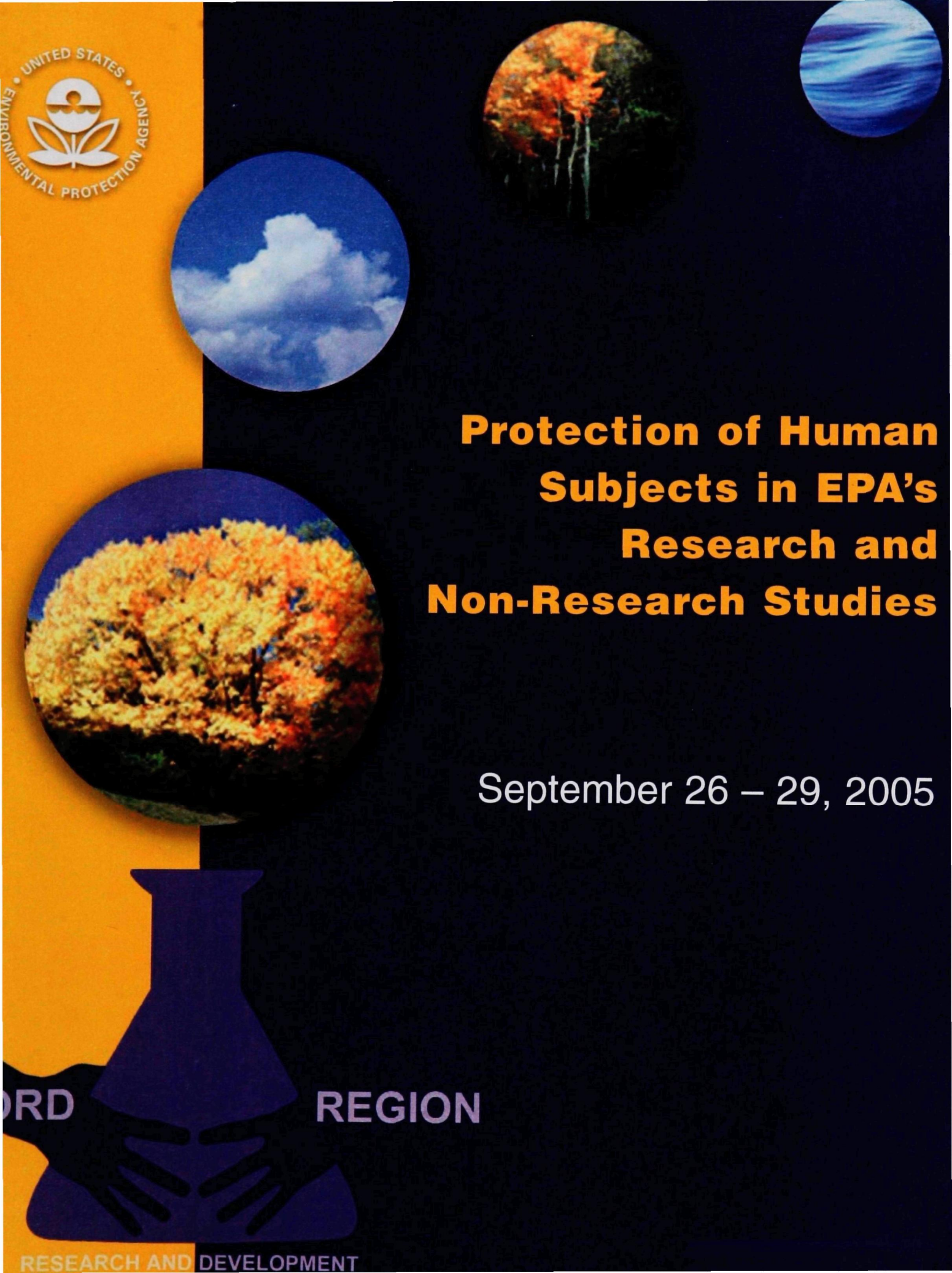

UNITED STATES
ENVIRONMENTAL PROTECTION AGENCY
Protection of Human Subjects in EPA's Research and Non-Research Studies
September 26 – 29, 2005
ORD
REGION
RESEARCH AND DEVELOPMENT

Protection of Human Subjects in EPA's Research and Non-Research Studies

Silver Cloud Hotel - Broadway
1100 Broadway
Seattle, WA 98122

September 26 – 29, 2005

Agenda

MONDAY, SEPTEMBER 26, 2005 (DAY ONE)

PM Moderators: Roseanne Lorenzana and Barbara Lither

1:00 – 2:00 p.m.	**Sign-In at Workshop Registration Desk and Pick Up Meeting Materials – (Broadway Room)**
2:00 – 2:15 p.m.	**Opening Remarks – Welcome and Introduction**
2:15 – 2:30 p.m.	**Objectives of the Workshop** Speaker: *Roseanne Lorenzana, EPA Region 10*
2:30 – 3:30 p.m.	**Human Subjects Research (Common Rule, EPA Order 1000.17, Change 1A, Current Agency Practices, Clarification of Definitions, EPA Use of Data From Third Parties, Genetic Information and Selecting an IRB)** Speakers: *Peter Preuss, ORD-NCEA, and Richard Hermann, ORD-NHEERL*
3:30 – 4:30 p.m.	**The Role of the Institutional Review Board (IRB)** Speaker: *Helen McGough, University of Washington IRB*
4:30 – 6:30 p.m.	**Meet & Greet Mixer (light refreshments provided)**

Tuesday, September 27, 2005 (Day Two)

AM Moderators: Patti Tyler and Joel Hansel

7:45 – 8:15 a.m.	**Continental Breakfast**
8:15 – 8:30 a.m.	**Highlights From Yesterday, Review of Tuesday Agenda**
8:30 – 9:30 a.m.	**Federalwide Assurance and Selecting an Institutional Review Board** Speaker: *Rebecca Calderon, Director Human Studies Division, ORD-NHEERL*
9:30 – 10:45 a.m.	**NHEERL Policy and Guidance** Speaker: *Richard Hermann, Director, Human Research Protocol Office, ORD-NHEERL*
10:45 – 11:00 a.m.	**Break**
11:00 a.m. – 12:00 noon	**Panel Discussion: NHEERL and NERL investigators involved in human research studies** Speakers: R*ebecca Calderon, Bob Devlin, Danelle Lobdell, Don Graff, ORD-NHEERL, and Kent Thomas, ORD-NERL*
12:00 noon – 1:00 p.m.	**Lunch**

PM Moderators: Amanda Hasty and Gilberto Alvarez

1:00 – 1:30 p.m.	**Managing Grants and Contracts Under the Interagency Grants Management System (IGMS)** Speaker: *Armina Nolan, Region 10, Grants Office*
1:30 – 2:00 p.m.	**Determination of Human Subjects Research vs. Public Health Practice** Speaker: *Roger Cortesi, ORD-NCEA*

2:00 – 2:30 p.m.	**Information/Responsibility Flow** Speaker: *Peter Preuss, EPA HSRRO and Director, ORD-NCEA*
2:30 – 2:45 p.m.	**Break** (light refreshments provided)
2:45 – 3:30 p.m.	**Interactions Between EPA and ATSDR** Speaker: *Dr. Anne Sowell, CDC/ATSDR, National Center for Environmental Health*
3:30 – 5:00 p.m.	**Open Forum/Panel Discussion With Q&A With Speakers/Experts From Previous Sessions**

Wednesday, September 28, 2005 (Day Three)

AM Moderators: Jean Zodrow and Maryann Suero

7:30 – 8:00 a.m.	**Continental Breakfast**
8:00 – 8:15 a.m.	**Highlights From Yesterday, Review Wednesday Agenda**
8:15 – 9:15 a.m.	**Presentation and Discussion on Human Subjects Studies Conducted by Regions:** • Libby, MT (Aubrey Miller, Region 8) • Pacific Islander Seafood Consumption (Ruth Sechena, University of Washington) • Human Mercury Biomonitoring in Alaska (Pat Cirone, Region 10) • Children's Asthma Study in Idaho (Don Cole as presented by Roseanne Lorenzana, Region 10)
9:15 – 9:45 a.m.	**Regional Case Studies – Q&A**
9:45 – 10:00 a.m.	**Break**

10:00 a.m. – 12:00 noon	**Breakout Groups- see "Breakout Session Agenda" page in notebook** **Participants in pre-assigned groups (Locations: Group 1 - Broadway; Group 2 - Madison/East; Group 3 -Boardroom; Group 4 - Madison/West)**
12:00 noon – 1:00 p.m.	**Lunch**

PM Moderators: Margaret Jones and Bruce Macler

1:00 – 2:00 p.m.	**Breakout Groups – continue morning session**
2:00 – 3:00 p.m.	**Group 1 (Madison Room) - Being a Child in an Epidemiologic Study** *(concurrent sessions)* Speakers: *Rebecca Calderon and Danelle Lobdell, ORD-NHEERL* **Group 2 (Broadway Room) – Ozone Study - Being in a Clinical Study** Speakers: *Bob Devlin and Don Graff, ORD-NHEERL*
3:00 – 3:15 p.m.	**Break** (light refreshments provided)
3:15 – 4:15 p.m.	**The Power of Perception: A Broader Perspective on Risk Communication** Speaker: *Alvin Chun, ORD, Office of the Administrator*
4:15 – 5:00 p.m.	**Open Forum - Additional Q&A Session for Regional Case-Studies or Breakout Groups**

Thursday, September 29, 2005 (Day Four)

AM Moderators: Alicia Alto and Suzanne Wuerthele

7:30 – 8:00 a.m.	**Continental Breakfast**

8:00 – 8:15 a.m.	**Highlights From Yesterday, Review of Thursday Agenda**
8:15 – 9:30 a.m.	**Special Protections for Children, Fetus, Elderly, Lower Socioeconomic Groups, English as a Second Language Groups** Speaker: *David G. Forster, Western IRB and University of Washington*
9:30 – 10:30 a.m.	**Overview of the Proposed Third Party Rule** Speaker: *Anne Lindsay, Deputy Director for Programs, Office of Pesticide Programs*
10:30 – 10:45 a.m.	**Break**
10:45 – 11:15 a.m.	**Where To Go for Help – Overview** Speaker: *Jean Zodrow, Region 10*
11:15 a.m. – 12:00 noon	**Draft Recommendations and Proposed Next Steps**
12:00 noon	**Adjourn**

List of Acronyms

AAHRPP	Association for the Accreditation of Human Research Protection Programs
ATSDR	Agency for Toxic Substances and Disease Registry
CDC	Centers for Disease Control and Prevention
FERPA	Federal Educational Rights and Privacy Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FOIA	Freedom of Information Act
FWA	Federal Wide Assurance
GAO	General Accounting Office
HIPAA	Health Insurance Portability and Accountability Act
HRPO	Human Research Protocol Office
HSR	human subjects research
HSRB	Human Studies Review Board
HSRRO	Human Subjects Research Review Official
IGMS	Interagency Grants Management System
IRB	Institutional Review Board
NAS	National Academy of Sciences
NCEA	National Center for Environmental Assessment
NCER	National Center for Environmental Research
NGOs	nongovernmental organizations
NHEERL	National Health and Environmental Effects Research Laboratory
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
OHRP	Office of Human Research Protections
OPP	Office of Pesticide Programs
ORD	Office of Research and Development
PHS	Public Health Service
QAPP	Quality Assurance Project Plan
SAB	Science Advisory Board
WIRB	Western Institutional Review Board

Table of Contents

Thursday, September 29, 2005 (Day Four)

AM Moderators: Alicia Alto and Suzanne Wuerthele

Summary

The Workshop on the Protection of Human Subjects in EPA's Research and Public Health Studies, organized by a cross-Agency planning group within the U.S. Environmental Protection Agency (EPA), was the first meeting to bring together Regional and Program Office staff, and ORD scientists to discuss the Regional activities that may be subject to human subjects review and processes described in EPA's Order 1000.17, change 1A, (40CFR Part 26) Policies and Procedures for the Protection of Human Subjects in Research Conducted or Supported by EPA and the Federal Common Rule (40 CFR 26).

As part of the workshop objectives, draft recommendations were developed, and following the workshop they have been finalized through the continuing work of those participants. The overall goal of the following workshop recommendations is to create a culture where the protection of human subjects is the number one priority of EPA-conducted or funded studies, regardless of whether they are research or public health practice.

1. **Increase management attention on human subject research (HSR):**

- Briefing for Deputy Regional Admininstrators (DRA's) from Seattle Workshop participants
- Briefing for DRAs and Regional Administrators (RAs) on Human Subjects Research (HSR) requirements by the Human Subjects Research Review Officical (HSRRO)
- Develop a briefing strategy for senior management
- Identify HSR activities on EPA's tracking system.

2. **Establish expertise or access to expertise in each Region:**

- Regions to develop and implement interim guidance and process
- Each Region to evaluate the extent of their involvement in Human Subjects Research and their needs for establishing a regional process for assuring compliance with the Common Rule and other applicable requirements. During this evaluation, the Regions may consider the need for identifying a process that may include a Human Subjects Coordinator to serve as a central point of contact in each Region. The Coordinator's role may include directing staff through the agency process for HSR; coordinating with the HSRRO in HQ and keeping current regarding HSR activities within the Region and across Regions.

3. **Request an opinion from the Office of General Counsel on the legal questions that were developed by the Workshop planning group:**

- Recommend that each Office of Regional Counsel designate a point of contact on HSR.

4. **Provide additional guidance for the Integrated Grants Management System (IGMS) to reflect the HSR determination and approval process:**

- The 12 Regional Grants Management Officers incorporate definition of HSR, its relevance to EPA's Grants Program, and its requirements into Project Officer training

- Insert language into grant solicitations to define HSR and public health practice; to inform potential grantees of the necessity of Institutional Review Board (IRB) review prior to funding approval of HSR
- Reconcile grant funding timelines with the HSR approval process; including consideration of provisional grant awards prior to HSR approval
- Create a tracking system for HSR and public health practice grants
- Modify Question 14 in IGMS, asking whether human subjects are involved, to include a following question as to whether the study is HSR. If the answer is "yes," require approval by the Agency's HSRRO; if "no," require attachment of the Regional decision memo.

5. **Create a Council composed of Human Subjects points of contact from each Region and National Program Office, and chaired by the Agency HSRRO to:**

- Develop consistent, written, Agency-wide guidance and policy for HSR and public health practice
- Develop an Agency-wide human subjects training plan and program
- Identify how to adapt the existing HSR tracking system for additional needs (e.g., query capability)
- Communicate across the Agency new developments in HSR
- Develop a HSR Web site, including a list of references and subject experts for public input and comment in the *Federal Register*
- Explore the Workshop suggestion that EPA create its own accredited, independent IRB
- Explore the Workshop suggestion to accredit IRBs used by the Agency.

6. **Workshop planning group to develop a straw proposal for the new HSRRO.**

7. **Review and provide comments on the Proposed Rule for Protections for Subjects in Human Research.**

8. **Ensure regional participation in determining specifics involved with implementing the Human Subjects Review Board required by EPA's 2006 Appropriations Act.**

Meeting participants have continued to work on addressing the workshop recommendations. There is much progress being made with the first recommendation with respect to increasing the regional awareness of human subjects research. For the second recommendation, Appendix A identifies contacts for assistance with human subjects research issues. Specific regional contacts for human subjects research issues also are provided.

Day One

U.S. Environmental Protection Agency
Office of Science Policy
Protection of Human Subjects in EPA's Research and Non-Research Studies Workshop
September 26-29, 2005
Silver Cloud Hotel
1100 Broadway
Seattle, WA

Meeting Summary

Monday, September 26, 2005 (Day One)

PM Moderators: Roseanne Lorenzana and Barbara Lither

Opening Remarks – Welcome and Introduction
Roseanne Lorenzana, EPA Region 10

Ann Williamson, Associate Director of Region 10's Office of Environmental Assessment, welcomed everyone to the workshop and commended Roseanne Lorenzana, Patti Tyler, and Jean Zodrow for their efforts in organizing the workshop. She pointed out that it took a team of about 20 individuals to coordinate this workshop, which answers a need to discuss the important issue of human subject research (HSR) studies. She introduced Dr. Lorenzana, who gave an overview of the logistics for this meeting, and thanked Ms. Tyler for all of her work in organizing the workshop as well as the contractors from The Scientific Consulting Group, Inc.

Objectives of the Workshop
Roseanne Lorenzana, EPA Region 10

Dr. Lorenzana pointed out that the purpose of the Office of Research and Development (ORD) regional workshops was to create connections between the Regions and ORD. She thanked ORD staff for their efforts in planning the regional OSP science topic workshops. For more information, she referred participants to EPA's intranet under "Region Workshop." The desired workshop outcomes include an understanding of EPA Regions' activities that qualify as "human subjects research"; the roles and responsibilities of EPA Regions and headquarters in the "HSR approval process; the processes that HSR must undergo to obtain approval; processes, contacts, and timeframes, as well as coordination and consistency approaches appropriate for EPA Regions; the vulnerabilities and liabilities of EPA Regions' staff; how the EPA Regions can provide better human subject study information; and EPA Regions' activities needed to protect human subjects involved in Regions'non-research activities." She then presented peer awards to the following individuals for their hard work in the planning efforts and also for advancing the team's efforts: Alicia Aalto, Region 8; Gilberto Alvarez, Region 5; Barbara Barron, Region 8 (in absentia); Rebecca Calderon, National Health and Environmental Effects Research Laboratory (NHEERL); Alvin Chun, Region 9; Brenda Groskinsky, Region 7; Joel Hansel, Region 4; Amanda Hasty, Region 8; Rich Hermann, NHEERL; Ariel Iglesias, Region 2; Margaret Jones, Region 5; Barbara Lither, Region 10; Bruce Macler, Region 9; Wendy O'Brien, Region 8;

Maryanne Suero, Region 5; Patti Tyler, Region 8; Lee Tyner, Region 3 (in absentia); Winona Victery, Region 9 (in absentia); Suzanne Wuerthele, Region 8; and Jean Zodrow, Region 10.

Dr. Lorenzana pointed out that the Regions did not have a shared knowledge of what defined a human subjects study, or what is research, or what EPA does to protect human subjects. Many of the participants had questions that were of a legal and/or policy nature. Participants were encouraged to write down their questions, which the group could then request advice from the Office of the General Counsel and for which responses could be provided at a future date.

Dr. Lorenzana explained that she saw Peter Preuss, Director of EPA's National Center for Environmental Assessment (NCEA) in ORD, at a March 2005 Society of Toxicology Workshop in New Orleans and asked him to hold a workshop on the issue of HSR studies. She introduced him as an expert on risk assessment, priority, and law as well as being EPA's Human Subjects Research Review Official (HSRRO). She pointed out that his presentation would attempt to clarify the Common Rule as it pertains to HSR. Richard Hermann also would speak on this topic following Dr. Preuss' presentation.

Dr. Lorenzana informed the participants that Dr. Hermann is board certified in clinical oncology, has several years of experience in ethics, has worked at ORD's NHEERL, and now is the Director of Human Research Protocol at NHEERL.

Human Subjects Research and Studies at the EPA

Presentation to:
Protection of Human Subjects in EPA's Research and Non-Research Studies
September 26 - 27, 2005

Peter W. Preuss, Ph.D.
EPA Human Subjects Research Review Official
Director, National Center for Environmental Assessment
Office of Research and Development

What is Human Subjects Research?

- Many different types of studies fall under this heading:
  - Epidemiological studies
  - Surveys
  - Studies involving intentional exposures, such as:
    - *Exposure and biomonitoring studies*
    - *Metabolism*
    - *Clinical trials*
    - *Repellent efficacy tests*

Value of Human Research

- Human subjects research has been central to many medical and public health advances
- Human subjects research has been central at the EPA for a number of key standards and regulations, for example:
  - Ozone
  - Particulate matter

Background and History

- There have been ethical transgressions in the past, such as studies carried out by the Nazis during World War II, and the Tuskegee syphilis study.
- These transgressions, among other things, led to increased ethical oversight of human subjects research.
- Nuremberg Code (1947)
  - Followed Nazi violations
    - *"The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random or unnecessary in nature."*
- Declaration of Helsinki (1964)
  - World Medical Association Declaration
    - *"The primary purpose of medical research involving human subjects is to improve…the understanding of the etiology and pathogenesis of disease."*

Background and History (2)

- The Belmont Report (1979)
  - Cornerstone of U.S. human subjects ethics documents
    - *Principles: respect for persons, beneficence and justice.*
- The Common Rule (1991)
  - A rule promulgated by 18 Agencies jointly that describes what may and may not be done, and the principles and practices that must be followed when the United States government (USG) is conducting or supporting human subjects research.

EPA Has Different Roles with Human Subjects Research Data

- EPA performs or funds human subjects research:
  - Studies in ORD laboratories
  - Extramural funding through ORD STAR grants
  - Program Offices and Regions
  - All must comply with the Common Rule
- EPA also retrieves and uses data generated by external research (*"third party"*). These parties are not necessarily subject to the Common Rule.

EPA Human Subjects Research: The Common Rule

- EPA follows the Common Rule (40 CFR 26).
- EPA promulgated the rule along with 17 other Agencies and Departments in June 1991.
- The internal Administration of the Common Rule is given by EPA Order 1000.17 (July 1999):
  - *Policies and Procedures for the Protection of Human Subjects in Research Conducted or Supported by EPA.*
  - This Order establishes a Human Subjects Research Review Official (HSRRO) to assure that all EPA conducted or supported research using human subjects comports with the Common Rule

The Common Rule (2)

- The Common Rule specifies requirements for approval by an Institutional Review Board (IRB), and informed consent requirements.
- Use of the Common Rule is mandatory for research conducted or sponsored by 18 signatories.
- Use of the Common Rule by parties outside of the USG is not required, but may have some voluntary compliance.
- Many private U.S. institutions adopt Common Rule standards for human subjects research.
- The Common Rule duty of EPA is to get certification that the research has received appropriate ethical review.
- EPA goes further. EPA requires the HSRRO to review and approve such research before human subjects can be involved. This is done in addition to other institutional reviews.

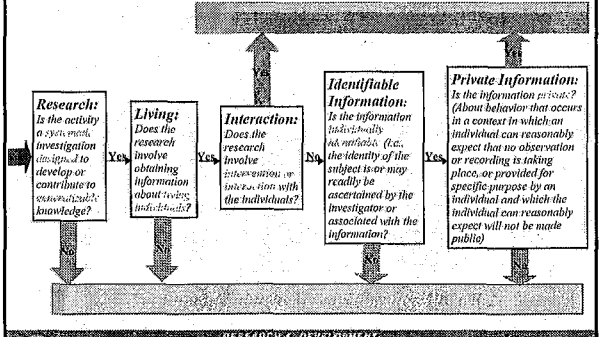
EPA Reviews under the Common Rule

- On occasion, EPA has decided that the IRB has overlooked possible risks to subjects. When this has happened, discussions have resolved the issue.
- On occasion, we have requested changes in the consent document.
- Over the past six years, EPA has averaged about fifty projects per year requiring decisions from the HSRRO.
- Of these, a small number have exposed people deliberately to environmental pollutants.

Examples of EPA Intentional Dosing Human Subject Research

- Physiological changes in healthy young adults exposed to concentrated coarse air particles (2003)
- Genetic susceptibility to Ozone-induced bronchial airway inflammatory responses in humans (2003)
- Physiological changes in healthy young adults exposed to concentrated ambient air particles and nitrogen oxides (2001)
- Assessment of airway phagocyte function in healthy individuals exposed to coarse mode air pollution particles (2001)
- Effect of Toluene exposure on human signal detection (2001)
- Physiological, cellular and biochemical effects of Diesel Exhaust in healthy young volunteers (2001)
- Infectivity and virulence of Cryptosporidium Genotype H oocysts in healthy adult volunteers (2000)
- Pharmacokinetics of 13C-Bromodichloromethane in humans (1999)
- Physiological changes in mild to moderate asthmatics exposed to concentrated ambient air particles (1999)
- Cardiopulmonary response of patients with chronic obstructive lung disease following exposure to concentrated air particles (1999)

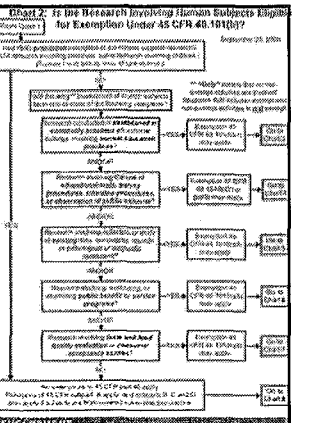
What is Human Subjects Research?



What Are HSR Exemptions?

- Certain HSR activities may be **exempt** from IRB review. These are identified in 40CFR26.101(b)(1)-(6).

  e.g., existing specimens or data, survey procedures
- Many IRBs choose to review exempt HSR activities on an expedited basis.
- For EPA, the HSRRO decides whether a human subjects study is exempt, not the principal investigator or project officer.



Process for Conducting HSR at EPA

- Requirements apply to all situations where EPA staff or funding are used to conduct HSR.
- Applies equally to Headquarters and Regions
- HSR must follow the Common Rule and EPA Order 1000.17
- HSR must have IRB approval
- HSR must have additional EPA approval from HSRRO
- Annual follow-up requirements on investigators through IRB

Process for Conducting HSR at EPA (2)

- Project officers provide the following paperwork, via the designated HSR coordinator in their laboratory, program or region, to Roger Cortesi/Peter Preuss (HSRRO):
  1. Federal Wide Assurance (FWA) number (institution and its associated IRB; http://www.hhs.gov/ohrp/assurances/)
  2. Copy of IRB approval for research
  3. Copy of consent form(s)
  4. Copy of research proposal and documentation provided to IRB
- Start early – return time ~2 weeks+

Proposed Changes to HSR at EPA

- Some proposed HSR rule changes applicable to EPA conducted or sponsored research:
  - Proposed categorical ban on all EPA intentional dosing studies of any environmental substance to children (<18) and pregnant women.
  - Proposal that all EPA intentional dosing studies of pesticides (banned in children and pregnant women) will need to be reviewed by the (to be constituted) Human Studies Review Board (HSRB)
  - Proposed formal adoption of DHHS additional protections for Children (Subpart D), Pregnant Women and Fetuses (Subpart B) – already instituted informally at EPA.

