term and long-term effects of air pollutants on human health. When conducting the research program, the Act states that the Administrator shall conduct studies, including epidemiological, clinical and laboratory and field studies as necessary to identify and evaluate exposure to, and effects of, air pollutants on human health. The Administrator has established this program within the agency’s Office of Research and Development (ORD).

The CAA amendments of 1990 require the EPA to set and periodically review National Ambient Air Quality Standards (NAAQS) for pollutants considered harmful to public health and the environment. The EPA’s controlled exposure studies help set these standards by identifying exposure-response relationships and providing more information on how the body interacts with particular pollutants. The EPA’s Office of Research and Development prepares multiyear plans in conjunction with the Office of Air and Radiation to determine the various human research studies that ORD will need to conduct to answer its key research questions. From fiscal years 2009 to 2013, the agency spent an average of about \$3.46 million per year, or slightly over \$17.3 million for the 5 years, and maintained about 19 full-time equivalents (FTEs) to support the EPA’s human subjects research conducted by ORD’s Clinical Studies Branch.

²According to the Department of Health and Human Services, 15 federal agencies adopted the Common Rule in 1991 by issuing regulations.

EPA's Human Studies Facility

The EPA's Human Studies Facility, located on the UNC campus, is primarily intended for research to support EPA standards and regulations and is equipped to study the health effects of airborne pollutants on humans. The facility has the capability to deliver gaseous pollutants at precise concentrations across a broad range of atmospheric conditions. Human subjects research exposure systems used by EPA include two small (36 square feet) and two large (300 square feet) study chambers and one neurophysiological test room.



A small chamber (36 square feet) used for diesel studies (left) and a large chamber (300 square feet) used for ozone studies (right). (EPA OIG photos)



Exam room where NHEERL conducts initial and follow-up physical exams on study participants. (EPA OIG photo)

The facility also has several exam rooms where EPA staff conduct physical exams on study subjects prior to their participation in a study. According to ORD managers, the agency uses the physical exams to exclude individuals who might be at risk for experiencing an adverse event during the study.

Key Criteria Governing EPA Research Involving Human Subjects

The EPA conducts research involving intentional exposures of human subjects to pollutants. The agency performs this research under a number of statutory, regulatory and agency orders, policies and guidance.

Title 40 CFR 26

Title 40 CFR 26 (the Common Rule) provides the regulatory framework under which the EPA conducts research involving human subjects. The regulation requires that the agency provide “written assurance” that it will comply with the Common Rule. The assurance must include, among other things, a “statement of principles” governing its responsibilities for protecting human subjects. It must also include the designation of an IRB to review research proposals. Additionally, it must include procedures for ensuring that unanticipated problems involving risks to subjects are reported to the IRB and other agency officials. The EPA possessed an active Federalwide Assurance from the Department of Health and Human Services to conduct human subject research during 2010 and 2011.

The regulation also sets forth the requirements for an IRB. These include the membership, functions and operations, and criteria for approval of research. In addition, the regulation sets requirements for informed consent. According to the regulation, the investigator must give the prospective study subject sufficient opportunity to consider whether or not to participate. In addition, the regulation requires that the consent form:

- Present the information in language understandable to the subject.
- Provide a description of any reasonably foreseeable risks or discomforts to the subject.
- Disclose alternative courses of treatment, benefits to the subject and identification of any experimental procedures.
- Contain a statement that participation is voluntary.

The regulation also requires that the prospective study subject be provided a copy of the consent form.

EPA Order 1000.17 Change A1

The agency issued EPA Order 1000.17 in 1977. In 1999, the policy was replaced with EPA Order 1000.17 Change A1, and it was amended in 2011 to ensure that the EPA complied with the Common Rule. It requires that the EPA’s HSRRO approve all research involving human subjects conducted or supported by the EPA unless otherwise exempt. The Order establishes a presumption that “studies involving risk of substantial injury to a human subject from the conduct of the study and that studies testing for irreversible health effects in humans will not be approved..., unless strongly persuasive additional justification acceptable to the Review Official (HSRRO) is submitted.”

National Health and Environmental Effects Research Laboratory Policy and Guidance

ORD's NHEERL is the only EPA laboratory that conducts controlled human exposure studies. The Laboratory issued a policy in 2004 and updated guidance in 2010 governing NHEERL human subjects research activities. The policy, along with the EPA Order, requires that all human subjects research be approved or determined to be exempt by the HSRRO. The HSRRO is independent from and not organizationally located within NHEERL. The NHEERL Human Research Guidance provides more detailed information on the NHEERL approval process. This includes which officials and staff must review the protocol prior to IRB submission. It also includes the special reviews required for controlled exposure studies. According to NHEERL guidance, any full scale controlled-exposure study of subjects to known pollutants must be reviewed by two external reviewers and receive a medical review if there is more than minimal risk. Once the IRB approves the study protocol, a study justification document is prepared which describes the risks to study participants versus the benefits to society, as well as why the study could not be conducted using animals. The entire package is then reviewed and approved by the Director of the Human Research Protocol Office (HRPO), the Environmental Public Health Division Director, the NHEERL Associate Director for Health, and the HSRRO.

The NHEERL guidance also provides detailed information on the informed consent process. For example, the document states that "informed consent is a process, not a form." Information must be presented in a way to allow subjects to decide voluntarily whether to participate. It must use "lay language," especially in describing the study purpose, duration, risks and benefits. The document suggests language be at the 8th to 10th grade reading level.

NHEERL guidance defines an adverse event as undesirable and unintended, though not necessarily unanticipated, injury or physical or emotional consequence to a human subject. These events can be serious and/or unanticipated. They also have different reporting requirements according to their severity. (Table 9 in Chapter 4 provides detailed definitions for each of these events). The more serious the event, the more quickly the principal investigator must report the event to the IRB. The report must be written and include information for the IRB to "judge whether or not the event raises new questions about risks to participants or the research design."

Health Impacts and Exposure Levels for Two Key Air Pollutants

ORD has conducted research involving intentional exposures of human subjects to fine particulate matter and diesel exhaust for over 10 years. Based on years of research, the EPA has established acceptable levels of exposure for fine particles, but has not established a level for diesel exhaust other than as a source of fine particulate matter.

Fine Particulate Matter

Particulate matter (PM) is a complex mixture of harmful solid and liquid particles. Fine particles that are less than or equal to 2.5 microns in diameter are known as fine particulate matter (PM_{2.5}). These particles are about 1/30th the thickness of a human hair. The greatest number of particles is usually concentrated in the “ultrafine” range. This range represents particles that are less than or equal to 0.1 microns in diameter or about 1/1000th to 1/10,000th the thickness of a human hair. Because fine and ultrafine particles can penetrate deeply into the respiratory tract, these smaller particles may be more likely to cause adverse health effects than larger particles. CAPS are fine particles collected from the immediate environment that are concentrated using specialized equipment. By concentrating air particles, ORD can mimic the levels of pollution that humans are exposed to in other areas, such as severe nonattainment areas in the United States and more polluted cities in the world.

NHEERL has two ambient-air-particle concentrators for studying the effects of concentrated particulate matter. Available systems include a coarse-particle concentrator for particle sizes from 2.5 to 10 micrometers and a fine/ultrafine-particle concentrator for particles 2.5 micrometers and smaller.



The turquoise, gray and red pipes are used to control the airstream conditions, temperature and humidity in a test chamber (left) and a bank of analyzers used for pollutant monitoring (right). (EPA OIG photos)

Diesel Exhaust

Diesel exhaust is produced when an engine burns diesel fuel. Diesel exhaust is a complex mixture of more than 40 toxic air contaminants. These include 19 known or suspected carcinogens, such as benzene, formaldehyde and 1,3-butadiene. Particles emitted from diesel engines are usually concentrated in the “ultrafine” range. Their small size makes them highly respirable and able to reach the deep lung. The improvement in the development of diesel technologies over the last few decades has led to diesel engines with reduced emissions.

Table 1 describes the health impacts from short-term and long-term exposures to PM_{2.5} and diesel exhaust. While some of these impacts are serious, the persons most at risk are children, elderly people and people with heart and lung disease. According to several EPA managers and documents we reviewed, EPA excluded persons most at risk from the subject population.

Table 1: Health impacts from exposure to fine particulate matter and diesel exhaust

Pollutant	Exposure	Respiratory impacts	Cardiovascular impacts	Other impacts
PM _{2.5}	Short-term exposure ^a	Aggravated lung disease, causing asthma attacks and acute bronchitis, and may also increase susceptibility to respiratory infections.	In people with heart disease, exposure linked to heart attacks and arrhythmias.	Mortality
	Long-term exposure	Respiratory-related disease and respiratory effects.	Cardiovascular-related mortality and cardiovascular effects.	Mortality and suggestive of lung and other cancers and reproductive and developmental effects.
Diesel exhaust/PM	Short-term exposure ^a	Respiratory effects including irritation to throat and lungs, a cough, nausea and exacerbated asthma.	Cardiovascular effects such as worsening heart disease ^b	Irritation to the eyes and nose and neurological effects such as lightheadedness.
	Long-term exposure	Respiratory effects including lung inflammation.		Lung cancer and mortality.

Source: OIG analysis of the EPA's Integrated Science Assessment for PM, EPA websites on particulate matter and diesel particulate matter, National Ambient Air Quality Standards for PM (December 2012) and the U.S. EPA. Health Assessment Document for Diesel Engine Exhaust (Final 2002). U.S. EPA Office of Research and Development, National Center for Environmental Assessment, Washington, D.C., EPA/600/8-90/057F, 2002.

^aAccording to the agency, short-term epidemiological studies generally involved exposures ranging from 1 to 5 days. The length of the exposure sessions for the five studies the OIG reviewed can be found in table 3.

^bHealth impacts for diesel exhaust were combined because sources did not distinguish between short- and long-term effects.

Exposure Levels for PM_{2.5}

The Clean Air Act required that the EPA establish standards, or acceptable levels of exposure, with an “adequate margin of safety” for each of the criteria pollutants. The EPA has set NAAQS for particulate matter. PM_{2.5} is one of the six principal or "criteria" pollutants. Table 2 lists the levels of exposure for PM_{2.5} for the 24-hour and annual levels. Primary standards provide public health protection, including protecting the health of “sensitive” populations such as asthmatics, children, and the elderly. Secondary standards provide public welfare protection, including protection against decreased visibility and damage to animals, crops, vegetation and buildings. Appendix A lists the PM_{2.5} concentrations associated with the EPA's Air Quality Index for Particle Pollution.

Table 2: NAAQS Standards for PM

Pollutant [final rule cite]		Primary/ secondary	Averaging time	Level ^b	Form
Particle pollution Dec 14, 2012 ^a	PM _{2.5}	Primary	Annual	12 µg/m ³	Annual mean, averaged over 3 years
		Secondary	Annual	15 µg/m ³	Annual mean, averaged over 3 years
		Primary and secondary	24-hour	35 µg/m ³	98th percentile, averaged over 3 years

Source: The EPA's summary of NAAQS standards, December 14, 2012.