Third Party Human Studies

- "Third party" studies are those not conducted or sponsored by a U.S. federal agency. Third parties include:
  - State Agencies (California Air Resources Board)
  - Other national governments (Health Canada,UK Medical Research Council, European Commission)
  - International organizations (WHO, OECD)
  - NGOs
  - Industry
  - Academia
  - Others
- Conditions of research (e.g., use of the Common Rule) may be unknown

Third Party Human Studies (2)

- Third-party studies may be retrieved from the literature by EPA or submitted to EPA by others
- Third-party studies may be published or unpublished
- Third-party studies may, or may not, have been done in accord with Common Rule
- Third-party studies may, or may not, be peer reviewed
- Submitters of third-party studies may be regulated entities, public interest groups, or others

Controversy Concerning Third Party Human Research

- In 1998, the Environmental Working Group issued a report, "The English Patients," that strongly criticized EPA's consideration of industry generated human studies on pesticides
- In response, EPA convened a SAB/SAP Ethics Panel to review OPP use of human subjects studies and procedures for accepting data from third parties (Report, September 2000)
- In fall of 2001, articles critical of EPA's approach to using human studies appeared in LA Times, NY Times, Washington Post, etc.

Recent Controversy (2)

- Since the 1996 FQPA, Office of Pesticide Programs has received some 20 third party intentional dosing studies of systemic toxicity in humans.
  - Funded by private industry with interest in pesticide registration
  - In general, intentional dosing of human subjects, with small number of subjects - limited broad scientific use.
  - Studies set up with increasing doses to determine:
    - *No Observed Adverse Effect Levels (NOAEL), or*
    - *Lowest Observable Effect Levels (LOEL)*
  - More such studies in the pesticide area were expected to be submitted responding to new safety standard in section 408 of the Federal Food, Drug and Cosmetic Act

National Academy of Sciences (NAS) Report

- The NAS Report, *Intentional Human Dosing Studies for EPA Regulatory Purposes*, was released February 2004
- Recommendations:
  - Creation of a board to review the protocols and justification for all intentional dosing studies conducted for EPA regulatory purposes.
  - Adoption of Common Rule Subpart D on research involving children.
  - Recommendation that there is societal benefit from studies that seek to improve the accuracy of EPA's decisions, but do not provide a public health or environmental benefit, so long as they can be reliably anticipated to pose no identifiable risk to study participants.
  - Acceptance of scientifically valid studies existing before new rules unless there is clear and convincing evidence that the conduct of those studies was fundamentally unethical or that the conduct was deficient relative to then-prevailing ethical standards.

RESEARCH & DEVELOPMENT
Building a scientific foundation for sound environmental decisions

EPA Proposed 3rd Party HSR Regulation

- Comprehensive rule adopting NAS recommendations for 3rd Party intentional dosing studies intended for submission under FIFRA.
- 3rd Party intentional dosing studies of pesticides:
  - must be conducted subject to the Common Rule;
  - are banned in children and pregnant women;
  - must be reviewed by the EPA Human Studies Review Board (to be established)
- Study acceptability requirements:
  - Studies conducted prior to the rule will be evaluated against a standard of not fundamentally unethical or significantly deficient compared to the ethical standards of the time.
  - Studies commenced after the rule must have been conducted consistent with the Common Rule.
- 90 day public comment process open
  http://www.epa.gov/oppfead1/guidance/fedreg-hs.pdf

RESEARCH & DEVELOPMENT
Building a scientific foundation for sound environmental decisions

Human Subjects Research (Common Rule, EPA Order 1000.17, Change 1A, Current Agency Practices, Clarification of Definitions, EPA Use of Data From Third Parties, Genetic Information and Selecting an Institutional Review Board (IRB))
Peter Preuss, ORD-NCEA, and Richard Hermann, ORD-NHEERL

Dr. Preuss informed attendees that he had received numerous e-mails (about 20-30 per day) from the group organizing this workshop. He began his presentation by defining HSR and explained that many different types of studies are included under this type of research such as epidemiological studies, surveys, and studies involving intentional exposures (e.g., exposure and biomonitoring studies, metabolism, clinical trials, and repellent efficacy tests). He added that HSR has been central to many medical and public health advances as well as in establishing a number of key standards and regulations at EPA for ozone and particulate matter. Dr. Preuss gave some background and history on HSR, pointing out the ethical transgressions in such studies as conducted by the Nazis during World War II and in the Tuskegee Syphilis Study. Such transgressions led to an increase in ethical oversight of HSR. The Nuremburg Code, established in 1947, states that "The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random or unnecessary in nature." In addition, the Declaration of Helsinki, established in 1964, states "The primary purpose of medical research involving human subjects is to improve...the understanding of the etiology and pathogenesis of disease."

Dr. Preuss encouraged the workshop attendees to read *The Belmont Report* (1979), which became the basis for all other U.S. human subjects ethics documents. *The Belmont Report*, he added, was well thought out and based on three very important principles with regard to human subjects studies: (1) respect persons, (2) conduct the studies equitably, and (3) include justice. In addition, he provided an overview of the Common Rule (1991), which was developed jointly by EPA and 17 other Agencies and describes what can and cannot be done as well as the principles and practices that must be adhered to when the U.S. government is conducting or supporting HSR. He then pointed out that EPA has different roles with HSR data. For example, EPA performs or funds HSR studies in ORD laboratories, Program Offices and Regions, and provides extramural funding through ORD STAR grants. All EPA HSR studies must comply with the Common Rule. EPA also retrieves and uses data generated by third parties, but these parties are not necessarily subject to the Common Rule. The internal administration of the Common Rule is executed under EPA Order 1000.17 (July 1999). The Order establishes an HSRRO to ensure that all EPA-conducted or -supported research using human subjects complies with the Common Rule. The Common Rule gives requirements for approval by an Institutional Review Board (IRB) and informed consent. On occasion, EPA has decided that the IRB has overlooked possible risks to subjects. In these cases, discussions usually resolve the issue. On other occasions, EPA has requested changes in the consent document. In addition, EPA requires that the HSRRO review and approve research before human subjects are involved in addition to other institutional reviews. It is the duty of EPA to get certification, meet the highest standards, and ensure that the proposed research goes through an IRB review and complies with the Common Rule. Over the past 6 years, EPA has averaged approximately 50 projects per year requiring decisions from the HSRRO. Of these, only a very small number of projects have been found to expose people deliberately to environmental pollutants.

Dr. Preuss discussed HSR exemptions and began by pointing out that certain activities may be exempt from IRB review, which are defined in 40CFR26.101(b)(1)-(6) and include existing specimens or data and survey procedures. Many of the IRBs choose to review exempt HSR activities on an expedited basis. EPA's HSRRO decides whether a human subjects study is exempt, not the Principal Investigator (PI) or Project Officer (PO). As part of the process of conducting HSR at EPA, he explained that the POs provide paperwork (i.e., Federal Wide Assurance [FWA] number, copy of IRB approval for research, copy of consent form(s), and copy of research proposal and documentation provided to the IRB) via the designated HSR coordinator in their laboratory, program, or Region, to Dr. Roger Cortesi and Dr. Preuss (EPA HSRRO). Right now, Dr. Preuss is the only person in EPA who can determine if the proposed research can be conducted; the Regions cannot make this determination. EPA has proposed some changes to HSR activities being conducted at EPA, including the following: (1) place a categorical ban on all EPA intentional dosing studies of any environmental substance to children (less than 18 years old) and pregnant women; (2) require that all EPA intentional dosing studies of pesticides (banned in children and pregnant women) be reviewed by a new group, the Human Studies Review Board (HSRB), which is being developed; and (3) encourage formal adoption of DHHS additional protections for Children (Subpart D), Pregnant Women and Fetuses (Subpart B), which is already instituted informally at EPA.

Dr. Preuss addressed concerns about third-party human studies. Third-party studies, he clarified, are those not conducted or sponsored by a U.S. federal agency and include state agencies, other national governments, international organizations, nongovernmental organizations (NGOs), industry, academia, and others. In addition, he pointed out that the conditions of the research might be unknown (i.e., whether the research followed the Common Rule). He referred to the 1998 Environmental Working Group report entitled "The English Patients" that strongly criticized EPA's consideration of industry-generated human studies on pesticides. In response, EPA convened an SAB/SAP Ethics Panel to review the Office of Pesticide Program's (OPP) use of human subjects studies and procedures for accepting data from third parties. In fall 2001, articles criticizing EPA's approach to using human studies appeared in the *LA Times*, *NY Times*, *The Washington Post*, and other newspapers. OPP has received about 20 third-party intentional dosing studies of systemic toxicity in humans, which were funded by private industry with an interest in pesticide registration. Studies were set up with increasing doses to determine either "no observed adverse effect levels" or "lowest observable effect levels." In February 2004, the National Academy of Sciences (NAS) issued a report on "Intentional Human Dosing Studies for EPA Regulatory Purposes." NAS recommended creation of a board to review the protocols and justification for all intentional dosing studies conducted for EPA regulatory purposes; adoption of Common Rule Subpart D on research involving children; acceptance of the societal benefit from studies that seek to improve the accuracy of EPA's decisions but that do not provide a public health or environmental benefit as long as they can be presumed to pose no identifiable risk to study participants; and acceptance of scientifically valid studies existing before new rules were established, unless clear and convincing evidence exists that the conduct of those studies was fundamentally unethical or that the conduct was deficient relative to then-prevailing ethical standards. EPA proposed a comprehensive rule adopting NAS recommendations regarding third-party intentional dosing studies intended for submission under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Study acceptability requirements include that studies conducted before the existence of the Common Rule be evaluated against a standard of not

fundamentally unethical or significantly deficient as compared to the ethical standards of the time, and studies begun after the Rule must have been conducted in compliance with the Common Rule.

Human Subjects Research Definitions and Details

Region/ORD Training Workshop on Protection of Human Subjects in EPA's Research and Non-Research Studies

September 2005

Richard Hermann, M.D., M.P.H.
Director
NHEERL Human Research Protocol Office

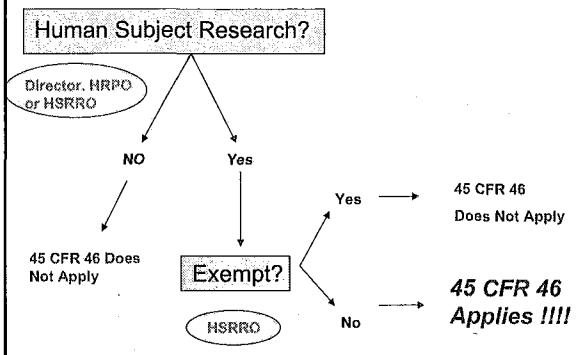
Why are we here?

- To protect the safety, confidentiality, privacy, and respect of our research volunteers
- Our system for protecting human subjects has come under intense scrutiny
- Several reports suggest lack of knowledge or understanding on part of investigators, IRBs, Institutional officials
- Increased penalties for non-compliance
- Erosion of public trust
- New mandates for ethics training

Department of Health and Human Services Office of Human Research Protections Determination Letters

- **May 2, 2005** University of Maryland Baltimore Professional
- **May 19, 2005** St. Joseph's Hospital Atlanta, Inc.
- **May 23, 2005** Columbia University / NY Presbyterian Hospital
- **June 29, 2005** Northwestern University
- **July 19, 2005** St. Joseph's Hospital Atlanta
- **July 28, 2005** Oregon Health and Science University
- **August 5, 2005** University of Miami
- **August 18, 2005** University of Illinois at Urbana-Champaign
- **August 18, 2005** University of Minnesota
- **August 25, 2005** National Institutes of Health

Does 45 CFR 46 Apply?



What is Human Subjects Research?

- ***Research***
  - means a systematic investigation, including research development, testing, and evaluation, *designed* to develop or contribute to *generalizable knowledge*.
- ***Human subject***
  - means a *living* individual about whom an investigator (whether professional or student) conducting research obtains (1) data through *intervention* or *interaction* with the individual, or (2) *identifiable private information*.

Identifiable Information

The identity of the subject is or may readily be ascertained by the investigator or associated with the information.

Private Information

Information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public(for example, a medical record)

Subject Identifiers

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

- Names
- Telephone numbers
- Any elements of dates (other than year if less than 89) for dates directly related to an individual, including birth date, admission date, discharge date, date of death.
- Any geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code
- Fax numbers

Subject Identifiers (cont'd)

HIPAA

- Electronic mail addresses
- Social security numbers
- Medical record numbers
- Health plan beneficiary numbers
- Account numbers
- Certificate/license numbers
- Vehicle identifiers and serial numbers (VIN), including license plate numbers
- Device identifiers and serial numbers (e.g., implanted medical device)

Subject Identifiers (cont'd)

HIPAA

- Web universal resource locators (URLs)
- Internet protocol (IP) address numbers
- Biometric identifiers, including finger and voice prints
- Full face photographic images and any comparable images
- Any other unique identifying number, characteristic or code, other than dummy identifiers that are not derived from actual identifiers and for which the re-identification key is maintained by the health care provider and not disclosed to the researcher

"De-identified" Data

- Data contains none of the 18 identifiers listed in HIPAA about the individual, employers, or household members.....OR.....
- Expert opinion that the risk of individual identification is very small
- Examples:
  - Data about how many times a procedure is performed on patients by age range
  - Patient health outcomes, age and sex with no individual identifiers

"Exempt" Research

45 CFR 46.101(b)

- Common Rule lists 6 major categories:

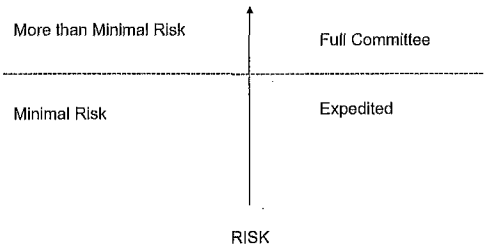
1) Educational practices, curricula
2) Educational tests, surveys, interviews, observation of public behavior
   - unless identifiers are present
   - unless risk of criminal or civil liability
   - unless risk of damage to finances, employment, or reputation
3) #2 if performed on elected officials or candidates

"Exempt" Research
45 CFR 46.101(b)

4) Existing data, documents or specimens if publicly *available or if investigator records in such a manner* that subjects cannot be identified
5) Public benefit or service programs
6) Taste and food quality evaluation, consumer acceptance studies (provided approved by FDA, EPA, USDA)

*** No exemptions if study involves prisoners, fetuses, pregnant women, human in vitro fertilization, or some types of children's research

Level of Risk Determines Level of IRB Review



Examples of Expedited Review

- Blood samples (routine methods, small amounts)
- Noninvasive collection of biological samples or clinical data (exm., hair, toenails, dietary history)
- Voice, video, digital recordings
- Individual or group behavior, surveys, interviews, oral histories
- Select types of continuing review

Dr. Hermann listed several reasons behind organizing such a workshop, one of which is to protect the safety, confidentiality, privacy, and respect of research volunteers. Other reasons include the fact that the system for protecting human subjects has come under intense scrutiny; several reports suggest a lack of knowledge or understanding on the part of investigators, IRBs, and institutional officials; there have been increased penalties for noncompliance with the Common Rule; there is an erosion of public trust; and there are new mandates for ethics training. Dr. Hermann pointed out that EPA took Subpart A of the Common Rule and made it formally 40CFR26. He added that the determination of what constitutes HSR and what is exempt are decisions made by Dr. Preuss. He then defined the terms "research" and "human subject." "Research" is a systematic investigation, including development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. A "human subject" is a living individual about whom an investigator (whether professional or student) conducting research obtains data through intervention or interaction with the individual, or identifiable private information. He added that identifiable information allows for the identity of the subject to be readily ascertained by the investigator or be associated with the information. Private information about behavior is such that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, information has been provided for specific purposes by an individual, and that the individual can reasonably expect the information will not be made public such as a medical record.

Dr. Hermann explained that there are several subject identifiers, such as the following listed by the Health Insurance Portability and Accountability Act of 1996 (HIPAA): names; telephone numbers; any elements of dates (other than year) directly related to an individual, including birth date, admission date, discharge date, and date of death; any geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code; fax numbers; electronic mail addresses; social security numbers; medical record numbers; health plan beneficiary numbers; account numbers; certificate/license numbers; vehicle identifiers and serial numbers (VIN), including license plate numbers; device identifiers and serial numbers (e.g., implanted medical device); Web universal resource locators (URLs); Internet protocol (IP) address numbers; biometric identifiers, including finger and voice prints; full face photographic images and any comparable images; and any other unique identifying number, characteristic, or code, other than dummy identifiers that are not derived from actual identifiers and for which the re-identification key is maintained by the health care provider and not disclosed to the researcher. Dr. Hermann added that the Common Rule lists six major categories of "exempt" research: (1) educational practices and curricula; (2) educational tests, surveys, interviews, and observations of public behavior; unless identifiers are present, there is risk of criminal or civil liability, or there is risk of damage to finances, employment, or reputation; (3) #2 if performed on elected officials or candidates; (4) existing data, documents, or specimens, if publicly available or if the investigator records in such a manner that subjects cannot be identified; (5) public benefit or service programs; and (6) taste and food quality evaluation, and consumer acceptance studies (provided or approved by FDA, EPA, USDA). Dr. Cortesi commented that Office of Human Research Protections (OHRP) has developed a list of what can be exempted. Dr. Hermann pointed out that the level of risk determines the level of IRB review of an HSR study. He concluded his presentation by providing examples of expedited reviews, including: blood samples (routine methods, small amounts); noninvasive collection of biological samples or clinical data (hair, toenails, dietary

history); voice, video, and digital recordings; individual or group behavior, surveys, interviews, and oral histories; and select types of continuing review.

Questions and Answers

One question raised by an attendee asked who has the ultimate responsibility on making a decision on whether a study is an HSR study. Dr. Preuss responded that either he or Dr. Cortesi should be consulted about such matters, as well as on matters that may be exempt. He added that he is the HSRRO for EPA and not just ORD. He has been advocating for the past 5 years that the HSRRO task be rotated/assigned to another staff person. He noted that the Administrator agreed to move the HSRRO out of ORD and into the Office of the Science Advisor. Another question raised was about whether there would be something in writing that a study is exempt from the Common Rule. Dr. Preuss responded that written information would be provided, and he pointed out that he is the only person who could make a decision whether a study is exempt. He also added that later in the workshop Dr. Hermann will discuss what is exempt and what is considered HSR.

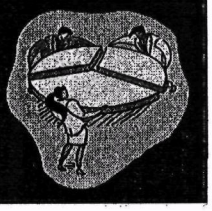
An attendee asked if any other process was available other than going through an IRB and then Dr. Preuss for approval. Dr. Preuss clarified that the Common Rule does not call for an Agency IRB. When a local institution sets up an IRB, it needs to be approved by DHHS, and it must meet all of the requirements laid out in the Common Rule such as having at least five members who would represent a broad spectrum of people. He added that it appears that EPA is moving in the direction of having an Agency IRB. Dr. Hermann pointed out that IHS has its own IRB process. Dr. Cortesi commented that the Common Rule requires the Administrator to ensure that research has been approved by the appropriate IRB. In addition, he stated that many institutions have given authority to their IRBs to decide what should be exempted. Dr. Preuss added that the Common Rule does not state that each Agency must have its own IRB; most agencies do not have their own IRB. If he or Dr. Cortesi are consulted and the study is considered to be HSR, then that researcher needs to go through the process required at the institution where the research will be conducted, such as preparing materials for the IRB (i.e., consent forms, protocols, etc.) to get approval from that IRB. Most larger universities have multiple IRBs so that cases can be approved quickly. Once IRB approval is received, a copy of that letter should be submitted to him and Dr. Cortesi, for review and approval for the work to begin. If no difficult issues are involved, the process should be complete within 2 weeks. A comment was made that, at the Centers for Disease Control and Prevention (CDC), grantees are not required to make the exemption determination. If a project is proposed and it is determined that it is an exempt study, it does not have to be submitted through the system for exemption determinations. Another question arose regarding whether genetic information from a small group such as a tribe would be considered identifiable information, even if the tribe's name was not attached to it. Dr. Hermann responded that it could be considered identifiable information. He added that if the right endpoints are available, then information might be identifiable. It is something to consider when looking at any sort of outcome that could be easily linked to a smaller group of individuals.

IRB Roles and Responsibilities

Helen McGough
Human Subjects Division
University of Washington
EPA Conference: Sept. 26, 2005

Protecting Human Subjects is a collective responsibility

- Researchers and research staff
- Institution's Human Subjects Protection Program
- Sponsor
- Research subjects



IRB: What is it?

- A group of people who meet face-to-face to evaluate research involving humans
- Membership:
  - At least 5 people
  - Not all one gender
  - At least one non-scientist
  - At least one scientist
  - At least one person unaffiliated with the institution hosting the IRB

IRB Roles and Responsibilities

- Institution
- Institutional Official
- IRB chairs and members

Institutional Responsibilities

- Institution supporting or conducting research must have an Assurance with US federal Office for Human Research Protections (OHRP)
  - Assurance may name its own IRB plus others
  - Assurance may name only others
- Institutions bear full responsibility for all research involving human subjects covered under their Assurance.

Institutional Responsibilities

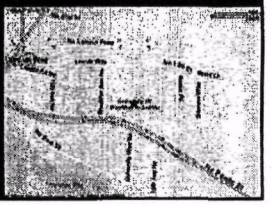
- All requirements of 45 CFR 46 must be met for all EPA and other ***federally-sponsored*** research
- OHRP strongly encourages institutions to apply the HHS regulations regardless of sponsorship, and to commit to this standard in their Assurance.

Institutional Responsibilities

- Designate one or more Institutional Review Boards (IRBs) to review and approve all nonexempt research covered by an the Assurance
- Provide sufficient space and staff to support the IRB's review and record-keeping duties

Institutional Responsibilities

- Ensure that appropriate Assurances and certificates of IRB review are submitted for all their federally sponsored research for their own site and for cooperating performance sites.



Institutional Official

- Authorized to act for the institution and assumes on behalf of the institution the obligations in the Assurance
- Sets the "tone" for an institutional culture of respect for human subjects
- Knowledgeable point of contact for OHRP

Institutional Official

- Appoints IRB members and Chair
- Provides IRB with necessary resources and staff
- Supports IRB decisions
- Ensures effective institution-wide communication and access to human subject information
- Encourages participation in human subject educational activities

IRB Chair

- Ensures IRB Carries Out its Responsibility
  - each approved protocol meets all requirements of 45CFR46
- Conducts or delegates expedited review of amendments or minimal risk projects
- Keeps Institutional Official informed
- Educates IRB Members and researchers

IRB

- Reviews and approves, requires modification in, or disapproves all research activities, including proposed changes in previously approved human subject research.
- Conducts continuing review of approved research at intervals appropriate to the degree of risk, but not less than once per year.

IRB

- Has the authority to suspend or terminate previously approved research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects.

IRB

- Must be familiar with:
  - the ethical principles of human subject research,
  - the requirements of the Federal regulations,
  - applicable state law,
  - the Institution's Assurance, and institutional policies and procedures for the protection of human subjects.

IRB

- Must have effective knowledge of
  - subject populations,
  - institutional constraints,
  - differing legal requirements, and
  - other factors which can foreseeably contribute to a determination of risks and benefits to subjects and subjects' informed consent.

Researcher/Research Staff

- Has primary responsibility for protecting the rights and welfare of human research subjects and for complying with all applicable provisions of their institution's Assurance.

Researcher

- Must be familiar with:
  - the ethical principles of human subject research,
  - the requirements of the Federal regulations,
  - applicable state law,
  - the Institution's Assurance, and
  - institutional policies and procedures for the protection of human subjects.

Researcher

- Conducts all research according to the IRB approved protocol and complies with all IRB determinations.
- Ensures that each potential subject understands the nature of the research and of the subject's participation and takes whatever steps are necessary to gain that comprehension.

Researcher

- Provides a copy of the IRB-approved informed consent document to each subject at the time of consent, unless the IRB has specifically waived this requirement.
- Retains all signed consent documents according to institutional policies, but at least three years beyond the completion of the research.

Researcher

- Promptly reports proposed changes in previously approved human subject research activities to the IRB.
- Does not initiate changes without IRB review and approval, except where necessary to eliminate apparent immediate hazards to the subjects.

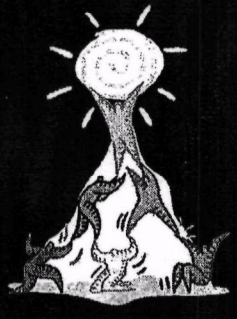
Researcher

- Reports progress of approved research to the IRB, when and how the IRB requires, but not less than once per year.
- Promptly reports to the IRB any unanticipated problems involving risks to subjects or others.

Choosing an IRB

- Must have an Assurance with OHRP if research is funded by EPA
- If award is made to an institution, that institution is responsible to provide IRB review
- If research involves more than one site:
  - One IRB can conduct review if other sites enter into an agreement
  - Each site may insist on site-level IRB review

It's a partnership!



The Role of the IRB
Helen McGough, University of Washington IRB

Ms. Barbara Lither, Region 8, ORC, introduced Ms. Helen McGough, Director of the Human Subjects Division at the University of Washington. Ms. McGough began her presentation by stating that protecting human subjects is a collective responsibility of the researchers and research staff, the institution's human subjects protection program, the sponsor, and the research subjects. She stated that her staff review approximately 65 protocols every year, and that she has been doing such reviews for 21 years. Ms. McGough pointed out that even she did not know what an IRB was early in her career when she was an anthropologist. She defined an IRB as a group of people who meet face-to-face to evaluate the ethics and safety of research involving humans. Membership of an IRB requires at least five people, not all of one gender, at least one non-scientist, at least one scientist, and at least one person unaffiliated with the institution hosting the IRB. The institutional responsibilities involve supporting or conducting research with an assurance from OHRP. Furthermore, institutions have full responsibility for all research involving human subjects covered under OHRP's assurance. All requirements of 45CFR46 must be met for all EPA and other federally sponsored research. OHRP strongly encourages institutions to apply the DHHS regulations, regardless of sponsorship, and to commit to this standard in their assurance. She added that it is not known how many commit to this standard.

Ms. McGough suggested that institutions designate one or more IRBs to review and approve all nonexempt research covered by the OHRP assurance. In addition, sufficient space and staff should support the IRB's review and record-keeping duties. She mentioned that currently she is struggling to pay IRB reviewers who are performing their IRB duties but who spend many hours conducting reviews. Institutions should ensure that appropriate assurances and certificates of IRB review are submitted for all of their federally sponsored research for their own site and for cooperating performance sites. An institutional official should be designated to act on behalf of the institution and to assume the obligations in the assurance. That individual should set the "tone" for an institutional culture of respect for human subjects and should be a knowledgeable point of contact for OHRP. The institutional official's responsibilities also include appointing IRB members and the Chair, providing IRB with necessary resources and staff, supporting IRB decisions, ensuring effective institution-wide communication and access to human subject information, and encouraging participation in human subject educational activities. There is a steep learning curve for the institutional official because this job usually falls on whoever is around (e.g., Dr. Peter Preuss for EPA). The IRB Chair ensures that the IRB carries out its responsibilities and that each approved protocol meets the requirements of 45CFR46, conducts or delegates expedited review of amendments or minimal risk projects, keeps the institutional official informed, and educates IRB members and researchers.

Ms. McGough described the responsibilities of the IRB: reviews and approves, requires modification in, or disapproves all research activities, including proposed changes in previously approved HSR; conducts continuing review of approved research at intervals appropriate to the degree of risk, but not less than once a year; and suspends or terminates previously approved research that is not conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. The researcher or research staff has primary responsibility for protecting the rights and welfare of HSR and for complying with all

applicable provisions of their institution's assurance. In addition, the researcher must conduct all research according to the IRB approved protocol and must comply with all IRB determinations. The researcher must ensure that each potential subject understands the nature of the research and of the subject's participation and take whatever steps are necessary to gain that comprehension. A copy of the IRB-approved informed consent document must be available to each subject at the time of consent, unless the IRB has waived this requirement. All signed consent documents are retained according to institutional policies at least 3 years beyond the completion of the research. The researcher should report proposed changes in previously approved HSR activities to the IRB. Changes to previously approved HSR activities cannot be initiated without IRB review and approval, except as necessary to eliminate apparent immediate hazards to the subjects. Progress of approved research should be reported to the IRB, when and how the IRB requires, but not less than once a year. Also, the researcher must report to the IRB any unanticipated problems involving risks to subjects or others.

Ms. McGough concluded her presentation with tips on how to choose an IRB. She stated that the Cherokee and Navajo Nations, for example, have their own IRBs. Currently, there are approximately 20 Indian Tribal IRBs. First, there must be an assurance with OHRP if the research is to be funded by EPA. Second, if an award is made to an institution, it is that institution's responsibility to provide IRB review. Third, if the research involves more than one site, one IRB can conduct the review if other sites enter into an agreement, and each site may insist on site-level IRB review. The University of Washington outsources its IRB reviews. Ms. McGough referred to a handout that she and Dr. Zane Brown, Chair, Human Subjects Review Committee A, compiled that lists the top 10 problems researchers face in getting their applications approved for HSR: consistency among documents (e.g., application, grant proposal, consent forms, etc.); shared responsibility; use of lay language; too much information; poorly written consent forms; poor assessment of risks and benefits; conflict of interests; not working out compensation for treatment of adverse events before submitting the application; not consulting with staff regarding problems before submitting the application; and not tracking numbers correctly (i.e., submitting the same information as the previous year) or checking funding sources. In addition, she added that researchers should consult with the IRB before submitting an application because they might receive good advice on what will or will not be acceptable in the application.

Ms. McGough referred to the genetic research performed on a small northern Arizona tribe in which the researcher kept blood samples frozen and then gave them to other researchers. This is a good example of a researcher not considering the potential harm this could bring towards the tribe. Another example of group harm can be found in the Tuskegee Syphilis Study conducted in Alabama in which adequate treatment was withheld from a group of poor black men with the disease.

Questions and Answers

One attendee asked Ms. McGough if she thought that the IRBs were going to make the decisions on HSR applications. She replied that it seems to be the direction in which EPA is headed. Another question arose regarding how researchers will know which IRBs are good and which ones are not. She advised visiting OHRP's Web Site to find reliable IRBs. Ms. McGough added that some of the questions researchers should ask are: How many meetings does the IRB hold for reviews? How many protocols does the IRB follow? Does the IRB invite the investigator to its meetings? What are the standards for the IRBs processes? What are the standards for consent forms? Finally, she suggested that researchers check the IRB's Web Site to see if the site is a good one and noted that word-of-mouth recommendations are usually a good way to select an IRB. Another question was asked regarding oversight of IRBs. Ms. McGough responded that there is no real oversight of IRBs; however, she belongs to the Association for the Accreditation of Human Research Protection Programs (AAHRPP), which is the only accredited organization that evaluates IRBs. If there is a problem with an IRB, it can be reported to OHRP, EPA, FDA, and so on. If the research involved is non-federal, non-regulated research, the only recourse would be to take the IRB to court.

Day Two

Selecting an Institutional Review Board & other related topics

Region/ORD Training Workshop on Protection of Human Subjects in EPA's Research and Non-Research Studies

September 2005

Rebecca L. Calderon, Ph.D. M.P.H.
Director
Human Studies Division

What is a Federal Wide Assurance (FWA)?

- The Federal Wide Assurance (FWA) is the only type of new assurance of compliance accepted and approved by OHRP for institutions engaged in non-exempt human subjects research conducted or supported by HHS. Under an FWA, an institution commits to HHS that it will comply with the requirements set forth in 45 CFR part 46, as well as the Terms of Assurance.
- FWAs also are approved by OHRP for federal wide use, which means that other federal departments and agencies that have adopted the Federal Policy for the Protection of Human Subjects (also known as the Common Rule) may rely on the FWA for the research that they conduct or support. Institutions engaging in research conducted or supported by non-HHS federal departments or agencies should consult with the sponsoring department or agency for guidance regarding whether the FWA is appropriate for the research in question. There are two versions of the FWA and the Terms of Assurance, one of each for domestic (U.S.) institutions and for international (non-U.S.) institutions.

Terms of Federal wide Assurance

- Human Subjects Research must be guided by Ethical Principles
  All of the Institution's HSR regardless of funding is subject to ethical principles
- Applicability – all HSR conducted or supported by any federal department or Agency that has adopted the Common Rule
- Compliance with Federal Policy for the Protection of Human Subjects and Other Applicable Federal State, Local or Institutional Laws, Regulations and policies EPA 40 CFR part 26
- Written Procedures –
- Scope of IRBs Responsibilities
- Informed Consent Requirements
- Requirements for assurances for collaborating Institutions
- Written Agreements with Independent Investigators Who are not Otherwise Affiliated with the Institution
- Institutions Support for the IRB
- Educational training
- Renewal of Assurance (every 3 years)

Where to look?

- http://www.hhs.gov/ohrp/assurances/

Voluntary accreditation

- The Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP), is a nonprofit organization that works with organizations that conduct human research to raise the level of protection for research participants. AAHRPP accredits organizations that can demonstrate they provide participant safeguards that surpass the threshold of state and federal requirements. The accreditation program utilizes a voluntary, peer-driven, educational model. For organizations interested in learning more about AAHRPP accreditation, visit www.aahrpp.org.

Commercial IRBs

- Specified service – contractual service
- Western Institutional Review Board (WIRB)
- Schulman Associates Institutional Review, Inc
- Sterling Institutional Review Board
- Independent Review Consulting, Inc

Considerations

- FWA – IRB listed (HSD – UNC)
- Collaborators
- State/local requirements
- Special populations (Indian Health Service)
- International Studies
- Multiple IRB – Primary then concurring
- Fed >> State >> Local

EPA IRB

- Recommendation to HSD to establish IRB - HSPPO
- ORD moving to harmonize
- ORD IRB?
- EPA IRB?
- Uniform and flexible
- HSSRO

the protection of participants in research should be our primary priority

Miscellaneous

- Messing up?
  - Administrative
  - Adverse Events
  - IRB but no EPA approval
  - No approval at all (surveys)

  Reporting requirements IRB and/or HSSRO

Miscellaneous

- EPA employee on IPA
- Paper Reduction Act
- Communication
  - Individual Consent Form
  - Community (Report or Presentation)
  - Officials
- Ownership of data
- Protection of confidentiality

Tuesday, September 27, 2005 (Day Two)

AM Moderators: Patti Tyler and Joel Hansel

Federal Wide Assurance and Selecting an IRB
Rebecca Calderon, ORD-NHEERL Human Studies Division

Dr. Calderon explained that a Federal Wide Assurance (FWA) is the only type of new assurance of compliance that is accepted and approved by OHRP for institutions engaged in nonexempt HSR activities conducted or supported by DHHS. Under an FWA, an institution commits to DHHS that it will comply with the requirements in 45CFR46 as well as the Terms of Assurance. FWAs are approved by OHRP for federal wide use, which indicates that other federal departments and agencies that have adopted the Federal Policy for the Protection of Human Subjects (also known as the Common Rule) may rely on the FWA for the research that they conduct or support. Institutions that engage in research conducted or supported by non-DHHS federal departments or agencies should consult with the sponsoring department or agency for guidance regarding whether the FWA is appropriate for the research in question. In addition, she stated that there are two versions of the FWA and the Terms of Assurance (one of each for domestic [U.S.] institutions and for international [non-U.S.] institutions). The Terms of an FWA provide information on the following areas: ethical principles for HSR; adoption of the Common Rule for all HSR activities conducted or supported by any federal department or Agency; compliance with the Federal Policy for the Protection of Human Subjects and Other Applicable Federal, State, Local, or Institutional Laws, Regulations, and Policies (EPA 40CFR part 26); written procedures; scope of IRB responsibilities; informed consent requirements; requirements for assurances for collaborating institutions; written agreements with independent investigators who are not otherwise affiliated with the institution; institutions' support of the IRB; educational training; and renewal of assurance (every 3 years). More specific information on each of these areas can be found at http://www.hhs.gov/ohrp/assurances/.

Dr. Calderon pointed out that the AAHRPP is a nonprofit organization that works with organizations conducting HSR to raise the level of protection for research participants. AAHRPP accredits organizations that can demonstrate they provide participant safeguards that surpass the threshold of state and federal requirements. The accreditation program uses a voluntary, peer-driven, educational model. Additional information on AAHRPP accreditation can be found at http://www.aahrpp.org. Some commercial IRBs include the Western Institutional Review Board (WIRB); Schulman Associates Institutional Review, Inc.; Sterling Institutional Review Board; and Independent Review Consulting, Inc.

Dr. Calderon mentioned the future job announcement for the HSRRO. However, Dr. Preuss would like to remain current on the HSR studies that are being conducted. She also stated that the approval for an HSR application takes approximately 8 months. Some people, she added, do not think that conducting a survey is HSR, but in fact it is. Also, she pointed out that all studies related to a specific community should be reported back to the local folks; however, there is much discussion ensuing about how much information should be reported back. Every grant contains boiler plate language that states all data collected may have to be provided to the

Agency. She also cautioned that researchers who are trying to obtain confidential information on individuals should be extra careful in how they obtain it.

Questions and Answers

An attendee presented a scenario in which funds are being allocated for a grant but the regional office has concerns that the IRB was not performing well. What should be the next step? Dr. Calderon responded that Dr. Cortesi or Dr. Preuss should be contacted. Another question was raised whether there was an exemption in the Freedom of Information Act (FOIA) for data confidentiality. Dr. Calderon responded that she did not think an exemption existed in FOIA. A comment was made that the IRBs in the state were not performing, and it seems that scientists could collaborate on studies. Is there any ban on international studies data collection? Dr. Calderon replied that some researchers have to certify the ethical use of the data. Researchers should always check if the country in which the data are being collected follows the Helsinki Accord. All federally funded research must undergo IRB review, at least during the past 4 years. Another question concerned the hierarchy of data ownership. Dr. Calderon responded that the data belong to the Federal Government, but ownership can be challenged legally. Another question involved whether there is any type of audit performed to ensure that a university actually did what it agreed to do? Dr. Calderon commented that a review can occur to make sure that a university conducting HSR activities is following protocol. She also suggested that participants talk to Dr. Preuss if managers are not ensuring that a protocol is followed. Incentives are needed for people to come forward and talk about any mistakes that might have been made in this regard. The comment was made that it is important to realize that it is the manager's responsibility to ensure that researchers report to them, the work is performed appropriately, a QA person is present, and that a timeline exists. Another comment was made that if there is a problem with a study following protocol, it should be reported to the IRB. Another attendee added that if anyone is involved in individual projects, problems should be caught early. Additionally, DHHS' Certificate of Confidentiality protects data from FOIA but applies only to identifiable information. With international studies, there is no guarantee that the study population will not be adversely affected. Grants can be pulled if there are any breaches of protocol. IRB review also is required if a survey instrument is to be tested on humans.

NHEERL Human Research Guidance Outline

Region/ORD Training Workshop on Protection of Human Subjects in EPA's Research and Non-Research Studies

September 2005

Richard Hermann, M.D., M.P.H
Director
NHEERL Human Research Protocol Office

NHEERL Human Research Policy

- Research must be conducted in a manner consistent with the Common Rule (40 CFR 26), EPA and NHEERL policy
- Provides guidance to NHEERL investigators and managers on the ethical conduct, review, and approval of all human research activities
- Ensures the safety and rights of human research subjects

NHEERL Human Research Policy (cont'd)

- Details the responsibilities of:
  - Principal Investigator
  - Branch Chief
  - Division Human Research Officer
  - Division Director
  - Director, NHEERL Human Research Protocol Office
  - NHEERL Associate Director for Health or Ecology
  - All NHEERL employees

NHEERL Human Research Guidance

- A "how to" manual for the preparation and review of the NHEERL protocol package
- First decision – does study meet the definition of Human Subjects Research?
- Human subjects? Research?
- Determination made by the NHEERL HRPO Director

Chapter 1 - Introduction

- Purpose
- Overview of Document
- NHEERL Human Research Protocol Office

Director of the NHEERL Human Research Protocol Office (HRPO)

- Oversees all HSR in NHEERL
- Ensures that the safety and rights of all human subjects are protected
- Advises on preparation of HSR protocols
- Assists investigators and managers to understand their responsibilities
- Maintains official NHEERL records

Chapter 2 – Historical Overview

- Nuremberg Code
- Declaration of Helsinki
- Belmont Report
- Common Rule
- EPA Order 1000.17, Change A1
- Health Insurance Portability and Accountability Act (HIPAA)
- NHEERL Human Research Policy

Chapters 3
Details on Common Rule

- Definitions of Research and Human Subject
- Role of IRB and need for Federal Wide Assurance
- Listing of remaining sections of the Common Rule

Chapter 4
EPA Order 1000.17, Change A1

- HSR must comply with Common Rule and be approved by Agency HSRRO
- HSRRO - Final word on exempt studies
- Approval process for foreign studies not covered by Common Rule

Chapter 5

Development, Review, and Approval of Human Subjects Research Protocols

Typical NHEERL HSR Protocol Package

- ***Consent Form***
  - A process, not just a form designed to help individually voluntarily decide whether or not to participate
  - Standard EPA-UNC Tort language and HRPO contact info
- ***Initial Internal EPA Reviews***
  - Scientific merit, safety
  - Statisticians, scientists, or medical personnel, etc
- ***Extramural Scientific Reviews*** -
  - Scientific merit
  - Value added by conducting human research rather than animal or in vitro research
  - Issues of ethics, subject safety, and subject risks

Typical NHEERL HSR Protocol Package (cont'd)

- ***Fact Sheet*** - non-technical, jargon-free style for internal EPA use, including the EPA Office of Public Affairs
  - Impact Statement - importance to Agency
  - Background of the study
  - Study Description
  - Timeline
  - Contact

Typical NHEERL HSR Protocol Package (cont'd)

- ***Study Justification Document***
  - Relevance to the Agency's mission
  - Why existing animal or tissue studies are insufficient
  - Anticipated public health benefit
  - Value added to decision-making
  - Subject safety
  - Researcher training
  - Communications strategy for communities and EPA Regions affected by study, if applicable
  - Reference to extramural reviews

Typical NHEERL HSR Protocol Package (cont'd)

- ***IRB Approval Documentation***
  - All correspondence to and from IRB – START to FINISH
- ***Ethics Training***
  - All study staff involved in the design, conduct of study, or data analysis (if UNC affiliated – CITI web-based training)
  - Major contractors also need proof of training
  - Oath of confidentiality for ancillary support.

HSR Protocol Package (cont'd)

- Full-scale exposure study
  - Reviews
    - Peer Reviewer 1
    - Peer Reviewer 2
    - Statistician
    - Physician
    - Other

HSR Protocol Package (cont'd)

- Full-scale exposure study
  - Approvals
    - Division Human Research Officer
    - Branch Chief
    - IRB
    - Dosing Review Officer
    - Division Quality Assurance Officer
    - Division Director
    - Director of NHEERL Human Research Protocol Office
    - NHEERL Associate Director of Health (or Ecology)
    - EPA Human Subjects Research Review Official

Approval Process for non-HSR

- Any study involving human data or tissue which does not meet definition of HSR
- NHEERL needs a transparent, reproducible, accountable process for review and approval.
- Division Director sends memo to Director of HRPO describing the study and the reason s/he believes the study does not meet the definition of HSR.
- Director of HRPO concurs (or not) and study begins. If not, then regular approval process.

Collaboration vs. Consultation

- Collaboration implies:
  - Involvement as a Co-PI or Co-I
  - Possession of personally identifying information, interaction with subjects
  - Involvement in other activities such as analyzing samples or interpreting data and drawing conclusions
  - Expectation of co-authorship of publications.
- Consultation implies:
  - Less direct involvement with a study
  - No interaction with subjects, no possession of personally identifying information
  - Generally does not result in recognition or co-authorship on publications.

Collaboration vs. Consultation (cont'd)

- Collaboration, but not consultation, implies that the NHEERL investigator is engaged in HSR, and such participation requires NHEERL approval as previously outlined

Chapter 6

Human Controlled-Exposure Studies

Human Controlled-Exposure Studies (cont'd)

- Deliberate exposure by any modality that may include inhalation, ingestion, intravenous administration, dermal exposure, or other methods
- As risks increase to subjects, potential benefit to society must be more compelling

Human Controlled-Exposure Studies (cont'd)

- Will not be initiated unless there are prior data:
  - Toxicity testing in laboratory animals
  - Other human exposure research, such as epidemiologic studies or controlled human exposures.
  - Studies of a very closely related chemical compound

Human Controlled-Exposure Studies (cont'd)

- Pollutant Selection and Administration Criteria
  - Must be present in the environment
  - Must be under consideration for introduction into that environment
  - Must have review of toxicology, epidemiology, structure-activity relationships, and exposure assessment

Human Controlled-Exposure Studies: Dosing

- Calculations of the pollutant dose that a typical subject will receive
- Comparison to doses that a typical individual would be exposed to in the environment
- Maximal allowable doses calculated
- Delivered by an on-site engineering support contractor with rigorous QA/QC procedures for accuracy and reproducibility

Human Controlled-Exposure Studies: Special Review

- ***Medical Review*** **-** controlled exposure to pollutants, procedures involving significant physical risk to subjects (e.g. bronchoscopy, methacholine challenge)
  - Known risks identified
  - Measures to reduce risk are in place
  - Appropriate medical criteria in place for selection of the proposed study subjects
  - Team qualified to deal with any foreseeable adverse events

Chapter 7

Epidemiological Studies

Epidemiological Studies

- Considerations
  - Subject burden
  - Community-based observational studies need communications plan for planning stages, for the conduct of the study, and for sharing the results
  - Plan shared with EPA Office of Public Affairs and local, state, and regional offices

Geographical Information Systems (GIS) Data

- Personal identifiers
- Appropriate confidentiality safeguards
- Report as aggregate data
- Special precautions for sparsely populated areas or rare outcomes

Chapter 8

Studies of Data and Human Tissues, Including in-vitro Research

Genetic Studies

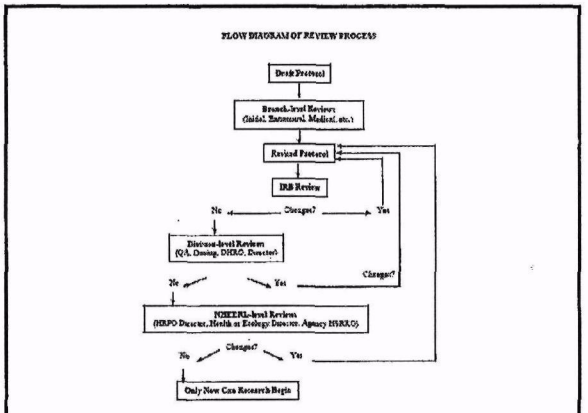
- Possibility of identifying individuals with a disease
- Most stringent safeguards for subject privacy and confidentiality
- Has implications on storage of specimens
  - Future genetic studies with identifiers?
  - Future genetic studies` without identifiers?

Chapter 9

NHEERL Employees as Research Subjects

NHEERL Employees as Subjects

- Strongly discouraged from conducting research on themselves
- No direct or indirect coercion of employees
- Supervisors are not allowed to ask employees they supervise to participate as subjects
- Approval and screening processes are the same as for other HSR protocols



Studies conducted by HSD

Total Open HSR Protocols - 58

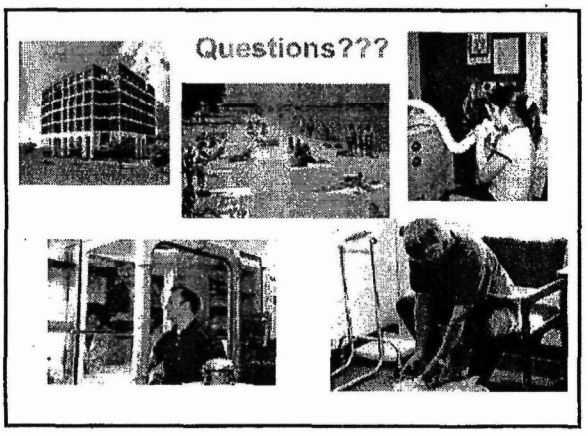
Clinical studies - 26

Epidemiologic studies - 32

Non-Human Subjects Research

Data studies - 5

Tissue specimen studies - 2



NHEERL Policy and Guidance
Richard Hermann, ORD-NHEERL Human Research Protocol Office

Dr. Hermann detailed the requirements of NHEERL's human research policy, which states that research must be conducted in a manner consistent with the Common Rule (40CFR26). NHEERL's human research policy provides guidance to NHEERL investigators and managers on the ethical conduct, review, and approval of all HSR activities, and details the responsibilities of the PI; Branch Chief; Division Human Research Officer; Division Director; Director, NHEERL, Human Research Protocol Office (HRPO); NHEERL's Associate Director for Health or Ecology; and all NHEERL employees. In addition, NHEERL's policy ensures the safety and rights of human research subjects. NHEERL's Human Research Guidance is provided in a "how to" manual for the preparation and review of the NHEERL protocol package. The first decision needed is determining whether the study meets the definition of HSR. This determination is made by the NHEERL's HRPO Director, who oversees all HSR in NHEERL; ensures that the safety and rights of all human subjects are protected; advises on the preparation of HSR protocols; assists investigators and managers to understand their responsibilities; and maintains official NHEERL records.

Dr. Hermann outlined NHEERL's Human Research Guidance document. The Nuremberg Code and the Declaration of Helsinki both have good principles and led to the development of *The Belmont Report.* The Common Rule was established next, which defines "research" and "human subject" as well as the role of the IRB and need for an FWA. The Common Rule was followed by EPA Order 1000.17, Change A1, which ensures that HSR complies with the Common Rule and is approved by the Agency HSRRO. Dr. Hermann pointed out that the approval process for foreign studies is not covered by the Common Rule. HIPAA was developed next. All of these regulations and policies led to the development of NHEERL's Human Research Policy. He explained that a typical NHEERL HSR protocol package includes consent forms; initial internal EPA reviews; extramural scientific reviews; a nontechnical, jargon-free fact sheet; a study justification document; IRB approval documentation; ethical training; and a full-scale exposure study. He added that in the approval process for non-HSR studies (studies involving human data or tissue that do not meet the definition of HSR), NHEERL needs a transparent, reproducible, accountable process for review and approval. The Division Director sends a memo to the Director of HRPO describing the study and the reason the study does not meet the definition of HSR, and the Director of HRPO concurs (or not) and the study begins. Otherwise, the study must undergo the regular approval process.