^aOn December 14, 2012³, the EPA revised its existing standards for PM.

^bUnits of measure are micrograms per cubic meter of air (µg/m³).

Exposure Levels for Diesel Exhaust

Diesel engines are one source of PM. The EPA has not established levels of acceptable exposure for diesel exhaust other than as particulate matter. The EPA has stated that long-term inhalation exposure to diesel exhaust is likely to pose a lung cancer hazard to humans.

EPA's Human Research Studies for PM and Diesel Exhaust

Over the last 10 years, the EPA has conducted 13 human exposure studies using CAPS and four studies using diesel exhaust. According to an EPA principal investigator, the exposure levels selected for a study reflect a balance between being high enough to produce biological responses but not so high as to produce clinical responses in a study subject. For example, a biological response would be a short-term, reversible response such as inflammation that goes away in a few days. In contrast, a clinically significant response could put a study subject at medical risk. Table 3 describes the five CAPS and diesel exhaust studies conducted in 2010 and 2011 that we reviewed.

³EPA published the final rule for 40 CFR Parts 50, 51, 52 et al., NAAQS for PM, in the Federal Register on January 15, 2013. The final rule became effective on March 18, 2013.

Table 3: EPA particulate matter and diesel exhaust human research studies conducted in 2010-2011

Study	Pollutant(s) that humans were exposed to	Pollutant concentration approved by IRB (PM or diesel exhaust)	Length of pollutant exposure approved by IRB	Study protocol description of study subjects approved by the IRB	Number of study subjects exposed in 2010 and 2011
XCON	CAPS (PM)	Up to 600,000 particles per cc	2 two-hour exposures: 1 PM and 1 clean air exposure ^a	Adults 25 to 70 years of age with metabolic syndrome ^b	23
OMEGACON	CAPS (PM)	Up to 600 µg/m ³	2 two-hour exposures: 1 PM and 1 clean air exposure	Healthy adults 50 to 75 year olds	17
KINGCON	CAPS (PM)	Up to 600 µg/m ³	2 two-hour exposures: 1 PM and 1 clean air exposure	45 to 65 years of age with mild asthma who were non-smokers	5
LAMARCK	Diesel exhaust and ozone	300 µg/m ³	3 two-hour exposures: 1 ozone, 1 diesel exhaust, and 1 clean air exposure	Healthy adults and adults with mild to moderate asthma	25
DEPOZ	Diesel exhaust and ozone	300 µg/m ³	4 two-hour exposures: 1 diesel exhaust and ozone, 1 ozone only, 1 diesel exhaust only, and 1 clean air exposure followed by a two hour exposure to ozone the next day	Healthy adults 18 to 55 years old	18
TOTAL					88^c

Source: OIG analysis of information provided by the EPA ORD NHEERL.

^aAll of the studies exposed human subjects to clean air as a scientific control.

^bThe National Cholesterol Education Program characterizes metabolic syndrome patients as having three of the following: increased abdominal girth, elevated blood pressure, dyslipidemia (abnormal amount of fats and cholesterol in the blood), elevated fasting triglycerides and elevated fasting glucose.

^cSeven individuals participated in two studies or 81 unique individuals participated in the 5 studies during 2010 and 2011.

The EPA offered to pay the human subjects participating in the five studies a maximum of about \$950 to about \$3,700. Study subjects are paid more to participate in lengthier, more complex studies. The UNC-IRB approved the payment amounts for these five studies.

Scope and Methodology

In response to a request by Congress, we assessed whether the EPA followed applicable laws, regulations, policies, procedures and guidance when it exposed 41 human subjects to concentrated airborne particles or diesel exhaust emissions during three specific studies (XCON, KINGCON and OMEGACON) that the EPA conducted in 2010 and 2011. Additionally, because of Congressional interest in the exposure of subjects to diesel exhaust emissions, we also reviewed two other EPA studies (DEPOZ and LAMARCK) where subjects were exposed to diesel exhaust during the 2010–2011 timeframe. For these studies, we evaluated (1) the sufficiency of the approval process; (2) the adequacy of the process for

obtaining the study subject's informed consent; and (3) the adequacy of the EPA's response to any adverse events.

To determine if the EPA obtained sufficient approval to expose subjects to specific levels of CAPS or diesel exhaust emissions, we obtained and reviewed federal and EPA regulations, policies and guidance concerning human subjects research. We reviewed the study protocols for all five studies, including the study applications, consent forms, and EPA HSRRO and IRB review and approval documents. We compared the EPA's and the IRB's documentation of decisions, actions and events with the requirements of the Common Rule (40 CFR Part 26). We also compared them to EPA Order 1000.17 Change A1 and ORD and NHEERL policies. We interviewed current and former managers and staff from ORD and the Office of the Science Advisor. We interviewed the principal investigators for the five studies we reviewed. We also interviewed managers and staff from the Office of Human Research Ethics (OHRE) at UNC who oversee the IRB for EPA's human subjects research conducted at the Human Studies Facility in Chapel Hill.

To determine if the EPA obtained adequate informed consent from human study subjects before exposing them to concentrated airborne particles or diesel exhaust emissions, we obtained and reviewed the 88 signed consent forms from 81 study subjects that were exposed to pollutants during 2010 and 2011 in the five studies. Seven individuals participated in two of the five studies we reviewed. Thus, 81 unique individuals participated in the five studies from 2010 to 2011. In addition, we interviewed nine study subjects who participated in at least one of the five studies. This included three human subjects who experienced adverse events, two study subjects who did not complete all exposure sessions, and four study subjects who did not experience an event. We also discussed informed consent procedures with the principal investigators for each of the five studies. The interviews provided us with information about how the EPA obtained informed consent from the study subjects, addressed adverse events and provided clinical follow-up.

To determine whether the EPA adequately addressed any adverse events that occurred, for each adverse event we obtained and reviewed the documentation of EPA's notification to the IRB. We also reviewed other notifications such as to the EPA HSRRO. Additionally, we determined whether the EPA revised the consent forms after an event. We also assessed whether the EPA provided clinical follow-up in accordance with the approved protocol. We reviewed the EPA and the IRB documentation of adverse events and medical notes about the subjects. We interviewed the principal investigators for the five studies we reviewed, as well as ORD managers and staff about the adverse events that occurred. We also interviewed managers and staff from OHRE at UNC. The EPA office having primary responsibility over the issues evaluated in this report is ORD's National Health and Environmental Effects Research Laboratory.

We conducted our review from November 2012 to January 2014 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform our review to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our objectives.

Prior Reports

Prior reports by the U.S. Government Accountability Office (GAO) applicable to the topics addressed by this evaluation included:

- GAO Report No. 09-448T: *Undercover Tests Show the Institutional Review Board System Is Vulnerable to Unethical Manipulation*, March 26, 2009.
- GAO Report No. 01-775T: *HUMAN SUBJECTS RESEARCH: HHS Takes Steps to Strengthen Protections, but Concerns Remain*, May 23, 2001.
- GAO Report No. HEHS-96-72: *SCIENTIFIC RESEARCH: Continued Vigilance Critical to Protecting Human Subjects*, March 8, 1996.

Chapter 2

Studies Obtained Required Approvals, but Sequence of Approvals Not Followed and Procedures Could Be Improved

The EPA obtained required approvals to expose study subjects to specific levels of concentrated airborne particles and diesel exhaust emissions. For each study, the EPA obtained approval to conduct the study from one of UNC's biomedical IRBs, internal NHEERL division and senior management, and the EPA's HSRRO. The EPA's HSRRO resides within the Office of the Science Advisor and is independent of ORD's NHEERL. However, in four of five studies, the branch chief approved the study on the NHEERL sign-off sheet after the initial IRB approval. In addition, several of the reviews did not occur in the order called for in NHEERL guidance, and information was missing on the NHEERL sign-off sheet for several studies. While EPA regulations and policy require that the IRB approve all study modifications, the EPA's regulations, policy and guidance do not address the review and approval process for study modifications, including when a study modification would be significant enough to obtain the HSRRO's approval. For example, we found a study modification approved by the IRB that doubled the concentration level of pollutant exposure but was not reviewed by the HSRRO. In our view, the EPA should revise its NHEERL guidance to include the review and approval process for study modifications, including a definition of significant study modifications that should be reviewed by the HSRRO. By revising its guidance, the EPA would help ensure that significant modifications receive a second independent review. In addition, while the investigators fulfilled their initial formal ethics training, we were unable to confirm whether they had met their continuing education requirements because NHEERL does not have a procedure for documenting the completion of the annual ethics refresher training.

Required Approvals Obtained to Conduct Five Human Research Studies, but Sequence of Approvals Did Not Follow NHEERL Guidance

The EPA obtained required approvals for the five human research studies we reviewed. However, the EPA did not follow NHEERL guidance for its NHEERL reviews and approvals. According to NHEERL guidance, the branch chief must review and approve the protocol, informed consent form, and all other items to be sent to the IRB before the principal investigator sends these items to the IRB. The guidance also states that all required reviews and responses are obtained in writing and approvals are recorded on the NHEERL sign-off sheet, and that initial reviews, such as the medical and statistical review, occur before the branch chief and IRB review. NHEERL requires that peer reviewer comments and principal investigator responses be sent to the IRB with the protocol. This helps ensure that the IRB sees the full research proposal, including any peer review comments.

After the IRB approval, the Division Quality Assurance Officer reviews the protocol, then the HRPO Director, and then the Division Director. In our review of the sign-off sheets, we found:

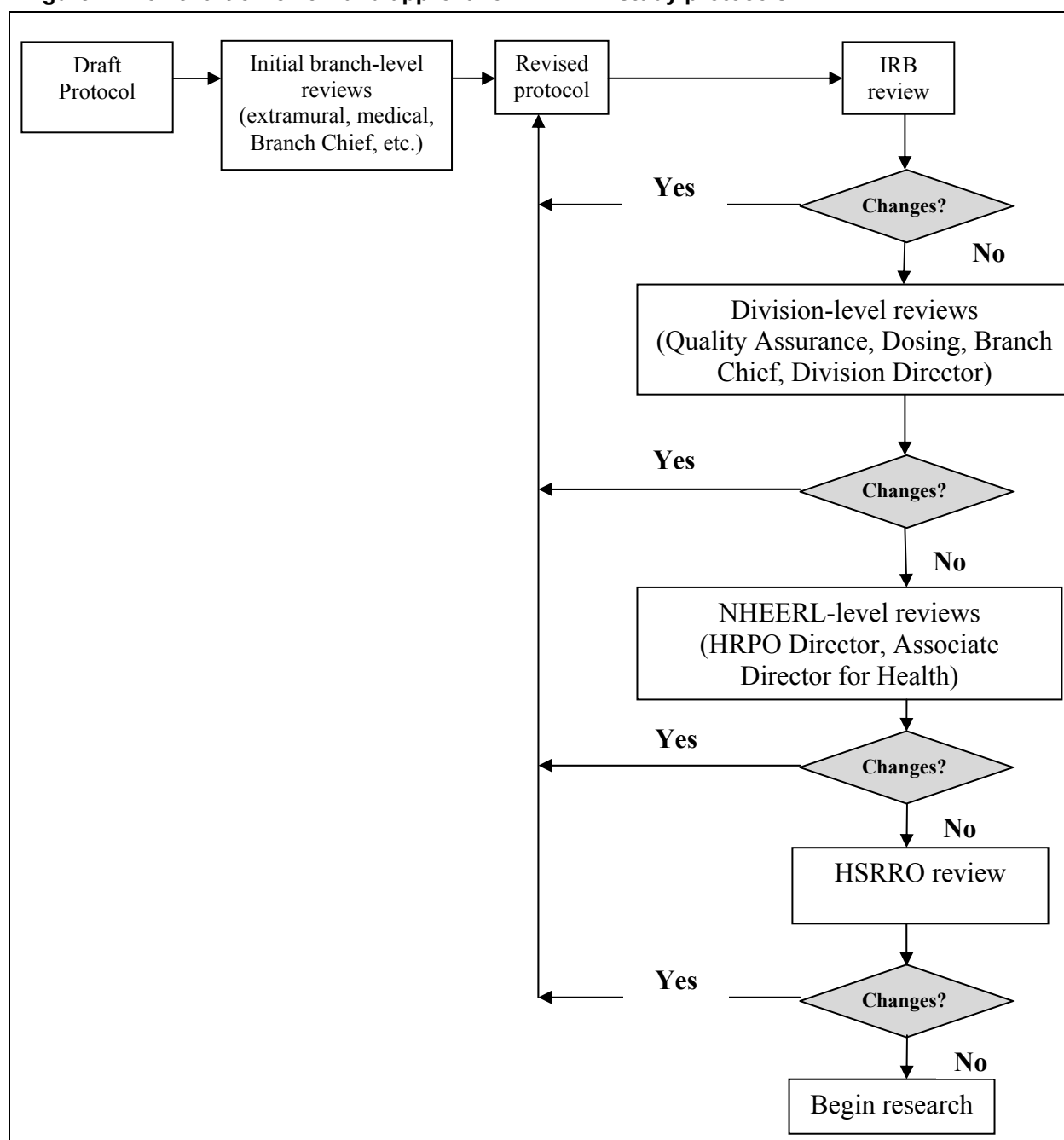
- In four of the five studies, the branch chief approved the study on the NHEERL sign-off sheet after the initial IRB approval.
- In three of the five studies, the physician signed the NHEERL sign-off sheet after the IRB approval.
- In two studies, the HRPO signed the NHEERL sign-off sheet after the division director, and in one study the HRPO signed before the Division Quality Assurance Officer.
- In two studies, NHEERL received peer reviews after the initial IRB approval of the study.
- In one study, the statistician's review occurred after the initial IRB approval of the study.

In one study, the sign-off sheet did not have dates for the statistician, physician, peer reviews, and the division director approval. When requested, the principal investigator was unable to provide us documentation with the missing dates. According to an NHEERL manager, there is no obligation to obtain sign-off in a particular order other than all signatures must be obtained before sending the package on for the approval of the Associate Director of Health. The EPA needs to ensure that NHEERL properly documents its review and approval steps for human research studies as stated in NHEERL guidance.

The EPA's regulations (40 CFR 26.109) require that an IRB review and approve initial study protocols as well as any study modifications before a study can begin or be modified. An IRB is an independent institution designated to review, approve and monitor approved research involving human subjects. The IRB reviews the study protocol, the consent form or forms and advertisements to recruit study subjects. The IRB also asks questions as needed to clarify issues before giving its approval. The protocols for each of the studies included information about the levels of pollutant exposure and the associated risks. In one case, the IRB made its approval contingent upon additional statements about the study risks being added to the consent forms. Once the EPA had addressed the IRB's questions or requirements to the IRB's satisfaction, the IRB approved each study.

EPA Order 1000.17 Change A1 requires the EPA HSRRO to approve human subjects research studies supported by the EPA. The EPA's HSRRO serves as an expert technical resource in matters of human research ethics and subject safety. The HSRRO also provides guidance and leadership in these areas. According to NHEERL guidance, each human research study should also receive NHEERL branch, division and management level reviews, in addition to IRB review and approval, before being sent to the EPA's HSRRO for review and approval. Figure 1 is a flowchart of the review and approval process.

Figure 1: Flowchart of review and approval of NHEERL study protocols



Source: OIG flowchart based on NHEERL Guidance, 2010.

ORD's NHEERL guidance incorrectly lists the HSRRO review under the NHEERL level reviews. The guidance also identifies the Division Human Research Officer (DHRO) as a division-level reviewer when no one has filled the position according to an NHEERL manager. NHEERL policy requires each NHEERL division conducting human subjects research to appoint a DHRO to ensure compliance with federal regulations and NHEERL human research policy. The HRPO has been fulfilling this role according to an NHEERL manager. Clarifying ORD's guidance and vesting the review responsibilities of the DHRO

in an existing position, such as the HRPO Director, will better ensure that initial study protocols and significant modifications receive thorough reviews.

The EPA received approvals from one of the UNC's biomedical IRBs and the EPA's HSRRO for each of the five studies as required by 40 CFR 26.109, EPA Order 1000.17 Change A1 and the NHEERL guidance. According to ORD managers, this two-level review process provides an additional level of protection to the study subjects that does not exist at most other research institutions. The EPA also documented the NHEERL branch and divisional reviews for the five studies using NHEERL sign-off sheets. We confirmed that the IRB reapproved the five protocols we reviewed annually and approved modifications to the studies. We also verified that the HSRRO approved the five studies before they began.

EPA Could Strengthen Protection of Human Subjects by Developing Guidance Concerning Study Modifications

While 40 CFR Part 26.109(a) and EPA Order 1000.17 Change A1 require the IRB to approve all modifications, the EPA's policies and guidance do not address the EPA internal review and approval process for modifications. In addition, the EPA's policy and guidance do not address when the approval of the HSRRO would be necessary for significant study modifications. Study modifications are common. The IRB approved 18 modifications for the XCON study, 19 modifications for KINGCON and 24 modifications for OMEGACON over the life of the three studies. Each modification application usually contained multiple changes to the study.

While some study modifications are considered minor, such as when new investigators are added to the study, other study modifications may be significant. The KINGCON study's June 2008 application stated that human subjects would be exposed to concentrated air particle levels between 50 and 300 $\mu\text{g}/\text{m}^3$. The application stated that an exposure session would be shut down if the exposure concentration exceeded 400 $\mu\text{g}/\text{m}^3$. However, in November 2008, the principal investigators modified the study to increase the upper limit of concentration to 600 $\mu\text{g}/\text{m}^3$. The EPA's application for IRB approval of the modification stated that the concentration increase did "not increase risk" to study subjects in the study. This study modification, which some may consider significant, was not sent to the HSRRO for review. NHEERL management told us that the Director of the HRPO within NHEERL determines whether to send a modification to the HSRRO. By revising its guidance, EPA would help ensure that significant modifications receive an independent review and properly address any changes in risks to human subjects.

Formal Ethics Training Requirements Met, but Procedure Needed to Track Annual Continuing Education Requirements

According to NHEERL guidance, the conduct of human subjects research carries special responsibilities with regard to ethical, medical and scientific issues. Society has imposed special requirements on investigators because of concern of potential maltreatment of human research subjects. Ethics training helps ensure that risks to human subjects are not overlooked. NHEERL guidance requires that all EPA investigators involved in human subjects research attend formal human research ethics training. The Collaborative IRB Training Initiative (CITI) is a Web-based program that is used to satisfy the ethics training requirement. CITI training contains modules on topics including ethical principles, IRB regulations, informed consent and vulnerable populations. UNC maintains an electronic database of individuals who have completed the CITI basic educational requirements. For the five studies we evaluated, the EPA investigators involved with human subject research had completed the formal human research ethics training requirement.

NHEERL policy and guidance also require that all personnel engaged in human subjects research complete continuing education (refresher training) on an annual basis. The annual continuing education requirement can be fulfilled by: 1) completion of the on-line CITI Refresher course, or 2) attendance at one lecture or seminar with a primary focus on human research issues. We could not determine if the annual continuing education requirements were met by the EPA investigators involved in human subjects research because there was no documentation of their completion. We asked the Environmental Public Health Division Director whether a procedure exists to record and track annual continuing education training. The division director told us that NHEERL lacked a procedure for tracking this requirement, but that a mechanism would be implemented immediately. In September 2013, the division director provided us with a copy of the database page that will be used to track the training and proposed revisions to NHEERL guidance.

One Human Research Study Exposed a Study Subject Above Concentration Targets but Followed Approved Protocol

The five human research studies we reviewed allowed subjects to be exposed above the study concentration targets. For example, the OMEGA CON protocol stated that an exposure was to be shut down if particulate concentrations exceeded $600\mu\text{g}/\text{m}^3$ for over six minutes. Evidence shows that EPA exposed one OMEGA CON study subject to pollutant concentrations that reached $751\mu\text{g}/\text{m}^3$, which exceeded the IRB-approved concentration target of $600\mu\text{g}/\text{m}^3$. EPA computer-generated real time data from the exposure chamber showed that the exposure session was shut down six minutes after the first concentration of $600\mu\text{g}/\text{m}^3$ was recorded. Additionally, the Director of OHRE at UNC stated that studies' approved pollutant concentrations are targets and not absolute safety

limits, and in this instance, where the level did exceed the targeted range, the protocol was followed and the study session was halted.

The other four human research studies we reviewed did not expose study subjects above the concentration limits.

Conclusions

The EPA obtained the required approvals for the five studies we reviewed. However, in four of five studies, the branch chief approved the study on the NHEERL sign-off sheet after the initial IRB approval. In addition, several of the reviews did not occur in the order called for in NHEERL guidance, and information was missing on the NHEERL sign-off sheet for several studies.

While the EPA regulations and policies require that the IRB approve all modifications, the EPA could improve its protection of human subjects if it established guidance for determining when study modifications are significant enough to require HSRRO approval. Additionally, while the investigators fulfilled the initial formal ethics training, we were unable to confirm that they had met the continuing education requirements because there was no procedure for documenting the completion of the annual refresher training. The EPA needs to ensure that the human research study team members obtain annual ethics training to properly protect study subjects.

Recommendations

We recommend that the Assistant Administrator for Research and Development:

1. Revise the NHEERL Human Research Guidance to include:
 - a. An EPA internal review and approval process for significant study modifications which include a definition and illustrative examples of significant study modifications. The review and approval process should indicate when significant study modifications should be sent to the HSRRO for review and approval.
 - b. A revised flowchart of the protocol review process listing the HSRRO as an independent reviewer and not part of the NHEERL-level review process and eliminating the DHRO review.
2. Implement a procedure for documenting that human subjects research study investigators have met the requirement for continuing annual ethics education.
3. Revise the NHEERL Human Research Policy to eliminate the DHRO position and transfer the duties of the DHRO to the HRPO Director.