Dr. Hermann explained the difference between collaboration and consultation. Collaboration implies a researcher's involvement as a Co-PI or Co-I; possession of personally identifying information and interaction with subjects; involvement in other activities such as analyzing samples or interpreting data and drawing conclusions; and expectation of co-authorship of publications. Consultation implies less direct involvement with a study; no interaction with subjects and no possession of personally identifying information; and generally does not result in recognition or co-authorship on publications. Collaboration, but not consultation, implies that the NHEERL investigator is engaged in HSR, which requires NHEERL approval.

Dr. Hermann defined human controlled-exposure studies as those studies in which deliberate exposure by any modality that may include inhalation, ingestion, intravenous administration, dermal exposure, or another method. As risks increase to subjects, potential benefit to society must be more compelling. In addition, human controlled-exposure studies will not be initiated unless there are prior data such as from toxicity testing in laboratory animals, other human exposure research like epidemiologic studies or controlled human exposures, or studies of a very closely related chemical compound. Human controlled-exposure studies also must follow pollutant selection and administration criteria. With regard to dosing, calculations must be made of the pollutant dose that a typical subject will receive. A comparison also must be made to doses that an individual would be exposed to in the environment. Maximum allowable doses should be calculated as well. Doses must be delivered by an onsite engineering support contractor with rigorous QA/QC procedures for accuracy and reproducibility. Finally, a medical review must be conducted of the controlled exposure to pollutants and the procedures involving significant physical risk to subjects (e.g., bronchoscopy, methacholine challenge).

Dr. Hermann pointed out that genetic studies have the possibility of identifying individuals who have a disease. The most stringent safeguards are put into place for subject privacy and confidentiality in genetic studies. There are, however, implications on the storage of specimens. He also stated that it is strongly discouraged that NHEERL employees conduct research on themselves, and supervisors are not allowed to ask employees they supervise to participate as subjects. The approval and screening processes are the same as for other HSR protocols.

Dr. Hermann concluded his presentation by listing the number of HSR studies conducted by NHEERL's Human Subjects Division. There were a total of 58 open HSR protocols, of which 26 were clinical studies and 32 were epidemiologic studies. For non-human subjects research, there were 5 data studies and 2 tissue specimen studies.

Questions and Answers

An attendee inquired that if a Region wanted to set up its own guidance, where would it be able to get training? Could Dr. Hermann's office provide guidance? Dr. Hermann affirmed that his office could provide guidance. He added that if anyone has a grasp of HSR, then they will have approximately a 90 percent chance of doing the right thing. Another question was asked regarding whether someone in a Regional office could be sent to Dr. Hermann for about 3 months of training. He replied that he could spend some time with them. In addition, he referred attendees to OHRP's online training manual and mentioned that CITI also provided online training. Dr. Hermann reiterated that a name could not be on the protocol. Groundwater data, soil data, etc. that are connected to places on the map where the data originates does not fall under data confidentiality rules. Dr. Hermann was asked if he was establishing Agency-wide guidance. Also, it would be useful to have some consistency in the guidance. He agreed and stated that the goal is to have consistency, which is critical to basic human subjects confidentiality protection. A comment was made that there are gaps in the system, such as the type of training that is needed. ORD would be willing to work with everyone to develop a better system. Another attendee asked where the details of the Guidance and Policy documents could be found. Dr. Hermann replied that they are available on the Web at the Human Subjects Division's QuickPlace and on EPA's Intranet workshop site. A comment was made that Dr.

Hermann was the person to contact at NHEERL, much like Dr. Preuss is the HSRRO for all of EPA. A question was asked whether anyone looked at sample protocols from one organization to another, especially with regard to ethical considerations. Dr. Hermann stated that EPA does not share protocols, but that a good point was being made regarding ethical considerations; the world of ethics is vast and it is important to stay abreast of changes. Another attendee wondered whether EPA's employee ethics training could be used for "ethics" training. Dr. Hermann agreed that it could be used.

Panel Discussion: NHEERL and NERL Investigators Involved in Human Research Studies
Rebecca Calderon, Bob Devlin, Danelle Lobdell, Don Graff, ORD-NHEERL; and Kent Thomas, ORD-NERL

Dr. Calderon asked the panel discussants to introduce themselves, address questions from the attendees, and discuss their experiences and background.

Dr. Devlin, Chief of the Clinical Research Branch (CRB), Human Studies Division, has been involved in more than 100 human studies involving elderly, children, and those in between with regard to exposure to sulfides, organic vapors, toluene, chlorine, and particulate matter (PM). Dr. Lobdell, an epidemiologist trained at a university medical school, not a school of public health, has been involved in studies with pregnant women. She conducted a pilot study for the National Children's Study. Dr. Graff, also at the CRB, does most of his work studying PM. He has experience outside EPA, as does Dr. Thomas, with a pharmacy background. Dr. Calderon is an epidemiologist with a background in studying microbes in drinking water.

Questions and Answers

One attendee commented that she was glad to hear that there was an attempt to have consistency across the Agency and asked how to better connect with the community. Dr. Lobdell responded that a pilot study was conducted that focused on the recruitment and retention issues regarding the National Children's Study. Some public support is needed, however, to accomplish this effectively. Two sets of focus groups were conducted, the first of which did not have a diverse ethnic representation (mainly Caucasians and African Americans), and thus a second set that targeted specific ethnic racial groups was conducted. In doing so, some different themes were heard that were not captured in the first set of focus groups (e.g., not providing hair samples because of Voodoo beliefs, etc.). Dr. Thomas added that one of five theme areas is community-based research. Another comment was made regarding how to talk to people in the community about protecting their children from pesticide exposure. To what extent are the researchers going to learn about these issues? Is it included in the protocol package? Dr. Calderon replied that it was being included in the protocol package, but not all types of studies allow for its inclusion. With regard to the National Children's Study, it will be included where possible (e.g., Arabic community needs information available in a different language). Dr. Calderon emphasized the importance of translating information accurately. Dr. Thomas pointed out that with regard to NHEERL's Research Program, more discussion is needed with the Regions to discover what types of studies are being conducted. With the release of the NAS report, it is important to be aware of the hazards.

Another attendee pointed out that in the Lead Research Program, she had a research study in which 90 percent was public health and that the 10 percent HSR element was eliminated to allow for the award of the grant. Dr. Calderon replied that black-and-white guidance could not be provided on this scenario. In discussions with those in the community, investigators sometimes become "twisted" in their study; in such cases, the study probably should not have been done. Community organizations should be contacted and then it should be determined whether the study should be continued or not. The greatest fear is about what unintended consequences might result. A comment was made regarding intentional exposures in that there is no benefit. What is the benefit to the Agency or to the community? Dr. Graff responded that it is a good point, but also it is a quagmire. The question arose regarding payment to human subjects. In conducting the study, there needs to be a beneficial outcome in the end, and it needs to be clear that there is a public health benefit.

Dr. Graff added, as an example, that some subjects receive a placebo in testing the flu vaccine but there is a beneficial outcome in the long run. Another example is the ozone study in North Carolina in which the ozone standard is lower now than in 1986, and the folks living there know it. It is important to speak in terms with which people are familiar. One attendee commented that this is a major cultural/ethical issue. EPA has a "bipolar" nature with regard to pesticides in that it regulates pesticides but also exposes people to pesticides. Dr. Devlin expressed that NHEERL's studies do not expose people to toxic levels of pesticides. Another question was raised regarding the use of children as research subjects. Will they be exposed to pollutants? Dr. Devlin replied that two studies have been done with children: the first was conducted in the 1980s in homes where parents smoke; the second study similarly involved children but in vulnerable populations. He was not aware of any other studies that exposed children directly to toxins. Dr. Graff added that it was recently decided that studies be conducted on children because their physiology is different than that of adults. He pointed out that intentional dosing studies could be done as a more ethical way of reporting effects. These studies are more observational. Dr. Calderon emphasized that children should never be coerced in any way to participate in a study. Studies should be considered in light of their recruitment techniques to ensure that children are not being coerced. Investigators also should take care not to allow parents to coerce their children into participating in a study. Dr. Thomas added that there are no known cases of the IRB looking into minimal risk effects of something on a child. A question was raised on how to balance the issues that arise in observational studies and those involving second-hand smoke. Dr. Devlin responded that a line has to be drawn somewhere. If the effects of diesel exhaust on people leads to cancer and there is any doubt that there might be irreversible damage, then the study should not be conducted. Another question involved the legal consent of a child participating in a study and the use of funds to educate the public about the study. Dr. Calderon replied that there is definitely a need for more communication to address these issues and to share information on how they have been handled thus far.

Grants Management

Armina K. Nolan
Region 10
GMO

Vulnerability of Grants

- External Investigations
  - Inspector General
  - General Accounting Office
- Congressional Concerns
  - Rescission
- Internal Improvements
  - New Policies and Procedures

Major Areas of Concerns

- Grantee Accountability
  - Environmental Outcomes
  - Performance of grantees and sub-recipients
- Program Management and accountability
  - Workload
  - New Training requirements

EPA Goals

- Enhance the Skills of EPA Personnel
- Promote Competition in Grants
- Leverage Technology to Improve Performance
- Strengthen EPA Oversight of Grants
- Support Identifying and Achieving Environmental Outcomes

IGMS Funding Recommendations

- Project Description
- Link the Project to Goals
- Statutory Authority

Is this a Research Grant?

- Research Grants Require 2 Extramural and 1 Intramural Review
  - PO must provide electronic summary
  - PO must enter electronic copy of response to contrary reviews
  - PO must indicate if the proposal is unsolicited

Does the project involve Human Subjects? Or Animal Subjects?

- PO must provide ORD Approver's name
- ORD Approver's Title
- And the Date of the Approval

Challenges to Grant Management

- Regions issue very few Research grants
- EPA Orders confusing
- Controversial projects

PM Moderators: Amanda Hasty and Gilberto Alvarez

Managing Grants and Contracts Under the Interagency Grants Management System (IGMS)

Armina Nolan, EPA Region 10, Grants Office

Ms. Amanda Hasty, EPA Region 8, introduced Ms. Nolan, who has worked for EPA for 15 years and for local government for 9 years. Ms. Nolan began her presentation by pointing out the vulnerability of grants in that they are subject to external investigations by the Inspector General (IG) and the General Accounting Office (GAO). In addition, there are often Congressional concerns related to some grants and contracts. As a result, there have been some internal improvements regarding policies and procedures. Some of the major areas of concern deal with grantee accountability, specifically with regard to environmental outcomes and the performance of grantees and sub-recipients. Program management and accountability is another area of concern, especially with regard to workloads and new training requirements. The Grants Office is motivated by fear about many things, including how GAO is evaluating the work done by the Grants Office. There are approximately 150 grant specialists at EPA, mostly business majors and accountants. There have been IG audits conducted on the Grants Office. About 15 IG audits have been done in Region 10 in the past 2 weeks alone. Ms. Nolan emphasized that EPA's goals are to enhance the skills of EPA personnel, promote competition in grants, leverage technology to improve performance, strengthen EPA oversight of grants, and support identifying and achieving environmental outcomes. IGMS' funding recommendations are that for each grant, there is a project description, the project links to the goals, and there is statutory authority. The Administrator's Office wants to know what proposals are in-house before they are even reviewed. This high level of scrutiny is a new development. She occasionally receives inquiries from the press. For example, she received two different telephone calls last week: one regarding a study in Oregon on the Columbia River and another regarding lead testing. The press is always seeking a story. She pointed out that the grant specialist for the Oregon study is at Headquarters and that there seems to be a policy not to answer any questions from the press, which does not help the Grants Office. Because everything is posted on the Web site regarding the grant, there is no need to avoid answering questions. It just makes everyone nervous, which impacts the service received from the Grants Office. Perhaps, there is some way to consolidate some of the research grants so that POs can deal with the same group of grant specialists and not have to re-educate them every time a research grant is requested.

EPA has a major plan for internal controls. One of the questions faced by IGMS is determining if something is a research grant. For research grants, two extramural reviews and one intramural review are required. The PO must provide an electronic summary, enter the electronic copy of response to contrary reviews, and indicate if the proposal is unsolicited. Another question IGMS has to address is whether the project involves human subjects or animal subjects. The PO must provide the name and title of the ORD approver and the date of approval. Some of the challenges to grants management are that Regions issue very few research grants, EPA Orders are confusing, and some projects are controversial. In the case of the transfer of human brains to a university for study, the media interpreted this as a case of brains being stolen. This is one of several examples that has caused EPA Headquarters to write a policy to protect human subjects. As a result, grants specialists are facing many new and exciting policies. The major areas of

concern are: Did the grantee do what they were supposed to? Did the work ever manifest itself in improving the environment or public health? There is trouble monitoring the grantee's work, which is part of the audits being conducted. It is being found that either the Grants Office or the POs are not doing a very good job in monitoring the research. Project descriptions are very interesting and are posted on the Web site, along with the link to the goal of the project. The other important thing that is posted on the Web is the statute of authority under which the grant was issued. The press often looks at the information posted on the Web site.

Questions and Answers

An attendee commented that the Regions identify few research grants and that it seems there are research studies being conducted that POs are not aware about because they are not trained properly. Ms. Nolan agreed and stated that there is the problem of research being conducted that the grant specialist was not informed about. She also added that more training would be given to POs. The job of the grant specialist is to award grants quickly and legally. She cautioned everyone to be aware that there are all sorts of political caveats.

HRPO Contents

- HRPO Home Page
- Additional Resources
- Assurances
- Checklists
- Human Subjects Documents
- Human Subjects Forms
- Informed Consent
- Meetings, Conferences, and Training

OCSO Contents

- About OCSO
- Advisory Committee on Immunization Practices (ACIP)
- Animal Policy Board
- Specimen Data Bank
- Excellence in Science Committee
- Human Research Protection Office
- Policies
- Scientific Integrity
- Technology Transfer

Human Research Protection Office

Guidelines for Defining Public Health Research and Public Health Non-Research

Revised October 4, 1999

PURPOSE

The Centers for Disease Control and Prevention (CDC) is committed to preventing disease and injury and improving health for all Americans. CDC is also committed to protecting individuals who participate in all public health activities. In the conduct of public health research, CDC follows the Code of Federal Regulations, Title 45, Part 46, The Public Health Service Act as amended by the Health Research Extension Act of 1985, Public Law 99-158, which sets forth regulations for the protection of human subjects.

This document, *Defining Public Health Research and Public Health Non-Research*, sets forth CDC guidelines on the definition of public health research conducted by CDC staff irrespective of the funding source (i.e., provided by CDC or by another entity). Under Federal regulations (45 CFR 46), the final determination of what is research and whether the Federal regulations are applicable lies with CDC and, ultimately, with the Office for Protection from Research Risks (OPRR). Thus, this document is intended to provide guidance to state and local health departments and other institutions that conduct collaborative research with CDC staff or that are recipients of CDC funds. The guidelines are intended to ensure both the protection of human subjects and the effective practice of public health.

BACKGROUND

In 1974, the Department of Health and Human Services (formerly the Department of Health, Education and Welfare) developed regulations to assure the protection of human subjects from research risks. These regulations were developed to address ethical issues raised in connection with biomedical or behavioral research involving human subjects. Because most biomedical research is funded by the National Institutes of Health (NIH), the regulations

were developed to deal specifically with the types of research funded by NIH. The regulations have been revised several times; currently the Department is operating under Title 45 Code of Federal Regulations Part 46, 1991 revision. The regulations will be referred to as 45 CFR 46.

The practice of public health poses several challenges in implementing 45 CFR 46. Although some public health activities can unambiguously be classified as either research or non-research, for other activities the classification is more difficult. The difficulty in classifying some public health activities as research or non-research stems either from traditionally held views about what constitutes public health practice or from the fact that 45 CFR 46 does not directly address many public health activities. In addition, the statutory authority of state and local health departments to conduct public health activities using methods similar to those used by researchers is not recognized in the regulations. Human subject protections applicable for activities occurring at the boundary between public health non-research and public health research are not readily interpretable from the regulations.

The regulations state that "research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge." Obtaining and analyzing data are essential to the usual practice of public health. For many public health activities, data are systematically collected and analyzed, blurring the distinction between research and non-research. Scientific methodology is used both in non-research and research activities that comprise the practice of public health. Because scientific principles and methodology are applied to both non-research and research activities, knowledge is generated in both cases. Furthermore, at times the extent to which that knowledge is generalizable may not differ greatly in research and non-research. Thus, non-research and research activities cannot be easily defined by the methods they employ. Three public health activities - surveillance, emergency responses, and evaluation - are particularly susceptible to the quandary over whether the activity is research or non-research.

The key word in the regulations' definition of research for the purpose of classifying public health activities as either research or non-research is "designed." The major difference between research and non-research lies in the primary intent of the activity. The primary intent of research is to generate or contribute to generalizable knowledge. The primary intent of non-research in public health is to prevent or control disease or injury and improve health, or to improve a public health program or service. Knowledge may be gained in any public health endeavor designed to prevent disease or injury or

improve a program or service. In some cases, that knowledge may be generalizable, but the primary intention of the endeavor is to benefit clients participating in a public health program or a population by controlling a health problem in the population from which the information is gathered.

Classifying an activity as research does not automatically lead to review by an institutional review board (IRB) for the protection of human subjects. Once an activity is classified as research, two additional determinations must be made: (1) does the research involve human subjects and, if so, (2) does the research meet the criteria for exemption from IRB review. This policy deals only with the first determination of whether a public health activity is research or non-research.

DEFINITIONS

Research - As defined in 45 CFR 46, research means "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."

Human Subjects - As defined in 45 CFR 46, a human subject means "a living individual about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information. Intervention includes both physical procedures by which data are gathered and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects."

Surveillance - The ongoing, systematic collection, analysis, and interpretation of outcome-specific data, closely integrated with the timely dissemination of these data to those responsible for preventing and controlling disease or injury (Thacker and Berkelman, 1988).

Emergency Response - A public health activity undertaken in an urgent or emergency situation, usually because of an identified or suspected imminent

health threat to the population, but sometimes because the public and/or government authorities perceive an imminent threat that demands immediate action. The primary purpose of the activity is to document the existence and magnitude of a public health problem in the community and to implement appropriate measures to address the problem (Langmuir, 1980).

Program Evaluation – An essential organizational practice in public health using a systematic approach to improve and account for public health actions (Centers for Disease Control and Prevention, 1999)

Evaluation - The systematic application of scientific and statistical procedures for measuring program conceptualization, design, implementation, and utility; making comparisons based on these measurements; and the use of the resulting information to optimize program outcomes (Rossi and Freeman, 1993; Fink, 1993).

POLICY

CDC is required to and has an ethical obligation to ensure that individuals are protected in all public health research activities it conducts. All CDC activities must be reviewed to determine whether they are research involving human subjects. When an activity is classified as research involving human subjects, CDC and its collaborators will comply with 45 CFR 46 in protecting human research subjects.

Some surveillance projects, emergency responses, and evaluations are research involving human subjects; others are not. Each project must be reviewed on a case-by-case basis. Although general guidance can be given to assist in classifying these activities as either research or non-research, no one criterion can be applied universally. The ultimate decision regarding classification lies in the intent of the project. If the primary intent is to generate generalizable knowledge, the project is research. If the primary intent is to prevent or control disease or injury or to improve a public health program, and no research is intended at the present time, the project is non-research. If the primary intent changes to generating generalizable knowledge, then the project becomes research.

GUIDANCE FOR COMPLIANCE

I. General

The Human Subjects Contact (HSC) in each Center, Institute, or

Office (CIO) determines whether the project constitutes research. If the HSC is unclear about classifying a project, the HSC should consult with the CDC's Deputy Associate Director for Science. This determination is made by examining the intent of the project. What is the primary purpose for which the project was designed?

General Attributes of Public Health Research - Intent of the project is to generate generalizable knowledge to improve public health practice; intended benefits of the project may or may not include study participants, but always extend beyond the study participants, usually to society; and data collected exceed requirements for care of the study participants or extend beyond the scope of the activity. Generalizable knowledge means new information that has relevance beyond the population or program from which it was collected, or information that is added to the scientific literature. Knowledge that can be generalized is collected under systematic procedures that reduce bias, allowing the knowledge to be applied to populations and settings different from the ones from which it was collected. Generalizable, for purposes of defining research, does not refer to the statistical concept of population estimation or to the traditional public health method of collecting information from a sample to understand health in the population from which the sample came. Holding public health activities to a standard of studying every case in order to classify an activity as non-research is not practical or reasonable.

General Attributes of Non-Research - Intent of the project is to identify and control a health problem or improve a public health program or service; intended benefits of the project are primarily or exclusively for the participants (or clients) or the participants' community; data collected are needed to assess and/or improve the program or service, the health of the participants or the participants' community; knowledge that is generated does not extend beyond the scope of the activity; and project activities are not experimental.

Other attributes, such as publication of findings, statutory authority (see discussion in next section), methodological design, selection of subjects, and hypothesis testing/generating, do not necessarily differentiate research from non-research because these types of attributes can be shared by both research and non-research projects.

A non-research project may generate generalizable knowledge after the project is undertaken even though generating this knowledge was not part of the original, primary intent. In this case, since the primary

intent was not to generate or contribute to generalizable knowledge, the project is not classified as research at the outset. However, if subsequent analysis of identifiable private information is undertaken to generate or contribute to generalizable knowledge, the analysis constitutes human subjects research that requires IRB review.

If a project includes multiple components and at least one of those components is designed to generate generalizable knowledge, then the entire project is classified as research unless the components are separable.

II. Specific

A. Surveillance - Surveillance is a term describing a method for public health data collection. Surveillance systems may be either research or non-research. Surveillance systems are likely to be non-research when they involve the regular, ongoing collection and analysis of health-related data conducted to monitor the frequency of occurrence and distribution of disease or a health condition in the population. Data generated by these systems are used to manage public health programs. They have in place the ability to invoke public health mechanisms to prevent or control disease or injury in response to an event. Thus, the primary intent of these surveillance systems is to prevent or control disease or injury in a defined population by producing information about the population from whom the data were collected. These attributes of surveillance that is non-research are generally found in state statute or regulation where the intent of the activity, its purposes, and uses of the data are specified. Surveillance systems that most easily fit into this category are ones in which the data are limited to describing the occurrence of a health-related problem (disease reporting) and systems in which no analytic (etiologic) analyses can be conducted. Subjects are rarely selected according to a design; rather, all cases are entered into the surveillance system because they are passive reporting systems. Hypothesis testing is not part of the system.

Surveillance systems are likely to be research when they involve the collection and analysis of health-related data conducted either to generate knowledge that is applicable to other populations and settings than the ones from which the data were collected or to contribute to new knowledge about the health condition. The information gained from the data collection system may or may not be used to invoke public health mechanisms to prevent or control disease or injury, but this is not a primary intent of the project. Thus, the primary intent of

these surveillance systems is to generate generalizable knowledge. Characteristics of surveillance systems that most easily fit into this category are: longitudinal data collection systems (e.g., follow-up surveys and registries) that allow for hypothesis testing; the scope of the data is broad and includes more information than occurrence of a health-related problem; analytic analyses can be conducted; and cases may be identified to be included in subsequent studies.

In general, lawful state disease reporting, monitoring requirements and other data collection activities conducted under state statute or under recognized public health authority are non-research. Disease reporting activities are not research. Disease reporting, for these purposes, is defined narrowly to include the reporting of the specific health condition or disease, demographic information; and accepted, known risk factors as specified in state statutes or regulations. When reporting systems collect data beyond standard reporting information, the reporting activity is not automatically considered to be non-research. Collection of data that would allow etiologic analysis is likely to be research.

If other activities are added to a surveillance project with the specific intent of generating new or generalizable knowledge, these additional activities are considered to be research. It becomes important to distinguish between disease reporting activities that are non-research and uses of the reported data that may be either non-research or research.

Sometimes, CDC funds state and local health departments to establish surveillance systems with dual intentions on the part of CDC: to build state capacity in disease reporting and for CDC to generate new knowledge. Disease reporting activities conducted at the state level are generally non-research. However, if CDC uses the data collected through such reporting to generate new knowledge, CDC would be engaged in research. CDC may consider state health departments to be engaged in the research depending upon their role. If state health departments are participating beyond merely providing the data, they may be considered as engaged in the research. Institutions providing information to state health departments would not be considered engaged in the research (see OPRR memorandum dated 1/26/99).

Some surveillance projects do not fit easily into the categories described above. For these projects, the primary intent and elements of the project must be examined carefully.

B. Emergency Responses - Most emergency responses tend to be non-research because these projects are undertaken to identify, characterize, and solve an immediate health problem and the knowledge gained will directly benefit those participants involved in the investigation or their communities. However, an emergency response may have a research component if: 1) samples are stored for future use intended to generate generalizable knowledge or 2) additional analyses are conducted beyond those needed to solve the immediate health problem. When investigational new drugs are used or drugs are used off-label, the emergency response is almost always research. The same applies to medical devices. For emergency responses, whenever a systematic investigation of a non-standard intervention or a systematic comparison of standard interventions occurs, the activity is research.

C. Evaluation – The terms "evaluation" and "program evaluation" are used interchangeably. Yet, there are subtle differences between the two terms (see definitions and reference provided above). Evaluation is a term, broad in meaning, that refers to the systematic use of scientific methods to measure efficacy, implementation, utility, and so on of a program in its entirety or its components. Evaluations may or may not be research. Program evaluations are a subset of evaluations. As defined here program evaluations are almost never research.

When the purpose of an evaluation is to test a new, modified, or previously untested intervention, service, or program to determine whether it is effective, the evaluation is research. The systematic comparison of standard or non-standard interventions in an experimental-type design is research. In these cases, the knowledge gained is applicable beyond the individual, specific program. Thus, the primary intent is to generate new knowledge or contribute to the knowledge in the scientific literature. Further, it is intended to apply the knowledge to other sites or populations.

When the purpose is to assess the success of an established program in achieving its objectives in a specific population and the information gained from the evaluation will be used to provide feedback to that program, the evaluation, referred to as program evaluation, is non-research. In the non-research scenario, the evaluation is used as a management tool to monitor and improve the program. The evaluation activity is often a component of the regular, ongoing program. Information learned from the evaluation has immediate benefit for the program and/or the clients receiving the services or interventions. The

information is often not generalizable beyond the individual program. Interventions and services that are evaluated are never experimental or new; they are known (either from empirical data or through consensus) to be effective.

Sometimes, the term "formative evaluation" is used to describe data collection activities that occur prior to the implementation of an intervention, service, or program. Whether the "formative evaluation" is research or non-research depends upon its intent. If the evaluation is conducted prior to implementing a new, modified, or previously untested intervention, the evaluation is part of the overall research project. If the evaluation is conducted to provide information on how to tailor a proven-effective intervention, service, or program in a specific setting or context, the evaluation is not research.

Evaluations of CDC's national programs, i.e., programs that CDC funds to all state health departments and in which evaluation is one component, are not research. These evaluation activities are on-going and involve generally the collection of minimal, standard data elements across all sites. The data are generally used at the local level as a management tool as well as at the national level for the same purpose. Sometimes, data from these evaluation activities will be aggregated at CDC and used for other purposes. When this occurs, subsequent use of the data may be research.

In some cases, program activities and evaluation activities are separable. For example, interventions or services are being provided; they have a history of being provided and there is an intention to continue to provide them. An evaluation is conducted to determine the efficacy of these program activities. In another example, a public health department, under its public health authority, may provide an untested intervention in an outbreak situation. An evaluation component is added. In both of these examples, because the intervention and evaluation activities are undertaken with different intentions and are separable, the intervention activities are not research but the evaluation activities are research.

APPENDIX

Examples of CDC surveillance, emergency responses, and evaluation activities that are non-research and research.

SURVEILLANCE:

Non-research -

National Notifiable Diseases Surveillance System (NNDSS) - States and territories have asked CDC to act as a common data collection point for data on nationally notifiable diseases. A notifiable disease is considered by the Council of State and Territorial Epidemiologists to be a condition for which regular, frequent, and timely information about individual cases is necessary at the national level for the prevention and control of disease. NNDSS data are collected and published weekly in the Morbidity and Mortality Weekly Report and annually in the Summary of Notifiable Diseases, United States. The NNDSS is essential to the day to day practice of public health. The primary intent of the surveillance system is to provide CDC and state and local health officials with information to detect and control outbreaks of disease. The NNDSS is also used to measure the impact of programs such as immunization. The intended benefits resulting from the NNDSS are for the residents of the states and local areas who contribute data to the system.

Diabetes Surveillance Report - Using public use data from several national surveys, a national diabetes surveillance system is produced. Data from the surveillance system are used to describe the burden of diabetes and its complications on a national and state level. The primary intent of the surveillance system is to provide information for the development of national and state public health priorities and policies regarding the prevention and control of diabetes. The intended benefits are for those who have diabetes or those who are at risk of developing diabetes.

Research -

A Sentinel Surveillance System for Lassa Fever in the Republic of Guinea - Four study sites were selected to identify and describe cases of Lassa fever. Cases were identified from hospital and outpatient admissions. The purpose of the project was to generate baseline information on the Lassa virus and human clinical Lassa fever in the Republic of Guinea. No public health interventions were planned as part of this project; there was no direct benefits for study participants. Thus, the primary intent was to contribute to the knowledge of Lassa fever.

Developmental Disabilities in Very Low Birthweight Children: Linkage of the Georgia Very Low Birthweight Study and the Metropolitan Atlanta Developmental Disabilities Surveillance Program - The

Metropolitan Atlanta Developmental Disabilities Surveillance Program, an ongoing CDC surveillance program to monitor trends in the occurrence of selected developmental disabilities in children living in the metropolitan Atlanta area, and the Georgia Very Low Birthweight Study, conducted in the 1980s to investigate the environmental and other risk factors for very low birthweight were linked for specific investigations of adverse developmental outcomes. Linkage of these primary files provides a unique opportunity to assist efforts to assess the occurrence of selected developmental disabilities in metropolitan Atlanta children and to identify causes of these conditions without the additional time and resource expenditure of additional field data collection. For these investigations involving secondary analyses of the linked primary data sets, no individuals were contacted; only information available from the linkage were used. The purpose of the project was to estimate the prevalence of cerebral palsy, mental retardation, and hearing and visual impairments and to identify pre- and perinatal medical and sociodemographic risk factors for these disabilities in a population-based cohort of very low birthweight children in Atlanta. The primary intent was to generate generalizable knowledge about developmental disabilities.

EMERGENCY RESPONSES:

Non-research -

Outbreak of Gastroenteritis - Three days after a cruise ship left Los Angeles, California for several ports in Mexico, CDC was notified that 24 of 1,899 passengers and 6 of 670 crew had presented to the ship=s infirmary with gastrointestinal illness. The purpose of the investigation was to determine the cause and extent of the outbreak and to prevent and control gastrointestinal illness among the ships passengers and crew. Although this type of investigation is often undertaken after the outbreak has occurred and therefore information gained is likely to benefit the ship=s next set of cruise passengers and crew, the primary intent of the investigation is to assist in controlling the current disease outbreak.

Recall of Six Lots of Influenza Vaccine - One of the pharmaceutical companies who manufactures influenza vaccine instituted a voluntary recall of six lots of influenza vaccine. The lots were recalled due to decreased potency of the A/Nanchang/933/95 (H3N2) component of the vaccine. CDC was notified by a state health department that a nursing home had vaccinated its residents with the recalled vaccine. The purpose of the investigation was to determine whether residents of this nursing home who received the vaccine

had a suboptimal immune response and required revaccination. The primary intent of this investigation was to prevent the occurrence of influenza among the participants if they demonstrated a suboptimal immune response; there was a potential for participants to receive a direct benefit in the form of revaccination if they participated.

Research -

Childhood Exposure to Nicotine-Containing Products in Rhode Island - Between January 1, 1995 and June 30, 1996, 90 cases of nicotine-containing products were reported to the Rhode Island Poison Control Center. No known population-based investigation has been conducted to determine risk factors associated with nicotine-containing products poisoning. The purpose of the Epi-Aid was to determine risk factors associated with childhood exposure to nicotine-containing products, and to develop appropriate control measures. Although there may be some benefit to the 90 children exposed in Rhode Island, the benefits from this study extend beyond the study participants to the population of children who are at risk of exposure to nicotine-containing products. In addition, there was no immediate health problem to be controlled. Thus, the primary intent of the investigation was to generate generalizable knowledge about the risk factors associated with childhood exposure to nicotine-containing products.

Azithromycin Used as Prophylaxis Against the Spread of Illness Due to Mycoplasma Pneumoniae in the Setting of an Outbreak - During the first week of freshman entering a post high school academic institution, a cluster of respiratory illness was recognized by the infirmary staff. Early serologic testing suggest Mycoplasma pneumoniae as the etiologic agent. About four weeks later 42% of the freshman and 17% of the upperclassmen reported a respiratory illness; 50% of those tested had serologic evidence of Mycoplasma pneumoniae infection. The lower attack rate among upperclassmen was likely a consequence of them returning to campus 15 days after the freshmen arrived. A trial of chemoprophylaxis with azithromycin was proposed. Highly effective control measures in the setting of an outbreak have not been described. There is limited information about the role of antimicrobials in controlling an epidemic of Mycoplasma pneumoniae. Thus, the primary intent of the investigation was to generate generalizable knowledge about the efficacy of azithromycin to prevent the spread of Mycoplasma pneumoniae in an outbreak situation.

PROGRAM EVALUATION:

Non-research -

Evaluation of School-based HIV Prevention Program - As part of the evaluation of the school-based HIV prevention program in Denver public schools, principals, teachers, student contact staff, students, and parents were interviewed. HIV program efforts in policy awareness, staff development, curriculum implementation, and status of students receiving HIV prevention education were assessed.

The purpose (primary intent) of the program evaluation was to provide information to Denver public schools that will be used to improve their school-based HIV prevention programs. The results from the evaluation were used to assess the success of the interventions in a specific population (Denver public school children) and to refine the interventions in that population.

IMPACT Progress Reports - The Office on Smoking and Health awarded 32 states and the District of Columbia health departments cooperative agreements to build capacity to conduct tobacco use prevention and control programs. These cooperative agreements are part of CDC=s Initiatives to Mobilize for the Prevention and Control of Tobacco Use (IMPACT), which is a nationwide effort to establish comprehensive, coordinated tobacco use prevention programs. Evaluation of IMPACT is comprised of awardees submitting semi-annual progress reports. Information in the evaluation includes staffing, coalition composition and efforts, status of a state tobacco control plan, development of a resource center, training efforts, community outreach and mobilization, and participation in CDC national campaigns.

The primary intent of these state tobacco control program evaluations is to assess the success of the intervention activities within each state. The information gained from the evaluation is used to refine the interventions in that state. In addition, the information is used nationally to evaluate the success of the IMPACT program.

Research -

Evaluation of Community Based Organization Intervention to Reduce Sexually Transmitted Disease (STD) Rates Among STD Patients in Miami - Male STD Patients were randomized to either the standard HIV prevention counseling or intensive counseling comprised of four sessions of HIV counseling from a community based organization. STD clinic records were reviewed to determine whether there was a difference in return rates

with new STDs between the groups. The objective of intervention and evaluation is to determine whether intensive counseling reduces the acquisition of new STDs among high risk people attending a STD clinic. The purpose of the project was to evaluate a new intervention for reducing the transmission of STDs. Knowledge gained from this evaluation would be used to generalize to other sites.

A Comprehensive Evaluation for Project DIRECT (Diabetes Intervention: Reaching and Educating Communities Together) - Project DIRECT is a community diabetes demonstration project targeting African American adults residing in Raleigh, North Carolina. The project is three-tiered and addresses diabetes care, community screening for persons at high risk for developing diabetes, and population based approaches to increase physical activity and reduce dietary fat intake (two risk factors for diabetes). The goals of the community project are to reduce preventable complications of diabetes via a health systems approach, increase the proportion of persons at risk for diabetes who are screened, and increase the proportion who participate in regular vigorous physical activity and eat a reduced fat diet. Baseline and follow-up population-based surveys are planned to evaluate the community intervention. The purpose of this project is to evaluate new and innovative interventions to prevent diabetes and its complications. Knowledge gained from this project will be used to develop similar intervention projects in other communities.

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This page last reviewed March 14, 2001
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Determination of Human Subjects Research vs. Public Health Practice
Roger Cortesi, ORD-NCEA

Dr. Cortesi provided copies of the HRPO Guidelines for Defining Public Health Research and Public Health Non-Research. He pointed out that the Guidelines were developed by CDC and follows 45CFR46, the Public Health Service Act as amended by the Health Research Extension Act of 1985, Public Law 99-158, which sets the regulations for the protection of human subjects. The Guidelines are intended for ensuring the protection of human subjects and the effective practice of public health. In the practice of public health, there are challenges in implementing 45CFR46. Part of the difficulty in classifying some public health activities as research or non-research lies in traditionally held views about what is defined as public health practice and that 45CFR46 does not address many public health activities. The key word in the definition of research for the purpose of classifying public health activities as either research or non-research is "designed." The major difference between research and non-research is in the primary intent of the activity. The primary intent of research is to generate or contribute to generalizable knowledge, while the primary intent of non-research in public health is to prevent or control disease or injury and improve health, or to improve a public health program or service.
Dr. Cortesi also pointed out, as stated in the Guidelines, that classifying an activity as research does not automatically lead to an IRB review for the protection of human subjects. Once an activity is determined to be research, there are two additional decisions that must be made: (1) Does the research involve human subjects? (2) Does the research meet the criteria for exemption from IRB review?

Dr. Cortesi also provided copies of the Council of State and Territorial Epidemiologists' "Public Health Practice vs. Research, A Report for Public Health Practitioners Including Cases and Guidance for Making Distinctions." He pointed out that this 2004 report provides a practical guide for state and local public health officials, their staff, and their partners on making distinctions between public health practice and research for activities conducted by, or under the authority of, state and local health departments. As indicated in the report, public health practice is concerned with protecting the public's health and includes epidemiological investigations, surveillance, programmatic evaluations, and clinical care for the population. Some of the important characteristics of public health practice are that it involves specific legal authorization for conducting the activity as public health practice at the federal, state, or local levels; includes a corresponding governmental duty to perform the activity to protect the public's health; involves direct performance or oversight by a governmental public health authority and accountability to the public for its performance; might legitimately involve persons who did not specifically volunteer to participate; and is supported by principles of public health ethics that focus on populations while respecting the dignity and right of individuals. Important characteristics of HSR are that it involves living individuals; involves, in part, identifiable private health information; involves research subjects who are selected and voluntarily participate (or participate with the consent of their guardian), absent a waiver of informed consent; and is supported by the principles of bioethics that focus on the interests of individuals while balancing the communal value of research.

Questions and Answers

An attendee referred to the manganese study in Ohio that is trying to determine its effects on the cognitive development in children. The question arose whether this study can be applied to other areas in the United States. Dr. Cortesi pointed out that this is a public health project. Dr. Preuss offered another perspective and stated that consultation with others should be made in such cases because these studies could be either a public health project or a human subjects study. Another attendee commented that if something addresses a public health problem, it could be considered public health research if only generalizable information is being tested. One attendee asked a question regarding generalizing the decision-making process. For example, in the case of tribes requesting grants and receiving funds from EPA for doing research, what will be done with the generalizable information that is collected? Also, what oversight will exist when humans are being used in research? Dr. Cortesi reiterated that one key way in making decisions is to discuss these issues with him and Dr. Preuss, as well as others, before making a decision. In addition, it would be a good idea to have the approval of a supervisor or higher level staff when making a request to Dr. Preuss.

Role of the Human Subjects Research Review Official (HSRRO)

Presentation to:
Protection of Human Subjects in EPA's Research and Non-Research Studies
September 26 - 27, 2005

Peter W. Preuss, Ph.D.
EPA Human Subjects Research Review Official
Director, National Center for Environmental Assessment
Office of Research and Development

What/Who is the Human Subjects Research Review Official?

- HSRRO established under EPA Order 1000.17 Change A1
  http://intranet.epa.gov/rmpolicy/ads/orders/1000_17a.pdf

  "All human subject research studies supported by EPA must either be approved or be determined to be exempt research by the EPA Human Subjects Research Review Official ... before any contract, grant, cooperative agreement, cooperative research and development agreement [CRADA], interagency agreement, or any formal agreement involving EPA support of such studies is awarded or entered into. All human subjects studies conducted by EPA also must be approved or determined to be exempt by the Review Official before work can start. Approval will be given only to research which complies with [the Common Rule]."
- I am the current HSRRO

Current Functions of the HSRRO

- Additional EPA oversight to assure compliance with the Common Rule (i.e., IRB approval, informed consent, etc.) and ethics standards
- Approval/disapproval of all EPA HSR, whether in house or extramural
- Authority to suspend or terminate HSR studies if non-compliance
- Issue single/multi-project assurances for institutions conducting research (EPA now relies on DHHS-OHRP FWAs)
- Consultative role in EPA HSR ethics considerations

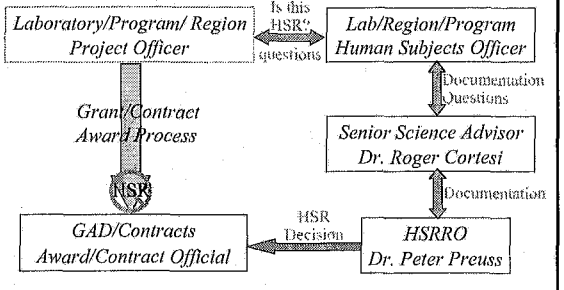
Increased Role of the HSRRO

- The HSRRO is to be moved to the Office of the Science Advisor in the Administrator's Office, in response to the NAS recommendation
- The HSRRO position competitively advertised
- Support staff anticipated
- The HSRRO role under the draft HSR rule is to:
  - Continue existing HSRRO responsibilities
  - Oversee the review of intentional dosing human study proposals by EPA and covered 3rd Parties (pesticides)
  - Conduct ethics screening of completed studies
  - Liaise with the Human Studies Review Board
  - Develop additional policies, training, and guidance

Regional Relationship to the HSRRO

- Regional responsibilities (1000.17 A1 6.b.):
  - "The EPA program or regional office that conducts or supports research covered by this Order is responsible for compliance with it. In the first instance the office will decide whether the project involves "human subjects" and is "research" as per [this order], and hence is a covered project."
  - The region "is responsible for notifying the EPA Award Official/Contracting Officer that human subjects are involved."
  - "The Award Official/Contracting Officer is responsible for ensuring that the written approval or exemption determination from the 'HSRRO" is submitted as part of the funding package ..."
  - De facto: The Region is responsible for obtaining HSRRO approval

Human Subjects Approval Process



Human Subjects Officers

- ORD laboratories, programs and regions may nominate "human subjects officers" to assist in the implementation of HSR policies and procedures to:
  - Work with project officers to make determinations on what is HSR
  - Assist project officers in preparing adequate HSR documentation for submission to the HSRRO
  - Coordinate with the HSRRO and Senior Science Advisor on questions and process for HSR approval
- Human subjects officers should be senior staff experienced with decision-making on HSR
- Not a substitute HSRRO. There is only one HSRRO to maintain consistency across the Agency
- This process may be modified by the new HSRRO

Human SubjectsTraining

- All EPA project officers undergo training on the EPA human subjects approval process
- EPA staff conducting human subjects research are required to annually complete CITI ethics training
  https://www.citiprogram.org/default.asp
- General HSR information is available at OHRP
  http://www.hhs.gov/ohrp/
- Additional training for EPA human subjects officers can be arranged regionally or at a central location
- Recognize that human subjects training needs can vary depending on the activity being considered, i.e:
  - Approval process for EPA supported HSR
  - Protection of subjects during the conduct of HSR
  - Ethics reviews of existing literature

Additional Responses to HSR Questions

- Is an IPA employee to a state covered?
  - See Rule on "any formal agreement involving EPA support for such studies."
  - Most institutions are covered by the Common Rule, so the impact is generally limited to obtaining HSRRO approval
- Do we have a list of human subjects officers?
  - Yes, Dr. Cortesi maintains list of ORD and Program officers
  - No, it is not maintained on a web site
- Ultimate responsibility?
  - Spelled out in Rule 1000.17 (Change 1)
  - Region/program supporting HSR is responsible for compliance with the Rule and to notify Grants/Contracts of HSR
  - Grants/Contracts is responsible to not award without HSRRO approval
  - HSRRO is responsible to ascertain Common Rule compliance
  - The institution conducting the research is responsible for the conduct of the research.

Information/Responsibility Flow
Peter Preuss, ORD-NCEA

Dr. Preuss began his presentation by asking the question of "What/Who is the Human Subjects Research Review Official (HSRRO)? He pointed out that the position was established under EPA Order 1000.17, Change 1A, which states that "All human subject research studies supported by EPA must either be approved or be determined to be exempt research by the EPA Human Subjects Research Review Official...before any contract, grant, cooperative agreement, cooperative research and development agreement (CRADA), interagency agreement, or any formal agreement involving EPA support of such studies is awarded or entered into. All human subjects studies conducted by EPA also must be approved or determined to be exempt by the Review Official before work can start. Approval will be given only to research that complies with [the Common Rule]." More information can be found at http://intranet.epa.gov/rmpolicy/ads/orders/1000_17a.pdf. Dr. Preuss is the current HSRRO, and his duties include providing additional EPA oversight to ensure compliance with the Common Rule (i.e., IRB approval, informed consent, etc.) and ethics standards; providing approval/disapproval of all EPA HSR, whether in-house or extramural; suspending or terminating HSR studies if they are noncompliant; issuing single/multi-project assurances for institutions conducting research; and consulting in EPA HSR ethics considerations. He pointed out that he has suspended entire laboratories from continuing HSR research if they were noncompliant.

Dr. Preuss discussed the increased role of the HSRRO. He pointed out that the HSRRO would be moved to the Office of the Science Advisor in the Administrator's Office, in response to NAS' recommendation. In addition, he stated that the HSRRO position would be competitively advertised and that support staff are anticipated to provide assistance to the HSRRO. The HSRRO role under the draft HSR rule is to continue existing responsibilities, oversee the review of intentional dosing human study proposals by EPA and covered third parties (pesticides), conduct ethics screening of completed studies, liaise with the HSRB, and develop additional policies, training, and guidance. Dr. Preuss also discussed the regional relationship to the HSRRO. He also indicated that the EPA program or regional office that conducts or supports research covered by the Common Rule is responsible for compliance with it. The office will decide whether the project involves "human subjects" and constitutes "research." The Region is responsible for notifying the EPA Award Official/Contracting Officer that human subjects are involved. The Award Official/Contracting Officer, however, is responsible for ensuring that the written approval or exemption determination from the HSRRO is submitted as part of the funding package. In addition, the Region is responsible for obtaining HSRRO approval.
Dr. Preuss informed the participants that ORD laboratories, programs, and Regions may nominate "human subjects officers" to assist in the implementation of HSR policies and procedures.
Also, human subjects officers should be senior staff experienced with decisionmaking on HSR. Human subjects officers, he added, are not a substitute for the HSRRO; there is only one HSRRO to maintain consistency across the Agency.

Regarding human subjects training, Dr. Preuss stated that all EPA POs undergo training on the EPA human subjects approval process. EPA staff who are conducting HSR are required to

complete an annual CITI ethics training (for additional information, see http://www.citiprogram.org/default.asp). General HSR information is available at OHRP (http://www.hhs.gov/ohrp/). Dr. Preuss added that additional training for EPA human subjects officers could be arranged regionally or at a central location. He also stated that Dr. Cortesi at the National Center for Environmental Research (NCER) maintains a list of ORD and Program Officers.

Questions and Answers

A question was raised whether it would be illegal to put a condition on a grant request before it is approved. Dr. Preuss responded that sometimes conditions are added to a grant. Another attendee asked how many Regions have human subjects officers. Dr. Preuss replied that there were none in the Agency. In response to a question on recordkeeping, Dr. Preuss noted that his signature on documentation is adequate. Another attendee commented that the process currently in place does not provide any incentive to conduct HSR. Dr. Preuss advised that it is not a good idea to conduct HSR without approval. It is very important to ensure that human subjects are well protected. Also, if something is determined to be a public health project, it is important to attach any files or documentation on how that decision was reached.

Interactions Between EPA and ATSDR

Anne Sowell, PhD
Human Subjects Contact
NCEH/ATSDR

Definitions

Definitions

- **Human Subjects -** living individuals about whom an investigator obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information (40 CFR part 26.102 (f))

Definitions

- **Identifiable Information –** information that would allow the person it describes to be identified: information may be identifiable even if it does not include name, address, social security number, or other common identifiers

Definitions

- **Private information –** information about behaviors occurring in a context which an individual would expect not to be observed or recorded, or information provided for a specific purpose which an individual would reasonably expect to not be made public (40 CFR part 26.102(f))

Definitions

- **Research -** a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge (40 CFR part 26.102(d))

Definitions

- **Generalizable Knowledge –** knowledge that can be applied in another context

Definitions

- **Exempt Research –** certain types of human subjects research projects specified in the Common Rule (40 CFR part 26.101 (b)) to which the remainder of the Rule does not apply

Definitions

- **OHRP-approved Assurance –** An agreement between an institution and the HHS Office for Human Research Protection (OHRP) that the institution will comply with the Federal regulations for protecting human research participants (45 CFR part 46) when engaged in non-exempt research involving human participants

Interactions Between EPA and ATSDR

- Most ATSDR projects do not include human subjects research.
- They are not designed to generate generalizable knowledge.
- ATSDR requires that participants in non-research studies receive a level of protection similar to that offered participants in research projects.

Interactions Between EPA and ATSDR

- Generally ATSDR and EPA work in parallel rather than in partnership because of differing skill sets and mandates.
- The ATSDR regional staff is an exception.
- ATSDR human research studies do not include EPA partners engaged in research.

Interactions Between EPA and ATSDR

- EPA may sponsor human subjects research projects, but not be engaged in research. In this situation there is no requirement for IRB oversight of the EPA activities.
- ATSDR grantees may also be EPA grantees. If they are receiving any HHS funds for human subjects research, they are obligated to follow the HHS rules.

ATSDR Activities

- Health Studies
- Registries
- Grants to state, tribal, or local partners
- Exposure Investigations
- Public Health Assessments
- Health Outcome Data Review
- Exposure Dose Reconstructions

"Health Studies"

- Investigation into the health effects of individuals exposed to an environmental contaminant
- Involves human subjects
- Is research, not exempt
- ATSDR is engaged or sponsoring
- IRB oversight needed

Registries

- Collection of names and contact information from individuals exposed to an environmental contaminant, possibly additional information
- Involves human subjects
- Often involves research intent
- ATSDR is engaged
- May or may not need IRB approval

"Exposure Investigation"

- Investigation to determine if environmental exposures high enough to cause health concerns are occurring
- Involve human subjects
- Not normally generalizable therefore not research
- ATSDR engaged in the project or sponsoring the project

Grants

- Advertised as research or non-research
- IRB approval required for award recipient and any sub-contractors engaged in non-exempt human subjects research
- Determination of exemption made by either grantee's institution or by ATSDR

Grants Including Human Subjects Research

- Award recipient must hold OHRP approved assurance
- Project must receive IRB approval
- Grant applications reviewed for human subjects research activities
- Funds are withheld until IRB approval obtained

Non-Research Grants

- Application considered non-responsive if human subjects research is included
- Grant funds may not be use for human subjects research
- Awardees may use other funds for related research activities
- If they have an OHRP-approved assurance, they must comply with HHS human subjects protection regulations regardless of funding source

The Human Subjects Research Decision Process

Does the project involve human subjects?