4. Develop management controls to ensure NHEERL management reviews and approvals are properly documented and follow NHEERL guidance.

Agency Comments and OIG Evaluation

The agency concurred with all recommendations in Chapter 2 and provided acceptable planned corrective actions and completion dates for recommendations 1(a), 1(b), 3, and 4. Recommendations 1(a), 1(b), 3, and 4 are resolved and open with corrective actions ongoing. NHEERL provided evidence that it has already completed the corrective actions for recommendation 2. This recommendation is closed and no further action is required. Appendix B contains the agency's response to our draft report. Appendix C contains our detailed evaluation of that response.

Chapter 3

EPA Obtained Informed Consent From Human Subjects, but Consent Forms Addressed Pollutant Exposure Risks Differently

The EPA obtained informed consent from human study subjects before exposing them to concentrated airborne pollutants or diesel exhaust in 2010 and 2011. Our interviews with nine human study subjects confirmed that:

- They read the consent form.
- They had the opportunity to review the consent form and ask questions.
- An EPA representative explained the form to them prior to their participation in the study.
- They signed the consent form.

In the five studies' consent forms, the EPA addressed the risks of medical procedures and described certain risks of being exposed to CAPS or diesel exhaust. However, we found that the five studies' consent forms inconsistently addressed the risks of being exposed to CAPS and diesel exhaust. Although the regulation (40 CFR 26, the Common Rule) requires that consent forms describe any "reasonably foreseeable risks or discomforts to the subject," the regulation does not define this phrase. In our view, the lack of such a definition contributed to this inconsistency. Furthermore, the EPA did not include the potential long-term cancer risks in the diesel exhaust studies' consent forms. According to an EPA NHEERL manager, this was because they only planned to perform short-term exposures and the risk of getting cancer from a single 2-hour exposure was minimal. In our view, the agency should inform study subjects of any potential cancer risks of a pollutant to which they are being exposed so that study subjects can make the most informed decision possible about whether to participate in a study.

EPA Followed Requirements of 40 CFR 26.116

According to 40 CFR 26.116, EPA investigators need to obtain informed consent from study subjects before research begins. NHEERL guidance states that procedures used to obtain informed consent should educate the potential study subjects using language they understand. We obtained copies of the 88 consent forms for the five studies and found that the 81 study subjects had signed the consent forms and, in some cases, had initialed each page of the form. We analyzed the consent forms for the five studies and determined that the EPA met the regulation's requirements as shown in table 4.

Table 4: Basic elements of informed consent in the five studies' consent forms

Basic elements of informed consent	Element fulfilled in studies listed below				
	XCON	KINGCON	OMEGAACON	LAMARCK	DEPOZ
1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed and identification of any procedures which are experimental.	✓	✓	✓	✓	✓
2) A description of any reasonably foreseeable risks or discomforts to the subject.	✓	✓	✓	✓	✓
3) A description of any benefits to the subject or to others which may reasonably be expected from the research.	✓	✓	✓	✓	✓
4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.	✓	✓	✓	✓	✓
6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.	✓	✓	✓	✓	✓
7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.	✓	✓	✓	✓	✓
8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.	✓	✓	✓	✓	✓

Source: OIG analysis comparing the five studies' consent forms with the requirements in 40 CFR 26.116(b).

Furthermore, interviews with nine study subjects confirmed that the principal investigator or other EPA representative met with them and reviewed the content of the consent forms with them. Eight of nine study subjects stated that they were allowed to take the consent form home prior to their participation in the study; one study subject could not remember. According to the study subjects we interviewed, an EPA representative went over the consent form with them to a great extent or to a very great extent.

Seven of nine study subjects stated that the consent form was easy to understand. One study subject stated the consent form was very wordy and that, in the subject's opinion, less scientific language should be used; another thought an executive summary was needed. Although both believed that improvements could

be made to the consent form to make it easier to understand, the two study subjects stated that EPA went over the consent form with them to a great extent.

Consent Forms Addressed Risks of Studies' Medical Procedures

The consent forms for the five studies addressed the risks and discomforts of the medical procedures involved in the studies. The consent forms discussed the minimal risks of heart rhythm and blood pressure monitoring and blood sampling, as well as the risks of more complex procedures such as brachial artery ultrasound. For example, an optional procedure in the KINGCON study was a bronchoalveolar lavage, which is used to obtain fluids and cells from the respiratory tract to analyze the pulmonary response to particle exposure. In this procedure, a bronchoscope is passed through the nostril to the back of the throat and wedged in an airway in the right lung. Sterile saline is injected into the lung and then suctioned into the bronchoscope. The EPA used five pages of the KINGCON 18-page consent form to describe the bronchoalveolar lavage procedure, including the purpose of the procedure, how it would be performed, reasons a potential subject should not participate in the procedure and the potential risks. A similar description was provided in the LAMARCK consent form.

Studies' Consent Forms Addressed Risks of Pollutant Exposures Inconsistently

We found inconsistencies in the content of the consent forms with respect to the risks of pollutant exposure to CAPS (PM) and diesel exhaust. As shown in table 5, the consent forms for all five studies compared the subject's exposure to the exposure they would receive while visiting a large city on a smoggy day. However, only one of five studies' consent forms provided the subject with information on the upper range of the pollutant he or she would be exposed to and only two of five alerted study subjects to the risk of death for older individuals with cardiovascular disease.

Table 5: Statements made in consent forms of the five studies reviewed

Studies	Comparison of study exposure to exposure visiting large city on a smoggy day	Information about the upper range of pollutant exposure	Information about risk of death for those with cardiovascular disease
XCON	Yes	Yes	Yes
OMEGACON	Yes	No	No
KINGCON	Yes	No	No
LAMARCK	Yes	No	No
DEPOZ	Yes	No	Yes

Source: OIG analysis of consent forms for XCON, OMEGACON, KINGCON, DEPOZ and LAMARCK studies.

In a 2003 fact sheet⁴, the EPA's message to the public about PM_{2.5} was that long-term exposure is associated with reduced lung function and even premature death,

⁴ Particle Pollution and Your Health (2003), U.S. EPA Office of Air and Radiation, EPA-452/F-03-001.

and short-term exposure is linked to heart attacks and arrhythmias for people with heart disease. A 2006 EPA assessment document⁵ further reports associations between short-term PM exposures and mortality and morbidity.

The XCON and DEPOZ study consent forms warned the study subjects that exposure to high levels of selected air pollutants (i.e., PM, the pollutant being tested in the XCON study and diesel exhaust, the pollutant being tested in the DEPOZ study) could lead to death in older people with cardiovascular problems. This warning was not in the OMEGACON, KINGCON, or LAMARCK consent forms, even though these studies also exposed study subjects to PM (OMEGACON, KINGCON) and diesel exhaust (LAMARCK). According to an NHEERL manager, the exposure risk for healthy individuals is minimal. Because the three studies' consent forms (OMEGACON, KINGCON and LAMARCK) lacked the warning that PM exposure can cause death in older people with cardiovascular disease, they are significantly different in their disclosure of exposure risk than the XCON and DEPOZ consent forms. This lack of warning about PM in OMEGACON, KINGCON and LAMARCK is also different from the EPA's public message about PM.

Only the XCON study consent form identified the upper range of pollutant exposure for each study subject. The other four studies' consent forms did not mention the level of pollutant exposure. Instead, the forms for the other four studies (DEPOZ, KINGCON, LAMARCK and OMEGACON) compared the subject's level of exposure during the study to the exposure they would receive visiting major cities on smoggy days. According to an NHEERL manager, this comparison to a major city was a practical way for the subjects to understand the relative risk of exposure. The manager explained that a person breathing $420 \mu\text{g}/\text{m}^3$ for 2 hours would inhale the same concentration as they would breathing $35 \mu\text{g}/\text{m}^3$ (the EPA's 24-hour standard for $\text{PM}_{2.5}$) for 24 hours in a city such as Los Angeles. The manager also stated that PM risk is focused on susceptible populations and that the risk is small for those with no overt disease. One human subject that we interviewed believed, in hindsight, that the pollutant exposure range should be included in the consent form.

The EPA has not defined the term "reasonably foreseeable risks" in its regulations. According to an August 2013 article in the Journal of Clinical Best Practices:

Since the regulations do not define "reasonably foreseeable risks, investigators, IRBs and oversight agencies might each interpret this phrase differently. These different interpretations can lead to confusion and controversy.... Inconsistent interpretations, by definition, lead to

⁵ Provisional Assessment of Recent Studies on Health Effects of Particulate Matter Exposure (2006), U.S. EPA Office of Research and Development, Washington, D.C., National Center for Environmental Assessment, EPA/600/R-06/063.

inconsistent protection of human research subjects, which can lead to inadequate protections in some instances.⁶

An NHEERL manager told us that consent forms differed because each was written by a different principal investigator. The manager also told us that NHEERL is developing new guidance for principal investigators that would help them harmonize the risk language in the consent forms. In our view, the lack of a definition of “reasonably foreseeable risks” in the EPA’s guidance for conducting human subjects research contributed to this inconsistency.

Consent Forms for Diesel Exhaust Studies Did Not Include Potential Cancer Risks From Long-Term Exposure

The LAMARCK and DEPOZ study consent forms did not include the potential cancer effects of long-term exposure to diesel exhaust. The EPA classifies diesel exhaust as “likely to be carcinogenic to humans by inhalation” and stated in its 2002 Health Assessment Document for Diesel Engine Exhaust⁷ that long-term inhalation exposure is likely to pose a lung cancer hazard to humans, as well as damage the lung in other ways depending on the length of the exposure. According to EPA’s 2002 Health Assessment document, the human evidence from occupational studies is considered strongly supportive of a finding that diesel exhaust exposure is causally associated with lung cancer, though the evidence is less than that needed to definitively conclude that diesel exhaust is carcinogenic to humans.

According to an NHEERL manager, long-term cancer risks from 2-hour exposures would be minimal. The manager also stated that cancer risk is calculated considering a lifetime exposure of 40 years.

The LAMARCK and DEPOZ protocols that went to the IRB contained language about the substance being carcinogenic and stated that the risk was minimal. Although the IRB was made aware of the principal investigator’s basis for considering the risk from short-term exposure to be minimal, human subjects were not informed of this risk in the consent forms. Table 6 shows what the principal investigator told the IRB about the risks from each study.

⁶ Resnick, D. “What is a ‘Reasonably Foreseeable Risk’? The Support Study Controversy.” Journal of Clinical Research Best Practices 9.8 (2013): 1-12.

⁷ U.S. EPA Health Assessment Document for Diesel Engine Exhaust (Final 2002). U.S. EPA Office of Research and Development, National Center for Environmental Assessment, Washington, D.C., EPA/600/8-90/057F.

Table 6: Principal investigator's explanation of risk to the IRB

Study name / pollutants	Statement of risk provided to the IRB in the EPA's study application
LAMARCK (Diesel exhaust and ozone)	"Diesel exhaust particles contain some probable carcinogenic polycyclic aromatic hydrocarbons, which in high enough concentrations and/or with repeated exposures may induce tumors. Diesel exhaust also contains aldehydes, some of which are possibly carcinogenic in high enough dose and with long enough exposure. However, the exposure concentrations to be used in this protocol are minimal. Overall, it appears that at the low DEP [diesel exhaust particle] concentration to be given one time for the exposure in this study, the risk of cancer, if it exists at all, is extremely low and certainly no more than what one would experience if one were to visit for a few days a particulate-polluted city in the US [United States] such as Los Angeles or New York City." (2009)
DEPOZ (Diesel exhaust and ozone)	"DE [diesel exhaust] particles contain some probable carcinogenic polycyclic aromatic hydrocarbons and other components, which in high enough concentrations and/or with repeated exposures may induce tumors. Diesel exhaust also contains aldehydes, some of which are possibly carcinogenic in high enough dose and with long enough exposure. However, the exposure time and concentrations to be used in this protocol are minimal relative to the durations required to induce lung cancer. Overall, there are no known long-term health risks in healthy individuals acutely exposed to DE at the PM concentrations given in this study." (2009)

Source: DEPOZ and LAMARCK study applications to the IRB.

According to a risk analysis conducted for another diesel exhaust study in 1999, the long-term cancer risk for an individual exposed to 20 or 100 micrograms per cubic meter of diesel exhaust for 2 hours was estimated to be in the range of 1 in 1 billion. The study subjects in LAMARCK and DEPOZ were exposed to levels that ranged from about 250 to 320 micrograms per cubic meter. The DEPOZ principal investigator estimated the risk to be about 3 in 1 billion because the exposure was three times higher.

An August 2013 article in the Journal of Clinical Best Practices states that "most people would want to know whether a medical procedure involves a risk of death, even if the chance of dying is very small." One study subject that we interviewed stated that it would have been useful to have had information about known long-term effects of exposure to diesel exhaust. In our view, the EPA should inform study subjects of the potential long-term cancer risk of any pollutant to which it exposes human subjects so that study subjects can make the most informed decision possible about whether to participate in a study.

Conclusions

The EPA obtained informed consent from the 81 study subjects that participated in the five studies in 2010 and 2011 as required by 40 CFR 26.116. However, the EPA inconsistently addressed pollutant risk in its consent forms. Only two of the five studies' consent forms included the risk of death from exposure to high levels of selected air pollutants such as PM and diesel exhaust, and only one study's consent form included the upper limits of exposure levels. Because EPA's regulations do not define "reasonably foreseeable risks," EPA investigators, the IRB and the HSRRO must define the term using their professional judgment, which leads to inconsistencies in addressing risks in the study consent forms. Such inconsistencies could lead to inconsistent protection of human subjects. The EPA needs to develop guidance to help ensure more consistent interpretation of

reasonably foreseeable risks. Furthermore, the EPA should provide the study subjects with a summary of the EPA assessments about the short- and long-term effects of the pollutants to which human study subjects will be exposed.

The EPA's diesel exhaust studies did not include language about the long-term cancer risks of diesel exhaust. The NHEERL manager explained that the cancer risk from diesel exhaust was not relevant to the 2-hour exposures included in the LAMARCK study. However, evidence suggests that at least some human study subjects would like to know if a study involves risk of death, even if the risk is very small. In the future, the EPA should include the long-term risk of cancer to potential subjects in its consent forms so study subjects can make the most informed decision about whether to participate in a study.

Recommendations

We recommend that the Assistant Administrator for Research and Development:

5. Revise NHEERL Human Research Guidance to include a definition for “reasonably foreseeable risks” including illustrative examples of the types of information that should be included in the consent forms.
6. Revise NHEERL Human Research Guidance to include procedures for ensuring that human subjects research consent forms consistently present the risks of the pollutants to which human subjects are exposed, including a summary of EPA assessments of short-term and long-term health effects and the upper pollutant concentration level for the pollutant to which the human subjects will be exposed.
7. Include in its consent forms any known or likely carcinogenic effects of pollutants that the EPA uses in human exposure studies, based on EPA, other federal health agency, or other organization's (as appropriate) assessment of such risks. If EPA uses the work of non-federal entities, the agency should document the basis for using non-federal information as opposed to the assessments of federal health agencies.

Agency Comments and OIG Evaluation

The agency concurred with all recommendations in Chapter 3 and provided acceptable planned corrective actions and completion dates for the recommendations. Recommendations 5, 6, and 7 are resolved and open with corrective actions ongoing. Appendix B contains the agency's response to our draft report. Appendix C contains our detailed evaluation of that response.

Chapter 4

Improvements Needed in EPA Guidance to Address Adverse Event Definitions, Reporting Timeframes and Clinical Follow-Up Responsibilities

The EPA addressed six adverse events in the five CAPS and diesel exhaust studies conducted in 2010 and 2011 by reporting them to the IRB and providing clinical follow-up after the events. The EPA's clinical follow-up for the six adverse events ranged from 1 day to 3 months after the event and included phone calls and emails by the EPA nurses. While the EPA's clinical follow-up appeared to be reasonable, the EPA's policies and guidance do not establish the EPA's clinical follow-up responsibilities. In our view, the EPA should revise its guidance to establish the agency's clinical follow-up responsibilities after an adverse event.

According to ORD managers, NHEERL is required to use the latest UNC-IRB standard operating procedures (SOPs) adverse event definitions and reporting timeframes to respond to adverse events. For the five studies we reviewed, this would have been the 2009 UNC-IRB SOPs. However, NHEERL's policies and guidance do not state that NHEERL has adopted UNC-IRB SOP's adverse event definitions and reporting timeframes. NHEERL guidance is outdated, with definitions for adverse events and reporting timeframes that are the same as the 2003 UNC-IRB SOP definitions and reporting timeframes. When evaluated against the NHEERL guidance reporting timeframes, the EPA reported two of the six adverse events to the IRB later than required. In addition, when evaluated against the EPA's NHEERL guidance definition for an adverse event, the EPA did not report two study events to the IRB in which both subjects experienced cardiac arrhythmias. In both instances, the subjects were not allowed to continue participating in the study and were advised to consult their physicians. The EPA should update its NHEERL guidance to make it clear what adverse event definitions and reporting requirements they should use when managing their human subject research studies to ensure the consistent protection of study subjects.

Clinical Follow-Up Provided but Guidance and Study Protocols Lack Clinical Follow-Up Responsibilities

The EPA identified six adverse events during three studies (DEPOZ, OMEGACON, and XCON) conducted in 2010 and 2011 and reported them to the IRB. The EPA did not identify any adverse events in two studies, KINGCON and LAMARCK. Table 7 summarizes each of the six adverse events.

Table 7: Summary of the six adverse events in 2010 and 2011

Study and date (month/year) of adverse event	Description of adverse event	Actions taken after adverse event was reported including revising the study's consent forms
OMEGACON, May 2010	Subject developed a migraine during exposure.	The EPA revised the consent forms to exclude future human subjects with a history of migraine headaches from participating in the study.
OMEGACON, May 2010	Subject had cardiac arrhythmia ^a after exposure to clean air.	Not applicable because the IRB did not consider the adverse event to be reportable.
OMEGACON, June 2010	Subject had cardiac arrhythmia after exposure to clean air.	Not applicable because the IRB did not consider the adverse event to be reportable.
DEPOZ, September 2010	Subject experienced decreased lung function after ozone exposures.	None. DEPOZ consent form already addressed the potential risk of airway obstruction.
XCON, October 2010	Subject experienced tachycardia ^b and atrial fibrillation ^c while exposed to ambient air pollution particles. The subject was later hospitalized overnight for observation.	NHEERL management met and determined that no screening could have feasibly been done to have predicted this issue. The XCON consent form already warned study participants not to participate if they had cardiovascular disease including coronary artery disease, heart failure, or rhythm disturbances.
DEPOZ, April 2011	Subject developed a persistent cough.	NHEERL established a corrective action plan where subjects who presented a cough within the first 15 minutes of exposure would be removed from the chamber. DEPOZ consent form already stated that exposure to ozone could cause a cough.

Source: NHEERL's information on human subjects who experienced adverse events.

^aAn arrhythmia is a problem with the rate or rhythm of the heartbeat. During an arrhythmia, the heart can beat too fast, too slow, or with an irregular rhythm.

^bTachycardia is a faster than normal heart rate. A healthy adult heart normally beats 60 to 100 times a minute when a person is at rest. If you have tachycardia, the heart rate in the upper chambers or lower chambers of the heart, or both, are increased significantly.

^cAtrial fibrillation is an irregular and often rapid heart rate that commonly causes poor blood flow to the body. During atrial fibrillation, the heart's two upper chambers (the atria) beat chaotically and irregularly—out of coordination with the two lower chambers (the ventricles) of the heart.

After each of the six EPA-identified adverse events took place, agency medical staff provided clinical follow-up, which we define as the necessary monitoring of the condition of a human research subject who experienced an adverse event to ensure their well being. The EPA's follow-up included subsequent communications with the subject regarding their health. The length of clinical follow-up varied from 1 day to 3 months. The EPA doctors and/or nurses provided the follow-up care. After several events, clinical follow-up included advising the study subject to make an appointment with their private physician or another specialist for medical care. Table 8 describes the clinical follow-up the EPA medical staff provided for each of the six EPA-identified adverse events.

Table 8: Clinical follow-up provided by the EPA for the six adverse events in 2010 and 2011

Study and timeframes of adverse event	Clinical follow-up provided by the EPA
OMEGACON, May 2010	Two days of follow-up including (1) giving the subject medicine for pain relief and a visit by NHEERL's on duty physician on the first day and (2) a follow-up conversation with the principal investigator on the second day.
OMEGACON, May 2010	Two days of follow-up including review of subject's holter monitor recording ^a by one doctor and two nurses. On the second day, the EPA medical staff advised the study subject to see a private physician because the principal investigator believed that the study subject had an underlying medical condition. The EPA provided the study subject with a copy of medical test results.
OMEGACON, June 2010	One day of follow-up plus an email from an NHEERL nurse three weeks afterwards. During the follow-up day, an NHEERL doctor and the principal investigator reviewed the study subject's holter monitor recording, and the NHEERL doctor reviewed the study subject's electrocardiogram. EPA medical staff advised the study subject to see a health care provider and a private cardiologist.
DEPOZ, September 2010	Follow-up occurred the day following the event. Follow-up included assessments by an EPA doctor and nurse. The study subject continued to participate in the study.
XCON, October 2010	Follow-up occurred over a span of seven days including (1) a nurse consultation with two NHEERL physicians; (2) review of holter monitor recordings; (3) observation of study subject; (4) study subject transfer to the emergency room with overnight monitoring at the UNC hospital; and (5) phone calls to the study subject by an NHEERL nurse.
DEPOZ, April 2011	Follow-up provided for 3 months after event including (1) being seen by an NHEERL physician; (2) receiving medication for 1 week; (3) emails and phone calls by an NHEERL nurse; and (4) scheduling an appointment for the study subject at the UNC Ambulatory Care Center Pulmonary Clinic.