- Will investigators be using identifiable private data about living individuals?

OR

- Will the investigators be interacting with people to obtain data or specimens?

Is the project research?

- Is the project a systematic investigation designed to develop or add to a knowledge base?

AND

- Will the data be generalizable?

Is the project exempt research?

1. Is the research conducted in educational setting on educational techniques or materials?
2. Does the research involve only educational tests, survey or interview procedures, or observations of public behavior, and will the data be unidentifiable or if disclosed not able to put the individuals at risk of harm?

Is the project exempt research?

3. Does the research involve only educational tests, survey or interview procedures, or observations of public behavior, and are the participants elected or appointed public officials or candidates for public office or protected by a federal statute that prohibits release of identifiable information during and after the research?
4. Does the research involve the use of existing data or specimens collected for non-research purposes which are either publicly available or not identifiable?

Is ATSDR engaged in research?

- Will ATSDR staff be interacting with participants?
- Will ATSDR staff have access to identifiable data or specimens?
- Is ATSDR responsible for the study design?
- Is ATSDR conducting the study?

Is ATSDR sponsoring the research?

- Is ATSDR funding the project?

OR

- Is ATSDR supplying the identifiable data?

What about ATSDR's partners in research projects?

ATSDR may conduct human subjects research with or sponsor human subjects research at another institution only if that institution holds an OHRP-approved assurance of compliance and certifies IRB approval to conduct that research.

For ATSDR funded or collaborative human subjects research projects

- Partner must have OHRP approved assurance.
- Partner may use own IRB or rely on a CDC IRB.

Research conducted by ATSDR on behalf of another organization

- ATSDR may conduct human subjects research for another organization which does not hold an OHRP-approved assurance.
- Any employee of that organization engaged in the research must be covered by CDC's assurance through an unaffiliated investigator agreement

Training

- No HHS policy requiring research ethics or human subjects protection training.
- NIH requires grantees conducting human subjects research to obtain such training.
- CDC/ATSDR does not have a similar requirement
- NIH and CDC/ATSDR require investigators to take research ethics training

- Training is available through several vendors.
- There are a number of online courses, some of which are free.

Interactions Between EPA and ATSDR

Anne Sowell, CDC/Agency for Toxic Substances and Disease Registry (ATSDR), National Center for Environmental Health

Dr. Sowell began her presentation by defining several terms, as follows:

Human subjects are "living individuals about whom an investigator obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information"(40CFR part 26.102 (f)).
Identifiable information is "information that would allow the person it describes to be identified; information may be indentifiable even if it does not include name, address, social security number, or other common identifiers."
Private information is defined as "information about behaviors occurring in a context which an individual would expect not to be observed or recorded, or information provided for a specific purpose which an individual would reasonably expect to not be made public."
Research is "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generablizable knowledge (40CFR part 26.102(d)).
Generalizable knowledge is "knowledge that can be applied in another context.
Exempt Research refers to "certain types of HSR projects specified in the Common Rule (40CFR part 26.101 (b)) to which the remainder of the Rule does not apply."
OHRP-approved Assurance is "an agreement between an institution and the DHHS OHRP that the institution will comply with the Federal regulations for protecting human research participants (45CFR part 46) when engaged in nonexempt research involving human participants."

Dr. Sowell discussed the interactions between EPA and ATSDR. She stated that most ATSDR projects do not include HSR activities, and they are not designed to generate generalizable knowledge. ATSDR requires that participants in non-research studies receive a level of protection similar to that offered to participants in research projects. In addition, ATSDR and EPA generally work in parallel rather than in partnership because of different skill sets and mandates. ATSDR HSR activities do not include EPA partners engaged in research. Dr. Sowell observed that EPA can sponsor HSR projects but not be engaged in research. ATSDR grantees also may be EPA grantees; if they receive any DHHS funds for HSR, they are obligated to follow DHHS rules. She added that ATSDR activities focus on health studies; registries; grants to state, tribal, or local partners; exposure investigations; public health assessments; health outcome data review; and exposure dose reconstructions.

Dr. Sowell described the HSR decision process at ATSDR. Some of the questions typically asked about an HSR study include: Does the project involve human subjects? Is the project "research"? Is the project "exempt research"? Is ATSDR engaged in the research? Is ATSDR sponsoring the research? In addition, ATSDR can conduct or sponsor HSR activities at another institution if that institution holds an OHRP-approved assurance of compliance and certifies IRB approval to conduct that research. For ATSDR funded or collaborative HSR projects, partners in the projects must have an OHRP-approved assurance and may use their own IRB or rely on a CDC IRB. ATSDR may conduct HSR on behalf of another organization that does not hold an OHRP-approved assurance. Also, any employee of that organization involved in the research

must be covered by CDC's assurance through an unaffiliated investigator agreement. Dr. Sowell ended her presentation on the topic of training and stated that DHHS policy does not require research ethics or human subjects protection training. The National Institutes of Health (NIH) require grantees conducting HSR to obtain such training. CDC/ATSDR does not have a similar requirement.

Questions and Answers

One attendee commented that exposure studies were generalizable. Dr. Sowell commented that exposure investigations provide few solid results; however, ATSDR must conduct them because of being responsive to the community. She said that it is rare to collect blood samples from humans; usually only environmental samples are taken. In addition, cancer cluster studies are not usually conducted by ATSDR; these studies are often conducted by CDC as case-controlled studies. Another question arose about how the determination is made of biological samples with exposure to a toxin or pollutant. Dr. Sowell noted that two divisions at ATSDR deal with this type of issue. If the exposure investigation is conducted in a Superfund site, peer review is required, which can be time consuming. She added that there is an OMB exemption to respond to a community emergency; there is no way to circumspect OMB's involvement, but the case can undergo IRB review quickly.

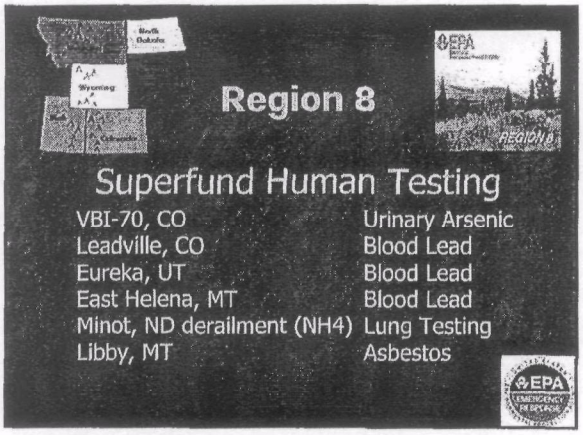
Open Forum/Panel Discussion With Q&A With Speakers/Experts From Previous Sessions

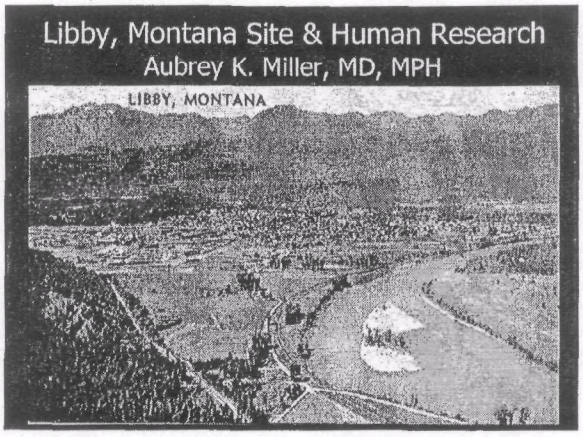
With regard to research vs. non-research studies, one attendee asked how to protect human subjects in these varied situations. In the case of exposure studies, for example, ATSDR tells homeowners if something is going to affect their property's resale value. EPA does not seem to do this. This type of situation is a big gap in EPA's practice right now, and something needs to be put into place to protect human subjects. An attendee asked if the Regions should adopt standards in this regard. The response was that although it is a good idea, it would be better if practices were consistent across the Agency. Moreover, when deciding to conduct a research study, oversight is needed to ensure that the project is conducted appropriately, ethical principles are being followed, good processes are in place, and identifiers are removed. A comment was made in regard to the lack of a real system for research involving human subjects; it is something that the Regions could develop themselves. With regard to the public health part of a study, consolidation of a system might not work. Another comment was made regarding the limited number of people in the Regions to handle grants properly. A suggestion was made for Regions to meet more often each year, which could help to reduce some of the burden. With regard to HSR, there is no intermediary position, so perhaps the processes at NCER could be transferred to the Regions.

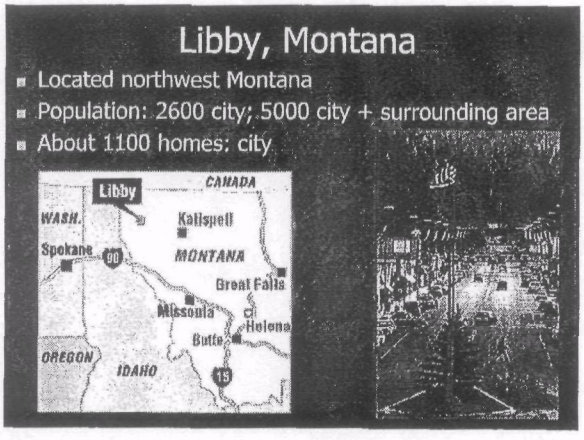
Another attendee added that if a study addresses the needs of the community, then it is not research. A comment was made regarding the fact that EPA was criticized years ago for producing questionable data, which has lead to an increase in the quality assurance and quality control on research projects. The response was given that the focus on public health is a very sensitive issue right now and that more resources are needed to address the situation. ORD will continue to conduct research and approve research grants.

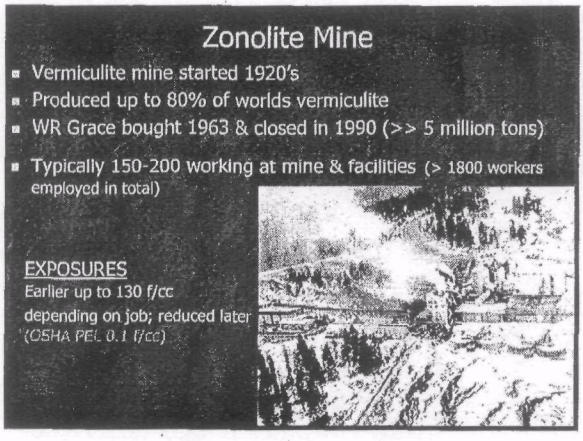
A question was asked if the process would change with a new HSRRO. The response given was that it is recommended at this time that only one official at EPA respond to questions. Regarding HSR activities, is there some way in ORD to obtain funding and get the project completed if the project cannot be conducted through a cooperative agreement? The suggestion was made for people from NCER to sit down with attendees of this workshop and review how they do things; it could be a helpful learning experience. Another suggestion was made to conduct the study as a RARE project and ORD will approve it. With regard to Dr. Preuss' tremendous responsibility as the HSRRO for the entire Agency, the suggestion was made to have a broader group of scientists to openly discuss these issues, even to bounce case studies off each other, perhaps in once-a-month type meetings. The comment was made that it is a good idea to not have just one person taking responsibility for the entire Agency. The HSRRO should be viewed as a consultant to the Regions. Another suggestion was made to have some type of group put together that could determine where things were going on the topic of HSR. A comment was made that when submitting a research application for approval, it has to pass peer review and it has to pass every requirement after peer review. Regarding the National Children's Health Study, who is the HSRRO? The response was that the NICHD at NIH is the HSRRO in this study. NIH meets all of EPA's requirements. Another question raised was who is responsible for a multi-site research study? The response was that the Science Advisory Council is responsible for it.

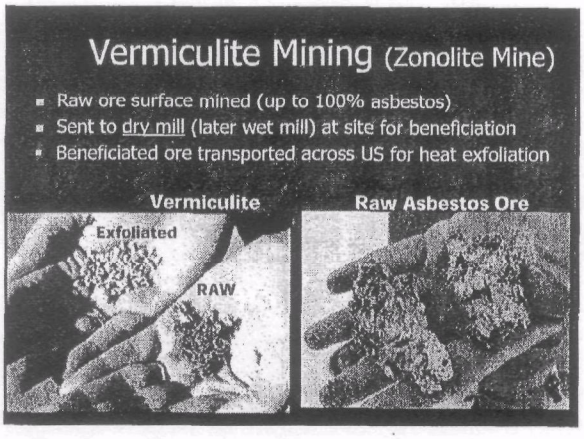
Day Three

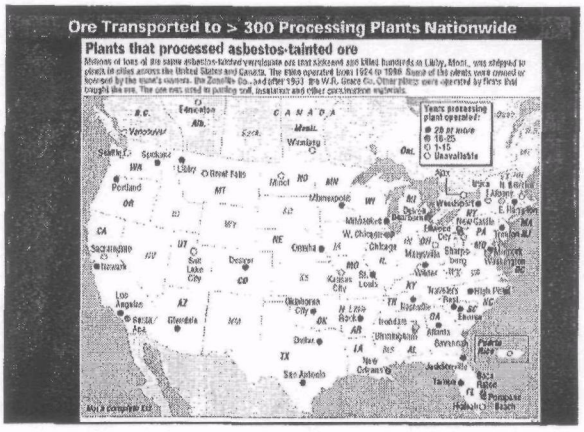

Region 8
Superfund Human Testing
VBI-70, CO — Urinary Arsenic
Leadville, CO — Blood Lead
Eureka, UT — Blood Lead
East Helena, MT — Blood Lead
Minot, ND derailment (NH4) — Lung Testing
Libby, MT — Asbestos
EPA


Libby, Montana Site & Human Research
Aubrey K. Miller, MD, MPH
LIBBY, MONTANA


Libby, Montana
Located northwest Montana
Population: 2600 city; 5000 city + surrounding area
About 1100 homes: city
Libby
CANADA
WASH.
Kalispell
Spokane
90
MONTANA
Great Falls
Missoula
Helena
Butte
OREGON
IDAHO
15

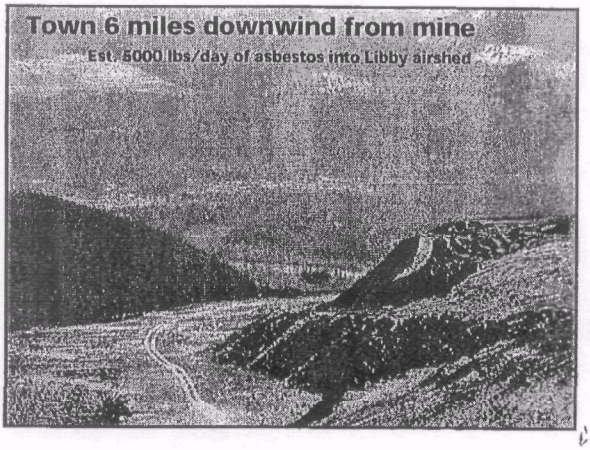

Zonolite Mine
Vermiculite mine started 1920's
Produced up to 80% of worlds vermiculite
WR Grace bought 1963 & closed in 1990 (>> 5 million tons)
Typically 150-200 working at mine & facilities (> 1800 workers employed in total)
EXPOSURES
Earlier up to 130 f/cc
depending on job; reduced later
(OSHA PEL 0.1 f/cc)


Vermiculite Mining (Zonolite Mine)
Raw ore surface mined (up to 100% asbestos)
Sent to dry mill (later wet mill) at site for beneficiation
Beneficiated ore transported across US for heat exfoliation
Vermiculite
Exfoliated
RAW
Raw Asbestos Ore


Ore Transported to > 300 Processing Plants Nationwide
Plants that processed asbestos-tainted ore
CANADA

Town 6 miles downwind from mine

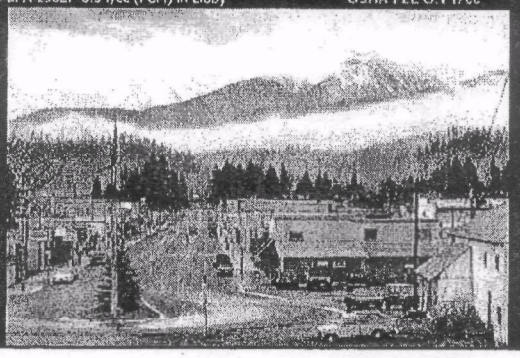
Est. 5000 lbs/day of asbestos into Libby airshed



Ambient Air

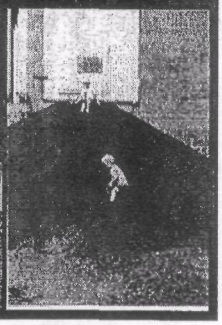
- Grace records 1975: 0.7 to 1.5 f/cc (PCM) downtown
- EPA 1982: 0.5 f/cc (PCM) in Libby

OSHA PEL 0.1 f/cc

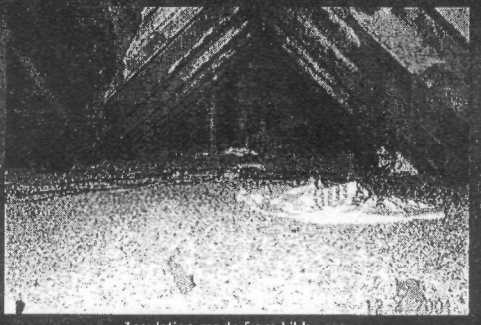


Libby Non-occupational Exposures Historical & Present

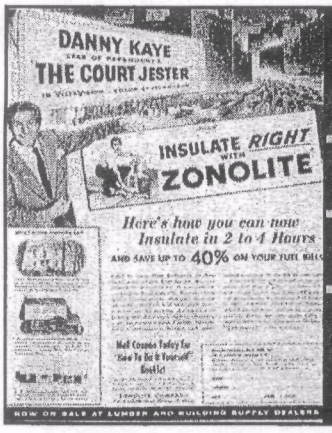
- Family Contact with workers
- Other
  - Playing in vermiculite piles
  - School Areas
  - Garden use



Vermiculite Attic Insulation



Insulation made from Libby ore



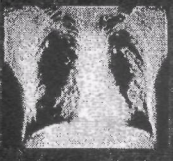
How Many Homes?

- EPA has no information prior to Grace.
- Estimates range between 10 - 35 million homes.
- EPA, ATSDR, & NIOSH issued national warnings in 2003.

Asbestos: Non-Cancer Diseases

Asbestosis: Fibrosis of lung parenchyma (air sacs)

Pleural Fibrosis: Scarring / thickening lining around lung



- All types of asbestos
- Mortality
  - Under-reported
- Severity
  - Dose, Duration, Personal Factors
- Usually 10+ yrs to develop (Latency Period)
- Clinical: No impairment to severe disease & death

Asbestos: Carcinogenic Disease

Cancer reported 1935

- Lung Cancer
- Mesothelioma

] Clearly associated

- GI Cancer — Most studies
- Other Cancers — Some studies
  - Laryngeal, Kidney, Ovaries

Libby Health Data Since 1999

- Mortality Studies
- **Medical Testing**
- Case-Series
- Other

Libby Medical Testing Groups Involved

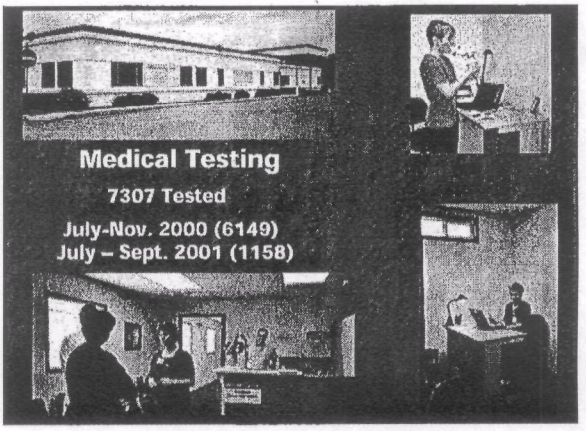
EPA Region 8
ATSDR
US Public Health Service Region 8
Montana DHHS
Libby local government & medical community

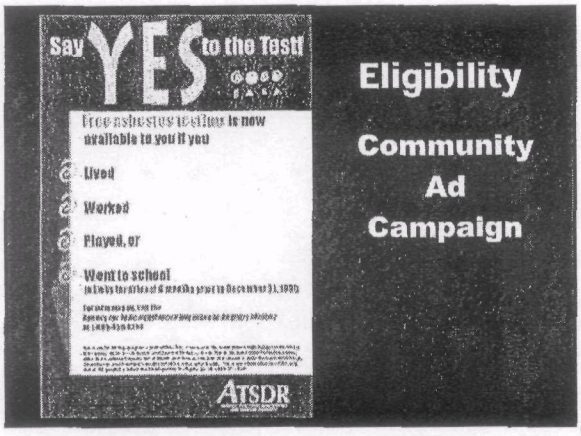
Major Roles & Responsibilities

- Protocol development was collaborative
- EPA: provided $11M & physical infrastructure
- ATSDR: actual testing & HSRB
- PHS Region 8: health care delivery efforts
  - HRSA, SAMHSA, CMS, MT Primary Care Assoc.

HSRB Requirements

- Full testing protocols
- Health pros & cons of all tests
- Info regarding any benefits of participation
- Draft letters to convey participant results
- All consent forms (easily understandable)
- Consent to send results to designated MDs
- Record keeping plans



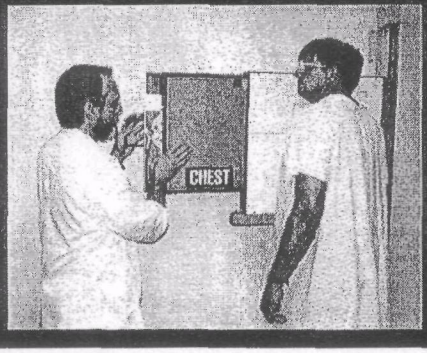


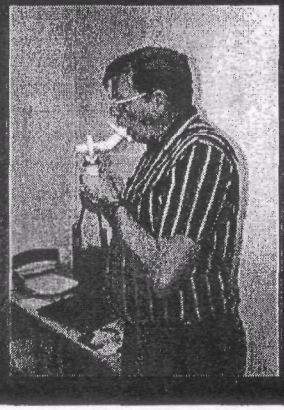
Eligibility

Community Ad Campaign

Assessment Interview

Chest X-ray





Pulmonary Function Test

Crude Pleural Abnormality Rates (%) All CXR Views, 2/3 B-readers *

All Participants	18 %

Ever WRG employed	51	Play Verm. Piles	
Secondary Contractor	35	Sometimes	19
Lived with WRG worker	26	Frequently	25
		Popped Verm.	
Verm. Insul. In Home	21	Sometimes	22
Vermiculite Gardening	20	Frequently	26
Handled Verm. Insulation		Recreated along road to mine	
Sometimes	21	Sometimes	17
Frequently	26	Frequently	21

*n=6668 participants (PA view only 14%)

*Peipins et al; Environ Hlth Persp.; 111:1753-1759 (2003).

HSR Medical Testing Issues

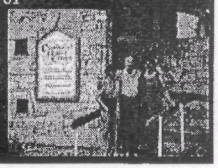
- Health Study vs Exposure Investigation
- Generalizable knowledge & intent
- Cost / Benefit of medical testing
  - Risks of procedures (kids vs adults)
  - Lack of effective treatments
  - Risk of losing/not getting insurance coverage
- Confidential Record Keeping

Health Care Issues

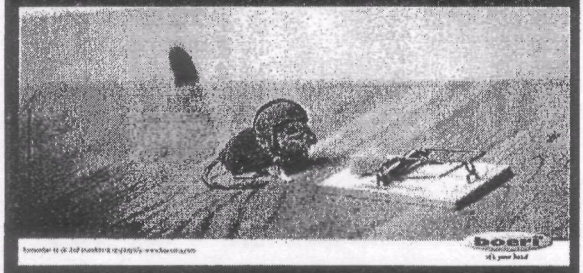
- Evaluation of those with abnormalities
- Needs Assessments
- Federal Programs / Financial Aid
  - Increase coverage medicare & medicaid
  - Eligibility designations (MUP, HPSA)
  - Community Health Center (opened Dec 01)

Health Care Results

- Development effective community coalitions
- Center for Asbestos-related Disease
  - Support for specialty care for those affected
- Community Health Clinic
  - Primary care for Libby & surrounding communities
  - Application submitted 5/01, started 12/01
- Mental health services

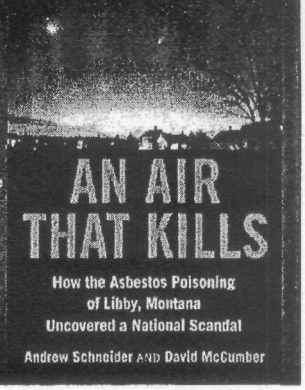


QUESTIONS????



More information is widely available on Libby & Asbestos Issues

EPA & ATSDR websites, books, scientific literature, news & magazine articles.