Source: NHEERL's information on human subjects who experienced adverse events.

^aA holter monitor is a type of portable electrocardiogram which keeps a continuous record of the heart rhythm, typically over a 24-hour period.

The EPA's consent forms for the five studies addressed what happens if an injury occurs to a study subject and informed the subjects that a physician would be available during the exposure session, if needed.



The console the EPA uses to observe and monitor human study subjects during exposures (foreground) and a human subjects air pollution test chamber (background). (EPA OIG photo)

However, the EPA's policies, guidance, the five study protocols and consent forms do not include the EPA's clinical follow-up responsibilities. While the follow-up NHEERL provided after each adverse event appeared reasonable, we could not compare it to any existing EPA criteria. ORD managers said that their clinical follow-up responsibilities do not include serving as a study subject's health care provider and they are not aware of circumstances under which they would be allowed to serve as a health care provider. We interviewed three study subjects who experienced adverse events. Two study subjects commented that the EPA investigators handled the adverse events in a professional manner. One subject suggested that the EPA follow up with study subjects who experience an adverse event with an inquiry letter about 2 to 3 months after the event to determine how they are doing. In our view, clinical follow-up is an ethical responsibility and the EPA should revise its guidance to establish the agency's clinical follow-up responsibilities for adverse events to ensure principal investigators and study team members understand their responsibilities. Once established, including a summary of the EPA's clinical follow-up responsibilities in the consent forms would better ensure that human subjects understand the EPA's clinical follow-up responsibilities prior to the occurrence of an adverse event.

NHEERL Guidance Does Not Reflect the Adverse Event Definitions and the Reporting Timeframes the Agency Reports Using

According to ORD managers, NHEERL uses the latest UNC-IRB SOP adverse event definitions and reporting timeframes to respond to adverse events. The Director of OHRE for UNC confirmed that it is the UNC-IRB's expectation that the EPA follows the UNC-IRB SOP. However, this expectation is not in writing. For the five studies we reviewed, this would have been the 2009 UNC-IRB SOP. However, the NHEERL guidance does not state that the EPA adopted the UNC-IRB SOP definitions and reporting timeframes. Further, NHEERL's guidance definitions and timeframes are out of date because it still uses the 2003 UNC-IRB definitions and reporting timeframes. As a result, we evaluated how the EPA addressed adverse events using NHEERL guidance definitions and timeframes. Additionally, we also evaluated the adverse events using the 2009 UNC-IRB SOP definitions of adverse events and reporting requirements. Appendix D summarizes the NHEERL guidance and 2009 UNC-IRB definitions for various types of adverse events and unanticipated problems. In our view, the EPA needs to update its NHEERL guidance to clarify the adverse event definitions and reporting timeframes it is using during their human research subject studies, in order to ensure the consistent protection of study subjects.

Two Adverse Events Not Reported In a Timely Manner When Evaluated Against Outdated NHEERL Guidance

The EPA did not report two of the six adverse events it identified in a timely manner when evaluated against NHEERL guidance, because NHEERL guidance was out of date. According to agency managers NHEERL has been following the

UNC-IRB SOP reporting requirements; however, these definitions and timeframes have not been reflected in the 2010 NHEERL guidance. Table 9 summarizes the reporting timeframes contained in the NHEERL guidance and the 2009 UNC-IRB SOP.

Table 9: Reporting timeframes for adverse events and unanticipated problems

Event/Problem	NHEERL guidance reporting timeframes for adverse events and unanticipated problems	2009 UNC-IRB SOP reporting timeframes for adverse events and unanticipated problems
Serious adverse events	Within 24 hours or by next working day if unanticipated; 5 working days if anticipated.	Unanticipated problems that are serious adverse events should be reported to the IRB within 1 week of the investigator becoming aware of the event.
Adverse event or experience	Within 10 working days if unanticipated.	Unanticipated problems that are adverse events should be reported to the IRB within 2 weeks of the investigator becoming aware of the problem. Adverse events that are not unanticipated problems are not required to be reported to the IRB.
Unanticipated problems	Within 10 working days.	Unanticipated problems that are not serious adverse events should be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.

Sources: The EPA NHEERL Guidance, 2010 and UNC IRB SOP Number 19.0, 2009.

In the XCON October 2010 adverse event, the study subject was hospitalized which, according to NHEERL's guidance, would be defined as a serious adverse event. The principal investigator reported the unanticipated adverse event to the IRB 3 working days after the event. Serious and unanticipated adverse events should be reported within 24 hours according to NHEERL guidance. An NHEERL manager explained to us that the event was considered unanticipated but not a serious adverse event. The EPA took the study subject to the hospital for overnight observation, but she was not admitted. The manager interpreted the NHEERL guidance as stating that a serious adverse event would require a study subject to be hospitalized for a prolonged period of time.

The EPA also did not report the DEPOZ April 2011 adverse event to the IRB in a timely manner according to 2010 NHEERL guidance. The study subject reported experiencing a persistent cough after an ozone exposure session. This adverse event was not serious but was unanticipated. The EPA reported the event to the IRB after 11 working days when the event should have been reported within 10 working days according to NHEERL guidance. Adverse events must be reported in a timely manner so that the IRB can expeditiously determine if it needs to take any action concerning a study, such as requiring the EPA to revise the study protocols or the consent forms.

Only one of the two events (DEPOZ, April 2011) would have been reported as untimely when evaluated against the 2009 UNC-IRB SOP reporting timeframes. According to the UNC-IRB SOP, unanticipated problems that are adverse events should be reported to the IRB within 2 weeks of the investigator becoming aware of the event; as noted above, the agency reported this adverse event after 11 working days, or 15 calendar days.

The other event (XCON, October 2010) was reported after 3 working days, or 5 calendar days. This event would not have been classified as a serious adverse event using the UNC-IRB definitions because the study subject did not require inpatient hospitalization. The NHEERL guidance defines a serious adverse event as one in which the study subject “requires hospitalization.”

Two Adverse Events Not Reported to the IRB When Evaluated Against Outdated NHEERL Guidance

Despite meeting the NHEERL guidance definition for an adverse event, the EPA did not report two study events to the IRB in which both subjects experienced cardiac arrhythmias. These events met the 2010 NHEERL guidance definition for an adverse event, which is an event that is “undesirable and unintended, though not necessarily unanticipated, [with] injury or physical or emotional consequence to a human subject.” However, when evaluated against the 2009 UNC-IRB SOP definitions, neither of these adverse events would have been reported because they did not meet the criteria. In both instances, the subjects were not allowed to continue participating in the study and were advised to consult their physicians. Table 10 describes the two unreported events and the EPA’s explanations for not reporting them.

Table 10: 2010 and 2011 events not reported as adverse events

Study and date (month/year) of event	Description of event	The EPA explanation for not reporting as adverse event
DEPOZ, November 2010	Study subject had ventricular ectopic heart beats during holter monitoring on the follow-up day of the study. The EPA medical staff told the study subject to follow-up with a physician.	According to an NHEERL manager, the heart irregularity was benign. However, because of this irregularity, the EPA could monitor the heartbeat, but the results could not be interpreted, which was one of the data points being measured in the study. Therefore, the individual was disqualified from further participation in the study.
XCON, February 2011	Within seconds of the PM exposure, the study subject had an increase in heart rate that lasted several seconds, as well as variable blood pressure readings over the next half an hour. The EPA medical staff told the study subject to follow-up with a physician.	After the study subject was removed from the exposure chamber, the study subject told two EPA physicians about experiences with a “racing heart” although the study subject had responded during a screening visit that heart rate seems normal and that there were no episodes of very rapid heart rate which starts and stops suddenly. NHEERL staff determined that the event did not relate to the research since the study subject was only exposed to CAPS for a short time. The EPA did not inform the IRB at the time of the event, but the principal investigator sent the IRB a memo in October 2012 (about 1.5 years later) explaining why the incident was not reported to the IRB. In an email dated October 15, 2012, the Director of the Office of Research Ethics for UNC concurred that this incident did not rise to the level of a reportable event.

Source: NHEERL medical notes on study subject participants.

During the OMEGACON study, the EPA reported two adverse events to the IRB (May 2010 and June 2010 in table 7) that were similar to the DEPOZ event (November 2010 in table 10). For the XCON event (February 2011 in table 10),

the study's principal investigator stated that the incident was not reported because the event was likely not related to the research.

When evaluated against the 2009 UNC-IRB SOP definitions, neither of these adverse events would have been reported because they did not meet the criteria, which is that the event must be both unanticipated in nature and related to the research. The two events were likely not related to the research. An EPA study team member discovered the heart rhythm problems of one study subject (DEPOZ, November 2010) the day after the pollutant exposure session on a testing follow-up day. The other study subject (XCON, February 2011) was only exposed to CAPS for a short time and informed the EPA study team after the short exposure about having racing heart symptoms prior to the study.

Other Matters

The congressional request also asked that we determine whether the HSRB and the HSRRO were notified of adverse events and if consent forms were revised as needed after an adverse event.

HSRB and HSRRO Notification Not Required After an Adverse Event

Neither the Common Rule nor the EPA's policy and guidance require the HSRB or HSRRO to be notified when adverse events occur. The EPA did not notify the HSRB about any of the five studies' adverse events. Although not required, the EPA notified the HSRRO about one adverse event (XCON, October 2010) where the subject was sent to the hospital.

One Study's Consent Forms Revised After an Adverse Event

The EPA revised one study's consent form due to an adverse event. During the OMEGACON study one human study subject developed a migraine during an exposure session (OMEGACON, May 2010). The EPA decided to revise the OMEGACON study's consent form to exclude potential human subjects with a history of migraines from participating in the study. The EPA did not revise the consent forms for the other adverse events. See explanations in table 7. We did not find that the consent forms for any of the other studies needed to be revised based on the identified adverse events.

Conclusions

The EPA needs to update its NHEERL guidance to clarify which adverse event definitions and reporting timeframes it is using. It is important to do so to provide consistent protection to the study subjects participating in NHEERL's human subjects research studies. Principal investigators must understand what adverse definitions and reporting requirements they should use so they can identify and report adverse events in a timely manner.

Although the EPA's policies and guidance do not include the EPA's clinical follow-up responsibilities, agency medical staff provided clinical follow-up to study subjects after each of the six EPA-identified adverse events. Establishing guidance for the agency's clinical follow-up responsibilities after an adverse event would enhance the protection of human subjects who experience adverse events. The EPA should revise its guidance to address this key area. The EPA should also include a summary of its clinical follow-up responsibilities in its consent forms so that human subjects understand the EPA's clinical follow-up responsibilities prior to the occurrence of an adverse event.

Recommendation

We recommend that the Assistant Administrator for Research and Development:

8. Revise the EPA's NHEERL Human Research Guidance to:
 - a. Clearly state that NHEERL has adopted UNC-IRB SOP definitions and reporting timeframes for adverse events and unanticipated problems and will continue to follow the most updated version of the SOPs.
 - b. Establish the EPA's clinical follow-up responsibilities after adverse and serious adverse events, including general timeframes for clinical follow-up.
 - c. Require principal investigators to include a summary of the agency's clinical follow-up responsibilities in each study's protocol and consent forms.