Wednesday, September 28, 2005 (Day Three)

AM Moderators: Jean Zodrow and Maryann Suero

Human Subjects Regional Case Studies:

Libby, Montana
Aubrey Miller, EPA Region 8

Dr. Miller presented HSR information from the Libby, Montana, site. The site has a population of 2,600, with 5,000 in the city plus surrounding areas and approximately 1,100 homes in the city. The city was involved in vermiculite (zonolite) mining, which began in the 1920s and produced up to 80 percent of the world's vermiculite. The W.R. Grace Co. bought the mine in 1963 and closed it in 1990, at a time that it was producing more than 5 million tons of vermiculite. There were 150-200 employees who worked at the mine and facilities and more than 1,800 employees in total. Raw ore surface mining resulted in 100 percent asbestos exposure. The raw ore was sent to a dry mill (later wet mill) at the site for beneficiation. The beneficiated ore was transported across the United States for heat exfoliation to more than 300 processing plants. Asbestos exposures in the earlier days at the mine were up to 130 f/cc (vs. OSHA PEL 0.1 f/cc) but were reduced later depending on the job type. The town of Libby was 6 miles downwind from the mine. Approximately 5,000 lbs/day of asbestos went into Libby's airshed. Non-occupational exposures to asbestos resulted from family contact with the workers, children playing in vermiculite piles, school areas, garden use, and attic insulation made from Libby ore. EPA has no information prior to the time that the W.R. Grace Co. bought the mine. Estimates range between 10-35 million affected homes.

EPA, ATSDR, and NIOSH issued national warnings against asbestos exposure in 2003. There has been evidence of non-cancer diseases such as asbestosis and pleural fibrosis as well as carcinogenic diseases such as lung cancer, mesothelioma, GI cancer, and laryngeal, kidney, and ovarian cancers. EPA Region 8, ATSDR, U.S. Public Health Service (PHS) in Region 8, Montana DHHS, and Libby local government and the medical community became involved in Libby's medical testing. Protocol development was collaborative. EPA provided $11 million and the physical infrastructure; ATSDR performed the actual testing; and PHS Region 8 became involved in health care delivery efforts. The HSRB requirements included full testing protocols, health pros and cons of all tests, information regarding any benefits of participation, draft letters to convey participant results, easily understandable consent forms that had to be evaluated, setup of a system involving consent to submit results to designated physicians, and record keeping plans. In 2000 and 2001, 7,307 people were tested. ATSDR developed a community advertising campaign to encourage residents of Libby to come for free asbestos testing. Assessment interviews, chest x-rays, and pulmonary function tests were conducted on study participants. HSR medical testing issues included whether the study was a health study or an exposure investigation; generalizable knowledge and its intended use; cost/benefit of medical testing (i.e., risks of procedures, especially radiation to kids; lack of effective treatments for asbestos; risk of losing/not getting insurance coverage); and confidential record keeping. Health care issues included evaluation of those with abnormalities, needs assessments, and federal programs/financial aid. Health care results included setup of a community health center, which

opened in December 2001; setup of the Center for Asbestos-related Disease; development of effective community coalitions; and provision of mental health services. Dr. Miller recommended that workshop attendees visit EPA and ATSDR Web Sites for more information on Libby and asbestos issues, as well as checking the scientific literature, news and magazine articles, and books such as *An Air That Kills: How the Asbestos Poisoning of Libby, Montana Uncovered a National Scandal* by Andrew Schneider and David McCumber.

IRB Case Study:

Asian and Pacific Islander Seafood Consumption Study in King County, Washington

Grant Award Details

- **Environmental Justice Community/University Partnership Grant EQ925003-01**
  - Application Date: Feb 1996
  - Study period: Aug 1996 to July 1998
  - Funding: $205,316

Background

API immigrants were hypothesized to consume greater quantities of SF, different species and different tissue parts when compared to the general US population.

Concerns:

- Self-harvesting in urban waters
- Increased risk of toxic chemical exposure

- Studies within API communities require specialized survey tools & methods because of cultural and language differences.

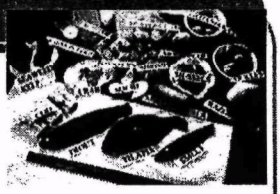
Strategies:

- University researchers partnered with Refugee Federation Service Center.
- Cultural guidance given by API community Advisory Committee.
- Culturally appropriate survey tools and methods were developed and focus group tested.

Methodology—Overview

- **10 API ethnic groups surveyed:** (Cambodian, Chinese, Filipino, Hmong, Japanese, Korean, Laotian, Mien, Samoan and Vietnamese)
- **Respondents were also:**
  - **1st or 2nd generation;**
  - **≥18 years old;**
  - **SF consumers; and**
  - **residents of King County, WA**
- **SF consumption survey administered by trained bilingual interviewers.**

- **The SF consumption survey solicited information about:**
  - **types/sources of SF;**
  - **preparation methods;**
  - **frequency of consumption and portion size consumed;**
  - **demographic information.**



•Seafood models were used to elicit more accurate serving size estimations from respondents.

•Random sampling strategies: community group rosters volunteers)

Study Oversight

- Multiple sources
  - Community Advisory Committee
  - Scientific Advisory Committee
  - UW-IRB

Community Advisory Committee

The Community Committee kept the design culturally appropriate by rejecting a cruel design, telephone survey or mail survey as offensive or threatening, and supported a one-on-one interview approach which used appropriate cultural protocol. They also rejected a statistical sampling method based on US census data. They felt it appeared to favor certain groups, and did not adequately include groups they considered most at risk - those arriving in the US most recently.

UW—IRB Review

- Once grant was funded and final work plan finalized, UW researchers applied for UW—IRB approval
- If risks to human subjects is low, e.g. a survey, approval usually given within 2 weeks.
- A mid-study methods change required 2nd UW—IRB approval

Please adjust your glasses

EPA IRB Approval

Study Outcomes

- EPA Report 910/R-99-003, May 99
- Original SF consumption data posted to EPA Website
- Journal Publication in: *J Exp Anal & Envir Epid.* (2003) 13, 256-266.

Asian and Pacific Islander Seafood Consumption Study in King County, Washington
Ruth Sechena, University of Washington

Dr. Sechena pointed out in her presentation that the study period covered August 1996 to July 1998, with grant funding of $205, 316. It was hypothesized that Asian and Pacific Islander immigrants consumed larger quantities of seafood, including different species and tissue parts, than the general U.S. population. Concerns about this special population involved self-harvesting in urban waters and the increased risk of toxic chemical exposure. Because of cultural and language barriers, studies within this population required specialized survey tools and methods. Some of the strategies employed to reach this population included University researchers partnered with the Refugee Federation Services Centers; cultural guidance was given by the Asian and Pacific Islander Community Advisory Committee; and culturally appropriate survey tools and methods were developed and tested on a focus group. In this study, 10 Asian and Pacific Islander ethnic groups were surveyed (e.g., Cambodian, Chinese, Filipino, Hmong, Japanese, Korean, Laotian, Mien, Samoan, and Vietnamese). The seafood consumption survey solicited information about the types/sources of seafood, preparation methods, frequency of consumption and portion size, and demographic information. Seafood models were used to elicit more accurate serving size estimations from respondents. The strategy behind random sampling was to use community group rosters of volunteers. The rosters, however, were difficult to obtain. The Community Advisory Committee kept the study design culturally appropriate by rejecting a creel design, telephone survey, or mail survey that would have been considered offensive or threatening and instead supported a one-on-one interview approach that used appropriate cultural protocols. In addition, the Community Advisory Committee rejected a statistical sampling method based on U.S. Census data because it appeared that certain groups were favored and that groups they considered most at risk, such as those entering the United States recently, were not adequately included. Dr. Sechena stated that once the grant was funded and a final work plan was finalized, University of Washington researchers applied for University of Washington-IRB approval. She further noted that if the risks to human subjects were low, as in the case of conducting a survey, approval would be given within 2 weeks but the survey had to be voluntary. A mid-study methods change, however, required that a second University of Washington-IRB approval be completed. The study outcomes resulted in publication of a Technical Report (Asian and Pacific Islander Seafood Consumption Study in King County, Washington, EPA Report 910/R-99-003, May 1999); publication of an article (Ruth Sechena, Shiquan Liao, Roseanne Lorenzana, Connie Nakano, Nayak Polissar, and Richard Fenske. Asian American and Pacific Islander seafood consumption—a community-based study in King County, Washington. *Journal of Exposure Analysis and Environmental Epidemiology* 2003;13:256-266); and posting of the original seafood consumption data on EPA's Web Site.

Human Mercury Biomonitoring in Alaska
Pat Cirone, EPA Region 10

Dr. Cirone pointed out that this study began with a fish tissue monitoring grant given by EPA to the State of Alaska to obtain data on levels of mercury found in humans. There were two components to this study: one was to measure tissue contaminants and the other involved mercury biomonitoring. She added that the Human Biomonitoring Program resulting from this study was considered routine public health practice and did not have to comply with the Common Rule or go through IRB review. The involvement of human subjects was to obtain hair samples from the community to determine the contaminant levels. The State of Alaska is still collecting fish tissue, but the results are not yet available. A document prepared in 2005 focused on the state's whole biomonitoring program rather than this particular study. Dr. Preuss added that this grant should have gone to him for approval.

Children's Asthma Study in Idaho
Doug Cole, EPA Region 5 (presented by Roseanne Lorenzana, EPA Region 10)

Dr. Lorenzana informed workshop participants that this study was conducted during the field-burning season in Idaho. The Idaho Department of Health and Welfare grant application for state-level collaboration to address childhood asthma was submitted in August 2003, and was for approximately $50,000 to investigate health risks associated with field burning in Northern Idaho. The study involved collecting and correlating existing health data with air quality/ meteorological data, and information on field burning activities in the Rathdrum Prairie of Northern Idaho during a 3-year period (2000-2002) to determine if there were any associations. The workplan, funding, and timeline did not anticipate the need for IRB approval or the development of a Quality Assurance Project Plan (QAPP). The applicant was not aware of the need for IRB approval and did not understand the approval process. As a result, there were significant difficulties and delays in starting this project.

Dr. Lorenzana pointed out the benefits of an IRB, which is to ensure that the rights and welfare of HSR subjects are adequately protected. An IRB has the authority to approve, require modifications in, or disapprove research. There are many IRBs throughout the United States. In Idaho, an IRB exists at Boise State University.

Dr. Lorenzana stated that the research for this study qualified for an exemption from the IRB approval process because it used an existing collection of health data and that any information being collected did not identify individuals. The exemption process, however, required a narrative from the applicant to Dr. Cole, after which he and the PO submitted a request to NCER. The exemption approval took 2.5 months. Generally, the QAPP plans should be submitted and approved for research projects. The IRB and QAPP approval process takes time and effort, and these should be factored in the project timeline and budget for tasks. Dr. Lorenzana advised grantees to check with their grant PO to determine if IRB approval is necessary or if an exemption is applicable.

Regional Case Studies—Questions and Answers:

A question was asked about the life cycle of the Libby, Montana case. The response was that the whole life cycle of the study was unclear. A participant added that at the CDC, protocols are given annually. If there is any major changes, the IRB conducts a review. Generally, approvals take approximately 6-8 weeks; exemptions take about 2-3 weeks. A question was raised whether the study should have gone through EPA for approval. At the time of the study, the study proposal was reviewed by ATSDR through their process. If the study was conducted today, it would have gone through Dr. Preuss.

Regarding the Asian and Pacific Islander Seafood Consumption Study in King County, Washington, a question was asked whether any attempt was made to contact the people in the community to warn them about eating the fish. Dr. Sechena pointed out that there were three phases involved in the study, and that the third phase involved determining how to reach the community. A comment was made that with ethnic communities, caution should be taken when giving out information to the folks in a community. A question was raised whether information

should have been given to the community sooner. Dr. Sechena added that the information was not available any sooner. In addition, she did not think that participation in the study would have been any different if that had occurred. An attendee asked if the study was approved by EPA. Dr. Preuss replied that the study was under the HSR umbrella, and he could not comment on each study without receiving it. Another question was asked regarding what to do with the collected data. A response was given that if the quality of the data is good and names are affiliated with the data, then the data can be used for analysis. Dr. Preuss pointed out that the system is set up for POs and Program Officers in the Regions to make the decision whether a study is HSR or not. Someone asked how POs would obtain funds for the study. Dr. Preuss replied that EPA would stand behind the PO in making the determination. He added that if a line item grant is being sought, certain things must be done; a system is in place, the steps are written down, and they just need to be followed for the grant to be awarded.

Regarding the Human Mercury Biomonitoring Study in Alaska, one attendee asked where the document with the data was stored. Dr. Cirone replied that it was being kept with the grant. Another attendee asked if anyone was planning to warn folks not to eat the fish if the study results showed a high health risk. Dr. Cirone stated that the study design was somewhat flawed, and she did not anticipate doing so. Another question was raised regarding what incentive existed to take this study to an IRB when CDC had an exemption for it. Dr. Cirone replied that this was a biomonitoring study; there was no CDC documentation, just a CDC reference. The earliest documentation dates back to 1999. This was a choice likely made early in the program.

Regarding the Children's Asthma Study in Idaho, the question was raised whether this study was an example of research and public health practice. Dr. Sowell pointed out that CDC and ATSDR have always been very careful in making the distinction between research and public health practice, and would consider this case to be research. Setting up a program and collecting samples for future use does not necessarily constitute research. Some of the work being done by the states is initially considered public health practice but crosses over into research. The question was asked about what happens when something is considered public health practice but then becomes research. The response was that there is no simple answer to that question. From the outset of a study, it has to be determined if it is going to be research. Thought should be given to whether the study will go beyond public health practice.

A question was asked whether IRB approval should be sought if EPA receives an HSR application from a university. Dr. Sechena was not sure if the University of Washington required the IRB approval or if it was specific to the grant. Regarding the University of Washington IRB approval, the question was asked whether the process was smooth and efficient. Dr. Sechena pointed out that there were no "red flags" identified for the study.

Report Outs From Breakout Groups:

Attendees at the workshop were assigned to one of four breakout groups. The facilitator of each breakout group was responsible for clarifying the purpose and outcomes for the session. A group representative was selected for each breakout group as well as a discussion leader. Key questions to be addressed were: (1) What "fatal flaws" do you see in the current model (the current processes being used)? (2) How might we be more successful? Which suggestions in the optional model (optional additions to the current model) might improve our processes? (3) What are some of the challenges we might face if we implement these ideas, and how might we overcome those challenges? (4) Who are the players that need to be involved in decisionmaking and where are the major decision points? After the discussions took place, each breakout group was asked to compile recommendations for management to help everyone to be more successful in reviewing HSR. Recommendations presented by each group representative included the following:

Group 1 Recommendations:

- Change the IGMS requirement so that grants can be awarded prior to human subjects studies review.
- Ask Dr. Preuss to write a memo to the regional RAs requesting an appointment of a RHSRRO.
- Develop a national workgroup of regional HSRROs to identify tracking needs for the existing system, including a query capability; develop a consistent human subjects studies training plan; have the workshop organizers, Patti Tyler and Roseanne Lorenzana, develop a recommendation package and identify one regional person to brief the RAs on the workshop recommendations.

Group 2 Recommendations:

- Have the Regions consider a human subjects official position (with a non-research ethics oversight).
- Create a culture where the ultimate goal is protecting human subjects, regardless of whether it is research.
- Develop and implement a training program.
- Develop written guidance, Web site, and list of contacts (subject experts), and publish these in the *Federal Register* for public input/comment.
- Identify and publicize the consequences for noncompliance of EPA Order (40CFR26, EPA Order 1000.17, Change A-1).
- Develop a briefing strategy for upper management.

- Suggest that EPA develop its own IRB.

- Develop a tracking system that is accessible in the Regions on the progress of decisions made regarding the HSRRO process.

- Develop a straw proposal for new HSRRO that is generated by the workshop and finalized by the workshop planning group.

- Have a question on human subjects immediately followed by a question on research in two parts: If "yes" to human subjects and "no" to research, then require an attachment of the regional decision memo; if "yes" to both, then require HSRRO approval.

Group 3 Recommendations:

- Increase management's focus/attention on HSR and include NRSC recommendations, ID on SCOUT, and Dr. Preuss on RA and DRA calls.

- Identify a point of contact for human subjects (HS Officer) with a regional advisory board.

- Have a joint decision made between Dr. Hermann and the regional HS Officer to determine if a study is HSR.

- Create a National HSO Council lead by the HSRRO.

- Maintain communication between the HSRRO and the regional HS Officer.

- Provide all EPA staff with ethics training.

- Provide training for all EPA Project Officers.

- Define HSR and public health practice on the grant solicitation and request the grantee to frame the proposal with these definitions.

- Create a tracking system.

Group 4 Recommendations:

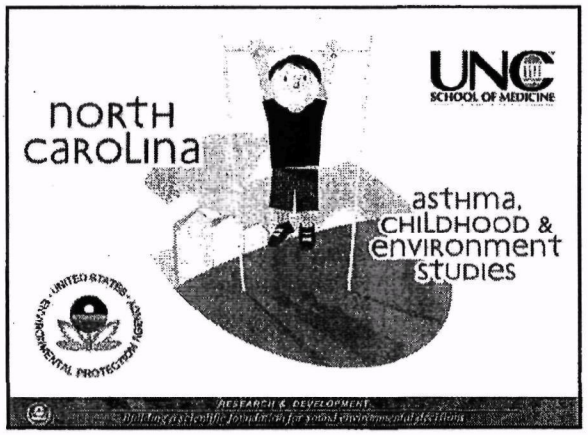
- Determine a point of contact for the Regions for HSR.

- Provide training at all levels appropriate to individual responsibilities.

- Promote awareness of HSR at all levels, including NPMs as national grant RFPs are often administered in the Regions.

- Develop a process like HSR for public health practice, and if necessary, third-party studies.

- Reconcile grant funding timelines or at least make potential grantees aware of the IRB response prior to funding.
- Allow for some room in the process for regional flexibility but maintain overall consistency.
- Allow for future revisions and modifications.



Scenario

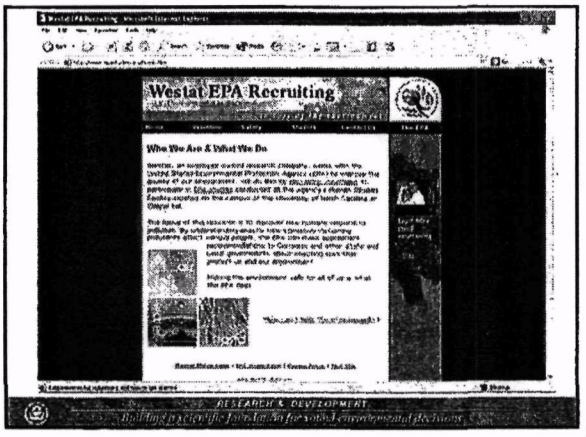
- You are a parent of a child with asthma
- A couple of days ago, your child had an appointment with his/her pediatrician

While at the appointment, your pediatrician showed you and your child this flyer about an asthma study that wants to explore the role of air pollution and asthma

After seeing this ad, you of course had many questions. What types of questions would you ask your child's pediatrician?

After answering some of your clinical questions in regards to asthma, your child's pediatrician suggests that you contact the study number to find out more information in regards to this study.

You decide to check out the study's website listed on the ad. http://www.epastudies.org



Here is the information you found on the website for this study

PACES

The purpose of this study is to examine the effects of particulate air pollution in the Chapel Hill/Carrboro area on the pulmonary health of moderate and severe asthmatic children ages 8-18 years old. This study includes a baseline medical evaluation with breathing and allergy tests, optional blood draw, cheek swabs, and urine and nasal fluid collections. If the baseline medical evaluation finds that the participating child is a moderate or severe asthmatic, the child will be asked to enroll in a six-week diary study. Each day during the diary study the participant will monitor their asthma symptoms using a portable breathing monitor and record their medication use with a PDA/mobile phone connected to their personal internet medical diary.

Just based on the information you have so far, what are some of the things you might discuss with your child in deciding whether or not to call and consider being part of this study?

You and your child decide to call the number. The recruiter describes the study for you and then asks you a series of questions.

Screening Questions

- Name
- Relation to child (parent, guardian, other)
- Phone
- Name of child
- Age of child
- Does your child and you have flexible daytime hours?
- Does your child or you have plans to leave the area within 3 months?
- Is your child presently in any other studies or ever in EPA studies?
- Does your child have asthma?
- Does your child have chronic respiratory disease?
- Does your child have any major medical conditions? Accidents? Operations?
- What type of medication is your child receiving?
- Address

In the end, you decide to make an appointment to enroll your child. You are sent in the mail, before your child's appointment, a study consent form as well as study restrictions.

Restrictions for Appointment

- Do not come with an upper respiratory infection – call and reschedule appointment
- For baseline visit have your child:
  - Avoid smoky areas
  - Drink plenty of fluids 24 hours before appointment
  - Not consume any caffeine day of appointment
  - Eat a light meal 1 hour before arriving
  - No rescue medicines for 6 hours, however, do use the medicines if needed – call and reschedule if use
  - Bring allergy skin test records if possible,
  - Bring all meds and peak flow meter if your child has one

The Appointment

- You bring the consent form
- Assent form
- Clinical screening for eligibility

The Forms

Consent

- Completed by parent or guardian
- Requirement for this study is to have both parents signature
- "Informed"
- Confidentiality
- Can refuse to participate in any aspect of study
- Can leave the study at any time

Assent

- Completed by the child
- Child agrees to participate – parents cannot force child to participate if he/she does not want to
- Same components as consent form, not as detailed

HIPAA Authorization

- "The Health Insurance Portability and Accountability Act of 1996" (known as "HIPAA")
- Provides permission for researchers to access information from a participant's medical records or health insurance records to use in this research study

Consent to Allow Storage of Biological Samples

- Separate consent
- Have several choices
  - Agree to allow storage of specimens with identifying information which might include genetic research
  - Request identifying code be removed and if removed may use as in above
  - Request identifying code removed and specimen can be stored but NO genetic testing
  - Request specimens be disposed of

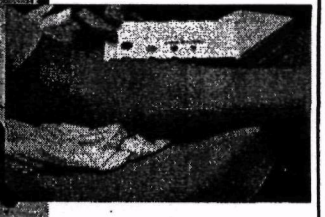
Screening

- Blood draw
- Urine sample
- Vital signs, pulse, blood pressure, respiratory, SpO2, temperature, weight and height
- Skin prick testing for allergies
  - Grass, weeds, trees, mites & insects, animals, molds
- Spirometry
- Exhaled NO measurement
- Exhaled breath condensate
- Nasal lavage
- Buccal cell collection

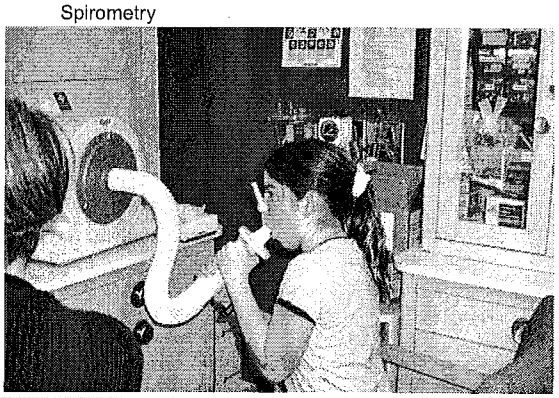
Urine collection

Vital signs, pulse, blood pressure, respiratory, SpO2, temperature, weight and height

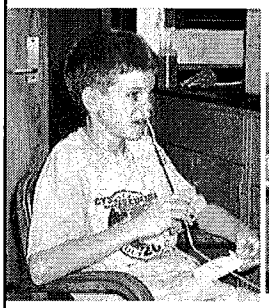
Skin prick testing for allergies:
grass, weeds, trees, mites & insects, animals, molds



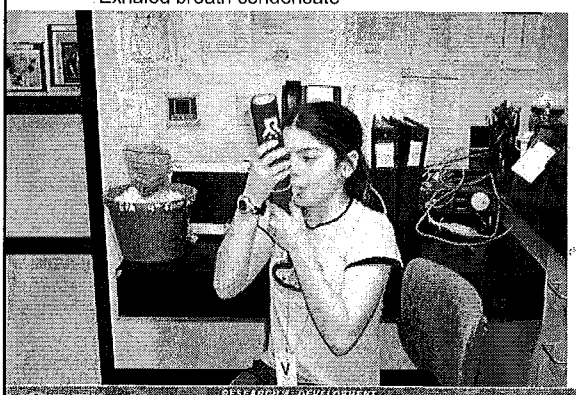
Spirometry



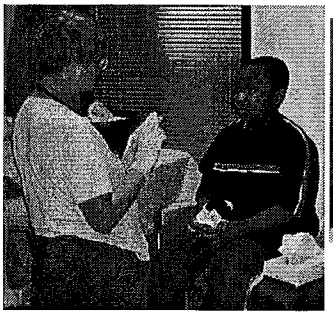
Exhaled NO measurement

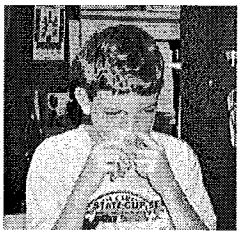


Exhaled breath condensate

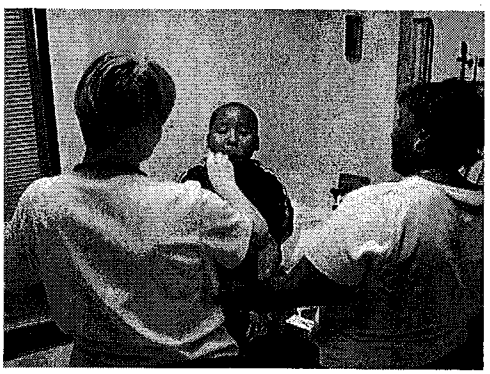


Nasal lavage





Buccal cell collection



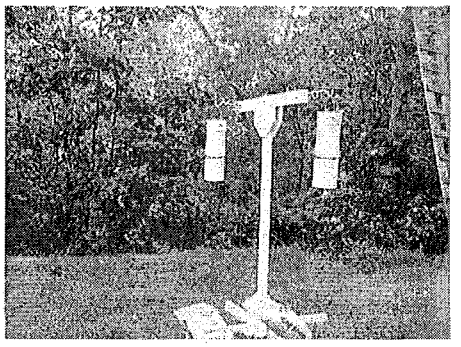
End of screening procedures

- Given phone number to call in case of emergency
  - Receives instructions to monitor for signs of adverse symptoms
- Receives compensation for screening
- Instructed that recruiters will call if eligible for second part of study

Screening Determined Your Child Eligible for Second Part of Study

- Receive phone call to schedule follow-up visit as well as home visit to set up air monitoring

Home air monitor – set up to be in your yard for 1 week



Your presence not needed for set-up or sample collection

Follow-up visit:
Receive instructions for use of PDA to input daily diary (once a day for 6 weeks) and for use of electronic peak flow monitor (twice a day for 6 weeks)

After 6 weeks, return to clinic to return peak flow meter and PDA to receive full compensation

PM Moderators: Margaret Jones and Bruce Macler

Group 1 Presentation: Being a Child in an Epidemiological Study
Rebecca Calderon and Danelle Lobdell, ORD-NHEERL

Dr. Lobdell began the presentation by referring to the North Carolina asthma, childhood, and environment studies conducted by the University of North Carolina (UNC) School of Medicine. She discussed a typical example of a study in which a flyer was provided to a parent of an asthmatic child by the pediatrician during a scheduled appointment. The flyer discussed an asthma study being conducted to explore the role of air pollution and asthma. The study involved three clinic visits during a period of 6-9 weeks. She pointed out that after viewing such a flyer, there were probably many questions that came to mind. After answering some of the clinical questions regarding asthma, the pediatrician suggested that the parent contact the study number to obtain more information about this study. The parent then browsed the study's Web site that was listed on the flyer. One of the major questions included finding out exactly what types of procedures (skin prick test or other) were to be performed in the study to determine the severity of asthma in a child. If the parent and child decided to call the number for the study, the recruiter would describe the study and ask some questions. In the end, the parent would decide to make an appointment to enroll the child in the study. A study consent form would be mailed, along with study restrictions. For the appointment, the parent would bring the consent form, assent form, and clinical screening results for eligibility. The consent form would be completed by the parent or guardian. The assent form would be completed by the child. Parents cannot force their child to participate if the child does not wish to participate.