Agency Comments and OIG Evaluation

The agency concurred with all recommendations in Chapter 4 and provided acceptable planned corrective actions and completion dates for the recommendations. Recommendations 8(a), 8(b) and 8(c) are resolved and open with corrective actions ongoing. Appendix B contains the agency's response to our draft report. Appendix C contains our detailed evaluation of that response.

Status of Recommendations and Potential Monetary Benefits

RECOMMENDATIONS						POTENTIAL MONETARY BENEFITS (in \$000s)	
Rec. No.	Page No.	Subject	Status ¹	Action Official	Planned Completion Date	Claimed Amount	Agreed-To Amount
1	17	Revise the NHEERL Human Research Guidance to include: a. An EPA internal review and approval process for significant study modifications which include a definition and illustrative examples of significant study modifications. The review and approval process should indicate when significant study modifications should be sent to the HSRRO for review and approval. b. A revised flowchart of the protocol review process listing the HSRRO as an independent reviewer and not part of the NHEERL-level review process and eliminating the DHRO review.	O	Assistant Administrator for Research and Development	9/30/14		
2	17	Implement a procedure for documenting that human subjects research study investigators have met the requirement for continuing annual ethics education.	C	Assistant Administrator for Research and Development	10/31/13		
3	17	Revise the NHEERL Human Research Policy to eliminate the DHRO position and transfer the duties of the DHRO to the HRPO Director.	O	Assistant Administrator for Research and Development	9/30/14		
4	18	Develop management controls to ensure NHEERL management reviews and approvals are properly documented and follow NHEERL guidance.	O	Assistant Administrator for Research and Development	9/30/14		
5	25	Revise NHEERL Human Research Guidance to include a definition for "reasonably foreseeable risks" including illustrative examples of the types of information that should be included in the consent forms.	O	Assistant Administrator for Research and Development	9/30/14		
6	25	Revise NHEERL Human Research Guidance to include procedures for ensuring that human subjects research consent forms consistently present the risks of the pollutants to which human subjects are exposed, including a summary of EPA assessments of short-term and long-term health effects and the upper pollutant concentration level for the pollutant to which the subject will be exposed.	O	Assistant Administrator for Research and Development	9/30/14		
7	25	Include in its consent forms any known or likely carcinogenic effects of pollutants that the EPA uses in human exposure studies, based on EPA, other federal health agency, or other organization's (as appropriate) assessment of such risks. If EPA uses the work of non-federal entities, the agency should document the basis for using non-federal information as opposed to the assessments of federal health agencies.	O	Assistant Administrator for Research and Development	6/30/14		

RECOMMENDATIONS						POTENTIAL MONETARY BENEFITS (in \$000s)	
Rec. No.	Page No.	Subject	Status ¹	Action Official	Planned Completion Date	Claimed Amount	Agreed-To Amount
8	33	Revise the EPA's NHEERL Human Research Guidance to: <ul style="list-style-type: none"> a. Clearly state that NHEERL has adopted UNC-IRB SOP definitions and reporting timeframes for adverse events and unanticipated problems and will continue to follow the most updated version of the SOPs. b. Establish the EPA's clinical follow-up responsibilities after adverse and serious adverse events, including general timeframes for clinical follow-up. c. Require principal investigators to include a summary of the agency's clinical follow-up responsibilities in each study's protocol and consent forms. 	O	Assistant Administrator for Research and Development	9/30/14		

¹ O = recommendation is open with agreed-to corrective actions pending
 C = recommendation is closed with all agreed-to actions completed
 U = recommendation is unresolved with resolution efforts in progress

EPA Air Quality Index for Particle Pollution (with concentration levels added)

AQI level	Risk level	Description of risk	PM_{2.5} concentration (range)
0-50	Good	None	0 to 12 µg/m ³
51-100	Moderate	Unusually sensitive people should consider reducing prolonged or heavy exertion.	12.1 to 35.4 µg/m ³
101-150	Unhealthy for sensitive groups	People with respiratory or heart disease, the elderly and children should limit prolonged exertion.	35.5 to 55.4 µg/m ³
151-200	Unhealthy	People with respiratory or heart disease, the elderly and children should avoid prolonged exertion. Everyone else should limit prolonged exertion.	55.5 to 150.4 µg/m ³
201- 300	Very unhealthy	People with respiratory or heart disease, the elderly and children should avoid any outdoor activity. Everyone else should avoid prolonged exertion.	150.5 to 250.4 µg/m ³
301-500	Hazardous	Everyone should avoid any outdoor exertion. People with respiratory or heart disease, the elderly and children should remain indoors.	250.5 to 500.4 µg/m ³

Source: EPA's Air Quality website (<http://www.airnow.gov/?action=aqibasics.aqi> and http://www.airnow.gov/index.cfm?action=resources.aqi_conc_calc).

Note: The Air Quality Index range for PM_{2.5} is 0 to 500.

Agency Comments on Draft Report

[This appendix includes OIG-created footnotes regarding subsequent communications with the agency after their response was received concerning their planned corrective actions and completion dates.]

February 18, 2014

MEMORANDUM

SUBJECT: Response to the Office of Inspector General (OIG) Draft Report titled, *Improvements in Policies and Guidance Could Better Ensure Protection of Human Study Subjects*, dated January 17, 2014

FROM: Lek G. Kadeli, Acting Assistant Administrator

TO: Arthur A. Elkins, Jr., Inspector General
Office of Inspector General

Thank you for the opportunity to respond to the OIG's draft report, *Improvements in Policies and Guidance Could Better Ensure Protection of Human Study Subjects*, (Project No.OPE-FY13-0001).

The Office of Research and Development (ORD) appreciates the OIG's recognition that the EPA followed all applicable regulations governing our human subjects research program. This acknowledgement is based on the OIG's findings, which demonstrated that EPA obtained all required approvals before initiating a study, obtained proper informed consents from research participants, complied with its clinical follow-up responsibilities for all research participants, and responded appropriately to adverse events, according to the latest guidelines of the University of North Carolina Institutional Review Board (the board of record for EPA research taking place in Chapel Hill).

EPA policy decisions must be based on sound science. To that end, ORD's human subjects research program generates critical and objective scientific data to inform the development of policies that may reduce the effects of air pollutants on human health.

While there is a critical need for studies involving human subjects, ORD also understands that the research must be conducted in an ethical and vigilant manner. As documented in the OIG's report, EPA has established guidelines for conducting this type of research that are far in excess of what is normally required by universities, industry, and other government agencies conducting human studies research. For example, ORD's research program can sometimes undergo over eight separate levels of approvals before a research study can be initiated, which may include statistical and medical review of the study, IRB review, Quality Assurance Officer review, and review by at least three other officials, whose approvals must be documented before a study can begin.

In conclusion, ORD appreciates the OIG's efforts and thorough evaluation of our research program. ORD concurs with the OIG's recommendations, which are primarily based on

enhancing our internal policies and guidance to further improve the EPA's human studies program.

Provided in the table below is ORD's response to the OIG's recommendations.

Rec. No.	Recommendation	Suggested Revisions to Recommendation(s) (If applicable)	Corrective Action	Estimated Completion Date
1.	Revise the NHEERL guidance to include: An EPA internal review and approval process for significant study modifications which include a definition and illustrative examples of significant study modifications. The review and approval process should indicate when significant study modifications should be sent to the HSRRO for approval. A revised flowchart of the protocol review process listing the HSRRO review as an independent reviewer and not part of the NHEERL-level review process and eliminating the DHRO review.		A job offer has been made to fill the HRPO position. Updating the NHEERL guidance policy will be the first task assigned to the HRPO. Included in the updated guidance will be a definition of what constitutes a significant study modification and who must review and approved such modifications. The flowchart will also be revised as suggested by the IG.	4 th Quarter FY 2014 (assuming the HRPO position is filled by the Spring of 2014).

See Appendix C, Note 1, for OIG Response

2.	Implement a procedure for documenting that human subjects research study investigators have met the requirement for continuing annual ethics education.		A procedure was implemented in the fall of 2013.	Completed
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See Appendix C, Note 2, for OIG Response

Rec. No.	Recommendation	Suggested Revisions to Recommendation(s) (If applicable)	Corrective Action	Estimated Completion Date
3.	Revise the NHEERL policy to eliminate the DHRO position and transfer the duties of the DHRO to the HRPO Director.		This will be done as part of the HRPO revision of the NHEERL guidelines.	4 th Quarter FY 2014.

See Appendix C, Note 3, for OIG Response

4.	Develop management controls to ensure NHEERL management reviews and approvals are properly documented and follow NHEERL guidance.		NHEERL guidelines will be modified to specifically indicate the order in which reviews and approvals should be obtained.	4 th Quarter FY 2014.
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See Appendix C, Note 4, for OIG Response

5.	Revise NHEERL guidance to include a definition for “reasonably foreseeable risks” including illustrative examples of the types of information that should be included in the consent forms.	Revise NHEERL guidance to include the federal definition of “minimal risk” including illustrative examples of the types of information that should be included in the consent forms. ⁸	NHEERL guidelines will be modified to include the federal definition of minimal risk as well as illustrative examples.	4 th Quarter FY 2014.
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See Appendix C, Note 5, for OIG Response

⁸In a subsequent communication, ORD agreed to implement the OIG recommendation, stating that “*NHEERL guidelines will be modified to include a definition for “reasonably foreseeable risks” including illustrative examples of the types of information that should be included in the consent form.*” The Agency also provided corrective actions and milestones for Recommendation 5.

Rec No.	Recommendation	Suggested Revisions to Recommendation(s) (If applicable)	Corrective Action	Estimated Completion Date
6.	Revise NHEERL guidance to include procedures for ensuring that human subjects research consent forms consistently present the risks of the pollutants to which human subjects are exposed, including a summary of EPA assessments of short-term and long-term health effects and the upper pollutant concentration level for the pollutant to which the subject will be exposed.		The HRPO will enhance what is currently in place regarding language about risks of pollutants to which subjects are exposed and will ensure this language be placed as appropriate in consent forms. Interim steps have already been taken to ensure that the communication of risk from studies are consistently presented throughout the consent form process.	4 th Quarter FY 2014.

See Appendix C, Note 6, for OIG Response

7.	Include in its consent forms any known carcinogenic effects of pollutants that the EPA uses in human exposure studies.	While the current consent forms do present information regarding the present risk of pollutants the EPA uses in human exposure studies, additional information will be included for any known carcinogenic effects of the pollutants (as reported by IARC, National Toxicology Program's Report on Carcinogens, or by the EPA IRIS Program). In general, the potential for carcinogenic effects is not anticipated to be greater than minimal. ⁹	This recommendation will be implemented immediately.	2 nd Quarter ¹⁰ FY 2014.
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See Appendix C, Note 7, for OIG Response

⁹ At the exit conference, the OIG and ORD amended Recommendation 7 to include not only pollutants with known carcinogenic effects, but also those pollutants with likely carcinogenic effects. ORD proposed that we use EPA's two highest cancer risk guidelines. According to EPA's 2005 Cancer Guidelines, these are "Carcinogenic to Humans" and "Likely to be Carcinogenic to Humans." In a subsequent communication, ORD agreed to the new language and confirmed that the corrective actions for Recommendation 7 would remain the same.

¹⁰ In a subsequent communication, the agency revised the corrective action date to June 30, 2014.

Rec. No.	Recommendation	Suggested Revisions to Recommendation(s) (If applicable)	Corrective Action	Estimated Completion Date
8.	<p>Revise the EPA's NHEERL guidance to:</p> <p>a. Clearly state that NHEERL has adopted UNC-IRB SOP definitions and reporting timeframes for adverse events and unanticipated problems and will continue to follow the most updated version of the SOPs.</p> <p>b. Establish the EPA's clinical follow-up responsibilities after adverse and serious adverse events, including general timeframes for clinical follow-up.</p> <p>c. Require principal investigators to include a summary of the agency's clinical follow-up responsibilities in each study's protocol and consent forms.</p>		<p>Changes to the NHEERL guidance document will be made to ensure that the NHEERL policy is always harmonized with the latest IRB policy. The IG is aware that EPA physicians are not legal health care providers. The guidelines will be modified to describe EPA's follow-up clinical responsibilities. EPA will discuss with the UNC IRB whether they want to see a summary of the Agency's clinical followup responsibilities included in consent forms, and include it if the IRB recommends we do so.¹¹</p>	4 th Quarter FY 2014.

¹¹ In subsequent communications, ORD agreed to implement OIG recommendation 8(c), stating that *"Changes to the NHEERL guidance document will be made to ensure that the NHEERL policy is always harmonized with the latest IRB policy. The NHEERL guidance document will be updated to specify EPA's follow-up clinical responsibilities,"* and clarified that a summary of these responsibilities would be included in study protocols and consent forms. The agency also provided corrective actions and milestones for Recommendation 8(c).

OIG Evaluation of Agency Comments

We appreciate the agency's comments and its recognition of our efforts to understand and thoroughly evaluate its human research studies program. Our evaluation of the agency's comments on our draft report recommendations is below. We also received a number of technical comments from the agency and made changes to the final report as appropriate.

Note 1- Response to Recommendations 1(a) and 1(b):

The agency concurred with our recommendation to revise the NHEERL guidance to include an EPA internal review and approval process for significant study modifications and to revise the flowchart to accurately portray the protocol review process. The agency provided a corrective action plan stating that a job offer has been made to fill the HRPO position, and that updating the NHEERL guidance to address the OIG's recommendation will be the first task assigned to the HRPO. This includes developing guidance on what constitutes a significant study modification, who must review and approve such modifications, and correcting the flowchart. The agency explained that the NHEERL guidance will be updated by September 30, 2014, unless the vacant HRPO position remains unfilled. We accept the agency's planned corrective actions in response to this recommendation. The recommendation is resolved and open pending the agency's completion of the agreed-to corrective actions.¹²

Note 2- Response to Recommendation 2:

The agency concurred with our recommendation to implement a procedure for documenting that investigators have met the requirement for continuing annual ethics education and began implementing such a procedure in the fall of 2013. The agency provided evidence of the corrective action taken. We accept the agency's corrective action in response to this recommendation. This recommendation is closed and no further action is required.

Note 3- Response to Recommendation 3:

The agency concurred with our recommendation to revise the NHEERL policy to eliminate the DHRO position and transfer those duties to the HRPO Director. The agency provided a corrective action plan stating that the transfer of these duties to the HRPO will be done as part of the HRPO revision of the NHEERL guidelines. The agency said this corrective action would be completed by September 30, 2014. We accept the agency's planned corrective action in response to this recommendation. The recommendation is resolved and open pending the agency's completion of the agreed-to corrective actions.

Note 4- Response to Recommendation 4:

The agency concurred with our recommendation to develop management controls to ensure NHEERL management reviews and approvals are properly documented. The agency provided a

¹² Subsequent to this action plan, NHEERL management provided us with clarification about the responsible party/office for recommendations 1, 3, 4, 5, 6, 7 and 8.

corrective action plan stating that the NHEERL guidelines will be modified to specifically indicate the order in which reviews and approvals should be obtained by September 30, 2014. We accept the agency's planned corrective action in response to this recommendation. The recommendation is resolved and open pending the agency's completion of the agreed-to corrective actions.

Note 5- Response to Recommendation 5:

The agency proposed an alternative to Recommendation 5. The agency proposed that we change our recommendation that NHEERL's guidance include a definition for "reasonably foreseeable risks" to recommend, instead, that the guidance include a definition of "minimal risk." After discussing the proposed alternative at the exit conference, NHEERL management concurred with our recommendation to revise NHEERL guidance to include a definition for "reasonably foreseeable risks." In a subsequent communication, the agency stated that "NHEERL guidelines will be modified to include a definition for "reasonably foreseeable risks" including illustrative examples of the types of information that should be included in the consent form." The agency provided a corrective action plan stating that this corrective action would be completed by September 30, 2014. We accept the agency's planned corrective action in response to this recommendation. The recommendation is resolved and open pending the agency's completion of the agreed-to corrective actions.

Note 6- Response to Recommendation 6:

The agency concurred with our recommendation to revise NHEERL guidance to include procedures for ensuring that consent forms consistently present the risks of pollutants, including EPA assessments of short-term and long-term health effects and the upper pollutant concentration levels of the pollutants. The agency stated that they will "enhance what is currently in place regarding language about risks of pollutants and that they have already taken interim steps to ensure that the communication of risks is consistently presented through the consent form process." Subsequent to providing the OIG with its action plan, NHEERL management clarified their proposed corrective actions for this recommendation. NHEERL said it would develop language to ensure that consent forms consistently present the same risks of pollutants, including the risks of short- and long-term health effects associated with pollutant exposure, and the upper-pollutant concentration. We accept the agency's planned corrective action in response to this recommendation, as clarified in subsequent communications with NHEERL management. The recommendation is resolved and open pending the agency's completion of the agreed-to corrective actions.

Note 7- Response to Recommendation 7:

The agency concurred with our recommendation to include in its consent forms any known carcinogenic effects of pollutants, and suggested that the recommendation include specific health institutions to ensure the credibility of a finding of carcinogenic effects. The agency also recommended that the International Agency for Research on Cancer, an associated body of the World Health Organization, be included in the list of agencies. We agree with the agency's suggestion to include other federal health agencies, and acknowledge the agency's desire to use other organizations such as the IARC, as appropriate. We have revised the recommendation to

specify EPA and other federal health agencies,¹³ as appropriate, and to recommend the agency document the basis for using non-federal information as opposed to the assessments of federal health agencies. During the exit conference, the OIG and ORD also agreed to amend recommendation 7 to include not only pollutants with known carcinogenic effects, but also pollutants with likely carcinogenic effects. In a subsequent communication, ORD agreed to the amended recommendation and provided a corrective action plan stating that it would revise its consent forms by June 30, 2014. We accept the agency's planned corrective action in response to this recommendation. The recommendation is resolved and open pending the agency's completion of the agreed-to corrective actions.

Note 8 - Response to Recommendations 8(a), 8(b) and 8(c):

The agency concurred with our recommendation to revise the NHEERL guidance to: (a) clearly state that NHEERL has adopted UNC-IRB SOP definitions and reporting timeframes for adverse events and unanticipated problems, (b) establish the EPA's clinical follow-up responsibilities after adverse and serious adverse events, and (c) require principal investigators to include a summary of clinical follow-up responsibilities in the study protocol and consent forms. We accept the agency's planned corrective actions to ensure that NHEERL guidance is harmonized with the latest IRB policy and to revise the guidance to describe EPA's clinical follow-up responsibilities. The agency provided a corrective action plan stating that it would revise the adverse events section of the NHEERL guidance to ensure that NHEERL policy is always harmonized with the latest IRB policy, and that it would describe EPA's follow up clinical responsibilities. The agency committed to completing these actions by September 30, 2014. We accept the agency's planned corrective action in response to recommendations 8(a) and 8(b). Recommendations 8(a) and 8(b) are resolved and open pending the agency's completion of the agreed-to corrective actions.

Regarding recommendation 8(c), the agency said that it would discuss with the UNC-IRB whether it wants to see a summary of the agency's clinical follow-up responsibilities included in consent forms, and include it if the IRB recommends the agency do so. After discussing the agency response at the exit conference, NHEERL management concurred with our recommendation to include a summary of the agency's clinical follow-up responsibilities in the study protocol and consent forms. In a subsequent communication, the agency stated that "Changes to the NHEERL guidance document will be made to ensure that the NHEERL policy is always harmonized with the latest IRB policy. The NHEERL guidance document will be updated to specify EPA's follow-up clinical responsibilities." Further, the agency clarified that a summary of these responsibilities would be included in study protocols and consent forms. The agency said this corrective action would be completed by September 30, 2014. We accept the agency's planned corrective action in response to this recommendation. The recommendation is resolved and open pending the agency's completion of the agreed-to corrective actions.

¹³Other federal health agencies would include the National Institute of Health, National Toxicology Program, Health and Human Services, the Center for Disease Control, National Institute of Environmental Health Sciences, and Agency for Toxic Substances and Disease Registry.

Definitions of Adverse Events and Unanticipated Problems

Event/Problem	NHEERL guidance definitions	2009 UNC IRB-SOP definitions
Serious adverse events	Fatal or life-threatening; results in significant or persistent disability; require[s] or prolong[s] hospitalization; result[s] in a congenital anomaly/birth defect; or, in the opinion of the investigators, represents other significant hazards or potentially serious harm to research subjects or others.	A serious adverse event is any adverse event temporally associated with the subject's participation in research that meets any of the following criteria: <ul style="list-style-type: none"> • results in death; • is life-threatening (places the subject at immediate risk of death from the event as it occurred); • requires inpatient hospitalization or prolongation of existing hospitalization; • results in a persistent or significant disability/incapacity; • results in a congenital anomaly/ birth defect; or • any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.
Adverse event or experience	Undesirable and unintended, though not necessarily unanticipated, injury or physical or emotional consequence to a human subject.	An adverse event or adverse experience is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Adverse events encompass both physical and psychological harms and occur most frequently in the context of biomedical research, although they can occur in the context of social and behavioral research. Adverse events that are not unanticipated problems are not required to be reported to the IRB.
Unanticipated problems	May or may not include specific events experienced by individual subjects, but are developments within the research activity that suggest a potential for increased risks to subjects or others.	An unanticipated problem refers to any incident, experience, or outcome that: <ul style="list-style-type: none"> • is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; • is related or possibly related to a subject's participation in the research; and • suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized. <p>Note that for UNC reporting purposes an event that satisfies the first two criteria will be considered reportable.</p>

Source: The EPA NHEERL Guidance, 2010, and UNC IRB standard operating procedure Number 19.0, 2009.

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