Under HIPAA authorization, permission is given to researchers to access information from a participant's medical or health insurance records to use in the study. A separate consent form is needed to allow storage of biological samples. Screening is conducted via blood draw, urine sample, vital signs, skin prick testing for allergies, spirometry, exhaled NO measurement, exhaled breath condensate, nasal lavage, and buccal cell collection. At the end of the screening procedures, a telephone number would be provided in case of an emergency, as well as instructions to monitor for signs of adverse symptoms. Compensation for screening would then be provided, and the study participant would be informed that recruiters would call if the participant is eligible for the second part of the study. If screening determines that the child is eligible for the second part of the study, a follow-up visit would be scheduled as well as a home visit to set up an air monitoring device. During the follow-up visit, instructions would be provided for use of a PDA to input the study participant's daily diary and for use of an electronic peak flow monitor. After 6 weeks, the study participant would return to the clinic to return the peak flow meter and PDA for full compensation.

Dr. Lobdell provided some examples of materials such as the consent form to participate in a research study provided to the parents of minors involved in the study; an assent form to participate in a research study provided to minors; UNC School of Medicine/UNC Hospitals information about storage and use of specimens with identifying information; an addendum to the consent form for storing blood, tissue, or body fluid with identifying information; and an addendum to the consent form for participating in a research study.

Questions and Answers

An attendee asked if the physician involved in such a study was liable in any way. Dr. Lobdell replied that the physician was not liable in this case. A comment was made that loyalty to a physician may coerce some patients to enter the study. It should be emphasized that the study is voluntary. Another attendee commented that it might have been less intrusive if the study was posted on a wall rather than given out as a handout or flyer. Dr. Calderon commented that postings on a wall are not as effective in obtaining volunteers. If a physician asks patients to volunteer, they are more likely to participate. An attendee suggested doing a mailing to patients. In addition, caution has to be used with mailings because of HIPAA rules. A question was raised regarding how to account for patients without insurance. Dr. Calderon responded that the study looked at recruitment in the school system, which was more successful than having advertisements in the paper or through medical offices. The Education Departments and their interpretation of the Federal Educational Rights and Privacy Act (FERPA) are preventing investigators from entering school systems to conduct studies because of societal concerns over privacy issues.

A question was asked whether parents calling the recruiter for the study would get their questions answered before being asked screening questions. Dr. Lobdell responded that their questions would be answered, but that there could be a couple of key screening questions that might be asked to determine if the child qualifies for the study. Someone asked what the parents' motivation was for entering their child in the study. Dr. Lobdell responded that in the National Children's Study, for example, altruism was a big motivator simply because many parents who had a child with a medical condition would want to help their child. Dr. Calderon added that participation in the study could lead the parent to better doctors or give them the assurance that they are doing the right thing for their child.

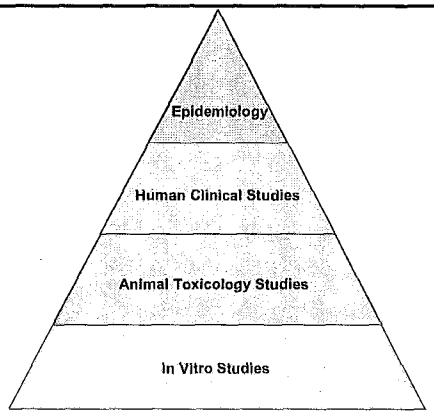
Dr. Calderon pointed out that it was critical to know if the child was involved in any other study. A simple blood test was done to screen out those involved in too many studies. A question was asked about the grade level of the flyer. Dr. Lobdell replied that the flyer was geared for an 8th grade reading level. One participant suggested adding a glossary to the end of the consent form because many parents would not know the meaning of some of the terms used. Dr. Lobdell agreed but suggested keeping the consent form very simple. She added that most people do not want to take the time to read a long consent form, and in some instances, are willing to just sign it without reading it. It is important to go over the consent form with the participant to ensure his/her understanding of the study. In addition, she suggested that the consent form always include a statement of confidentiality. It should be made clear that the patient's level of care would not change as well. Finally, payment should be included for participation in the study, which is a big incentive for the child to participate. Dr. Calderon added that usually the payment goes to the child. Dr. Lobdell pointed out that if parents sign the consent form, there also must be an assent form signed by the child.

Controlled Human Exposure Studies Within the EPA

Robert Devlin
Human Studies Division
US Environmental Protection Agency

Human Data Is Critical When It Comes To Standard Setting

- Species of interest for risk assessment purposes
- Many aspects of humans cannot be readily accounted for in animal studies
  Longevity, diet, lifestyle, disease, genetic variability
- 10x uncertainty factors



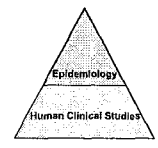
Strengths of Epidemiology Studies

- Species of interest for risk assessment purposes
- Studies humans exposed to "real world" particles in "real world" scenarios
  acute or chronic effects
- Can examine potentially susceptible populations
- End points are highly relevant
  mortality
  morbidity

Limitations of Epidemiology Studies

- Causality difficult to demonstrate
- Difficult to eliminate confounders
  (PM, O_3, NO_2, air toxics)
- Can be difficult to accurately measure exposure, especially personal exposure
- Outcomes usually limited
  Hard to examine biological plausibility, mechanisms
- Can be costly and time consuming

Strength of Controlled Human Exposure Studies



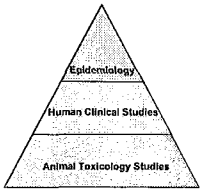
- Species of interest for risk assessment purposes
- Randomization of treatment (can establish causality)
- Control of exposure conditions (single, binary, mixtures)
- Susceptible populations can be studied
- Capability of making sophisticated, mildly invasive measurements in a laboratory setting
- Use of intervention agents (e.g. anti-inflammatory drugs)
- Can form a bridge/link to field studies and animal studies

Limitations of Controlled Human Exposure Studies

- Ethical issues limit agents to which humans can be exposed
  - No carcinogens
  - No agents that cause irreversible damage
- Ethical issues limit who can be exposed
- Small number of subjects studied
- Acute effects primarily studied
- Limitation on kinds of end points that can be used
- Costly to perform

Strengths of Animal Studies

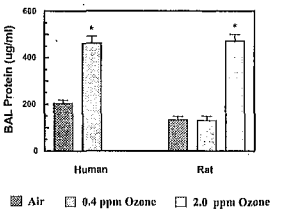
- Can use more invasive procedures
- Can study acute as well as chronic effects
- Can study susceptibility using genetic or other models
- Relatively inexpensive to perform compared with human studies



Limitations of Animal Studies

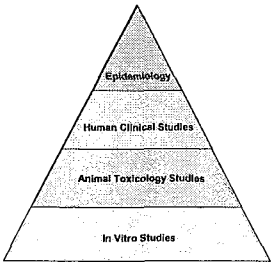
- Extrapolation to humans must be performed
  - short life span
  - diet, exercise, housing conditions
- Disease models may not mimic human susceptibility
- Many end points are not comparable to measurements made in humans

Rats Exposed to 2.0 ppm O_3 Have Similar Changes in BAL Protein as Humans Exposed to 0.4 ppm O_3



Strength of In Vitro Studies

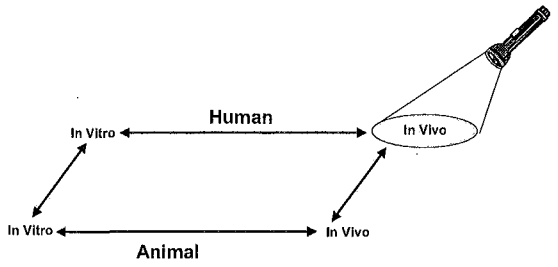
- Identification of underlying mechanisms by which air pollutants damage lung cells
- Rapid screening of complex mixtures to identify components responsible for causing adverse health effects



Limitation of In Vitro Studies

- Cells removed from their normal 3 dimensional environment.
  - Artificial environment
- No blood supply with potentially important factors.
- Exposure not likely the same as in vivo.
- Hard to measure functional changes in organ systems

Animal to Human Extrapolation



Early Controlled Human Exposure Studies

- **Amdur et al., 1953**
  sulfur dioxide inhalation up to 8 ppm caused dose dependent change in respiratory pattern
- **Frank et al., 1962**
  sulfur dioxide caused increased airway resistance
- **Young et al., 1964**
  ozone caused alterations in lung function in subjects exposed to 0.6 and 0.8 ppm while at rest
- **Bates et al., 1972**
  first study with intermittent exercise
  low concentrations of ozone caused alterations in lung function

Human Studies at EPA

- **There has been an active human studies program at EPA since 1973**
- **More than 5000 human volunteers have been studied with no adverse affects on any volunteer**
- **Human studies done at the EPA have played a key role in setting and modifying several standards**
  Ozone 1 hr & 8 hr standards

Pollutants That Have Been Studied By EPA Researchers:

- **Criteria Air Pollutants**
  Ozone, SO_2, NO_2, PM, Acid Aerosols
- **Water disinfection by-products**
  BDCM
- **Fuel additives**
  MTBE
- **Air Toxics**
  Toluene, Chlorine
- **Indoor Air**
  VOCs, Bioaerosols

Potentially Sensitive Subpopulations that Have Participated in EPA Clinical Studies

- **Asthmatics**
- **COPD**
- **Smokers**
- **Diabetics**
- **Metabolic Syndrome**
- **People with Angina**
- **Elderly**
- **Young**
- **Women**
- **Minorities**
- **Athletes**
- **"Responders"**

Organ Systems/Tissues That Have Been Studied In Humans

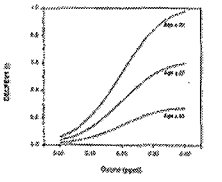
- **Breath**
  biomarkers of exposure
  biomarkers of affect
- **Skin**
  inflammation
  host defense
- **Blood**
  inflammation
  coagulation/clotting
  host defense
  immune function
  acute phase response
- **Urine**
  metabolites
  biomarkers/mediators
- **Respiratory Tract**
  physiology
  dosimetry
  inflammation/injury
  host defense
- **Brain/CNS**
  cognition
  behavior
  neurophysiology
- **Eyes**
  inflammation
  cell damage/irritation
  tear film stability
- **Heart**
  physiology

Measuring Pollutant-Induced Changes in Controlled Human Exposure Studies

- Cardiovascular Physiology
- Respiratory Physiology
- Cellular/Biochemical Changes in Respiratory Tract
- Pharmacokinetics
- Respiratory Tract Dosimetry
- Immune Status
- Neurobehavior Effects

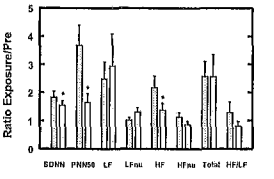
Physiological Measurements

Lung Physiology



Ozone causes reductions in lung function in healthy volunteers: Effects at different ages

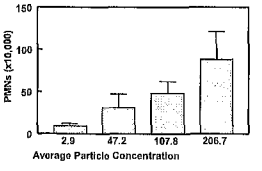
Cardiac Physiology



Exposure to PM causes decreased heart rate variability in healthy elderly volunteers

Cellular/Biochemical Changes In Respiratory Tract

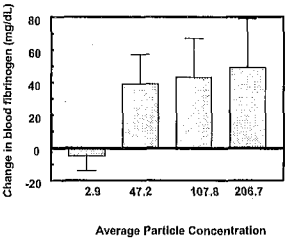
Volunteers are exposed to concentrated air pollution particles in the Chapel Hill air in a unique chamber.



Higher concentrations of particles induce more lung inflammation as measured by increased levels of PMNs.

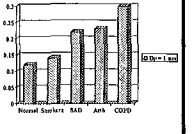
Vascular Changes

PM exposure causes a rise in blood fibrinogen

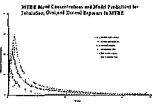


Pharmacokinetic and Dosimetry Research

Humans with lung disease have a greater uptake of particles than normal healthy humans.



Comparison of blood levels of MTBE following inhaled, oral, or dermal exposure.



Expectations for the Future

- Increased reliance on human data
- Susceptible populations
- "omics" technology is changing everything
  Biomarkers of exposure, effect, susceptibility

EPA's Goal for Protecting Human Health

The challenge is to make a convincing case that human studies done in a safe and ethical manner can play a key role in helping the EPA set standards that will protect the health of all Americans

Group 2 Presentation: Ozone Study—Being in a Clinical Study
Bob Devlin and Don Graff, ORD-NHEERL

Dr. Devlin began the presentation by asking a few questions such as: What is the benefit of doing HSR? Should EPA be conducting HSR? What benefit is there to EPA in doing HSR? With regard to EPA human exposure studies, he pointed out that each study has its own strengths and limitations. The strengths of epidemiology studies are in species of interest for risk assessment purposes, in studying humans exposed to "real world" particles in "real world" scenarios such as asbestos or tobacco smoke, in examining potentially susceptible populations, and in highly relevant endpoints. The limitations of epidemiology studies lie in that causality is difficult to demonstrate; confounders are difficult to eliminate such as PM, 0_3, NO_2, or air toxics; it can be difficult to measure exposure accurately such as indoor air exposure; biological plausibility or mechanisms may be hard to examine; and the studies can be costly and time consuming. The strength of controlled human exposure studies is in the species of interest for risk assessment purposes; randomization of treatment; control of exposure conditions (e.g., studying children requires a high threshold); studying susceptible populations; having the capability of making sophisticated, mildly invasive measurements in a laboratory setting; using intervention agents (e.g., anti-inflammatory drugs); and forming a bridge/link to field studies and animal studies. The limitations of controlled human exposure studies include the ethical issues that limit agents to which humans can be exposed (i.e., no carcinogens, no agents that cause irreversible damage); ethical issues that limit who can be exposed (e.g., children, elderly); small number of human subjects studies; acute effects being studied primarily; limitation on kinds of endpoints that can be used; and cost of human studies, as compared to animal studies.

Dr. Devlin discussed the strengths of animal studies, which include using more invasive procedures, studying acute as well as chronic effects, studying susceptibility using genetic or other models, and realizing much lower costs, as compared to human studies. The limitations of animal studies, however, includes performing extrapolation to humans, disease models not mimicking human susceptibility, and having many endpoints that are not comparable to measurements made in humans. *In vitro* studies are strong in the identification of underlying mechanisms by which air pollutants damage lung cells, and in the rapid screening of complex mixtures to identify components responsible for causing adverse health effects. The limitations of *in vitro* studies, however, is in the fact that cells are removed from their normal three-dimensional environment; there is no blood supply with potentially important factors; exposure is not likely the same as *in vivo*; and it is hard to measure functional changes in organ systems.

Dr. Devlin added that studies should be designed that include all exposures and results should be extrapolated from them (e.g., combining all studies on current ozone standards). He pointed out that there has been an active human studies program at EPA since 1973, and more than 200 different studies have been conducted. More than 5,000 human volunteers have been studied with no adverse effects. EPA researchers have studied pollutants such as criteria air pollutants (ozone, SO_2, NO_2, PM, acid aerosols); water disinfection by-products (BDCM); fuel additives (MTBE); air toxics (toluene, chlorine); and indoor air (VOCs, bioaerosols). Potentially sensitive subpopulations that have participated in EPA clinical studies include asthmatics; smokers; diabetics; those with COPD, metabolic syndrome, or angina; elderly; young; women; minorities; athletes; and "responders." In addition, human studies conducted at EPA have been a key factor

in setting and modifying several standards. In controlled human exposure studies, cardiovascular physiology, respiratory physiology, cellular/biochemical changes in the respiratory tract, pharmacokinetics, respiratory tract dosimetry, immune status, and neurobehavioral effects are measured for evidence of pollutant-induced changes. Expectations for the future include an increased reliance on human data, susceptible populations, and "omics" technology (e.g., biomarkers of exposure, effect, and susceptibility). EPA's challenge in protecting human health is to make a convincing case that human studies are conducted in a safe and ethical manner, which can then be a key factor in helping EPA set standards to protect human health.

Conducting a Controlled Human Exposure Study at EPA's Human Studies Division

Donald Graff
Human Studies Division
US Environmental Protection Agency

Protocol Preparation

Physiological Changes in Healthy Young Adults Exposed to Concentrated Chapel Hill Coarse Air Particles: the CRUSTY study

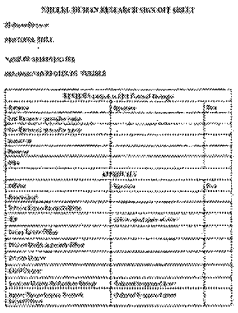
- **What is the research question?**
  Do coarse air particles cause adverse health effects?
- **Who needs the data?**
  EPA Office of Air and Radiation
- **Why is the data needed?**
  Support the PM NAAQS

Protocol Preparation

- **Protocol and Consent forms from the IRB of record**
- **Major sections of the protocol:**
  - Investigators and personnel
  - Purpose and rationale
  - Description of study design, methods, and procedures
  - Benefits to individuals or society
  - Sample size calculations and methods of data analysis
  - Confidentiality and data security
  - Compensation
- **Consent form**

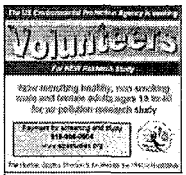
Protocol Review

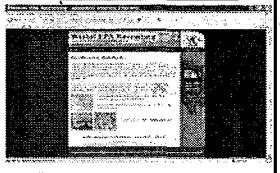
- **External review**
- **Internal review prior to IRB submission**
  - Branch Chief
  - Human Research Official
  - Informal division review
- **IRB review**
- **Internal review after IRB submission**
  - QA
  - Division Director
  - HRPO Director
  - ADH/E
  - HSRRO



Volunteer Recruitment: Westat

- **Focused advertisement placement depending on the needs of the study**
- **Some screening can occur over the phone to verify study qualifications**
- **Volunteers who pass the phone screening are scheduled to meet with the Westat recruiter for a more in-depth medical history screening**





Medical Screening

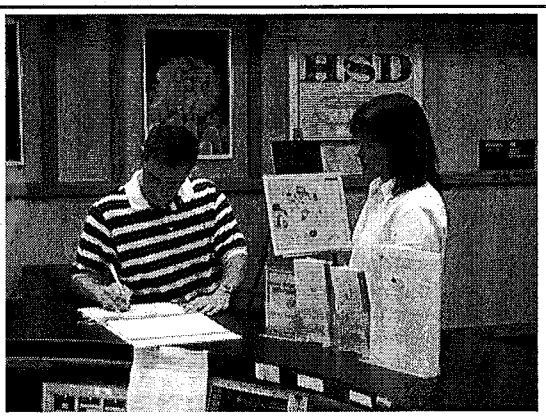
- **Medical station staff consists of 3 nurses and 9 EPA and UNC physicians**
- **Medical screening and physical exam**
  - Review of medical history information collected by Westat
  - Evaluates subject's health status for study involvement
  - Usually involves a physical assessment and blood-work
- **If the volunteer passes the physical exam Westat schedules training or study exposure visits**

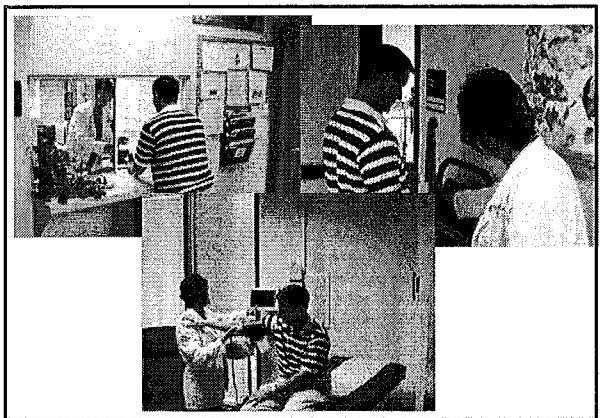
Informed Consent

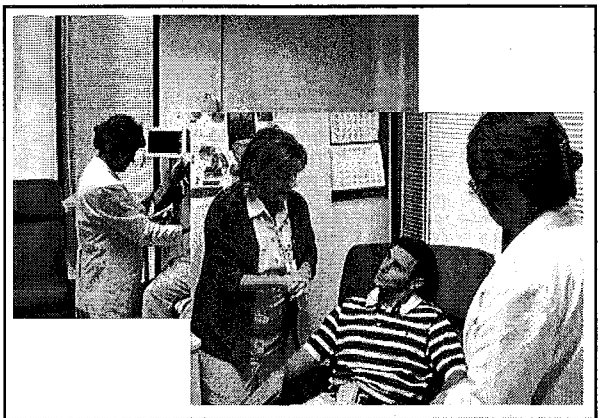
- **Major sections of consent form:**
  - Study purpose
  - Reasons volunteers should not participate
  - Step-by-step description of the volunteer's participation
  - Possible risks or discomforts
  - How privacy will be protected
  - What will happen if a study-related injury occurs
  - Questions regarding rights as a research subject
  - Compensation for participation
  - Sample storage

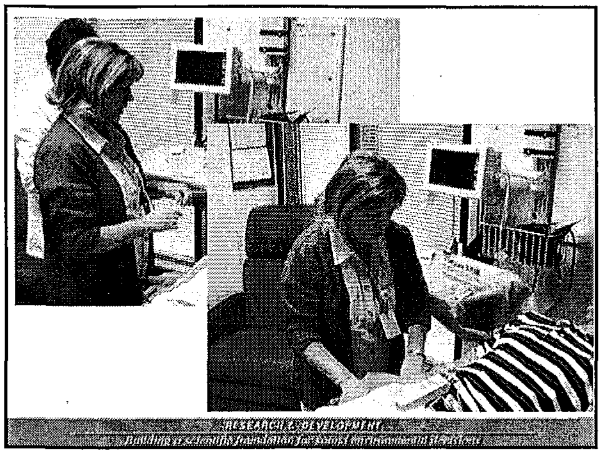
Informed Consent

- **Always written and explained in layman's terms**
- **Volunteer and investigator each sign two consent forms, one stays in the study file and one goes with the volunteer**
- **Always make it clear that participation is voluntary and the participant can withdraw from the study at any point**
- **Always inform the volunteer of new information gained from the study that might influence their willingness to continue to participate following enrollment**





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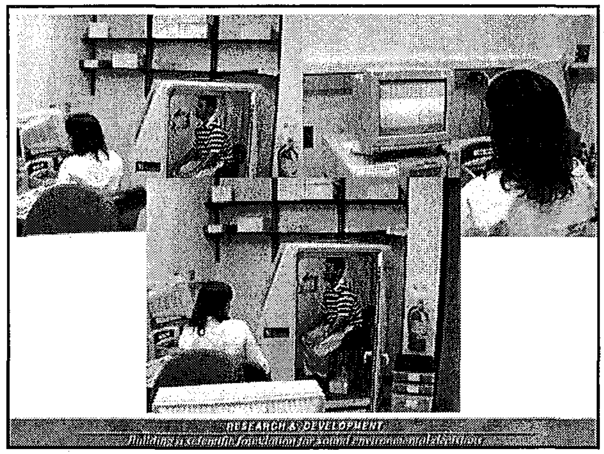
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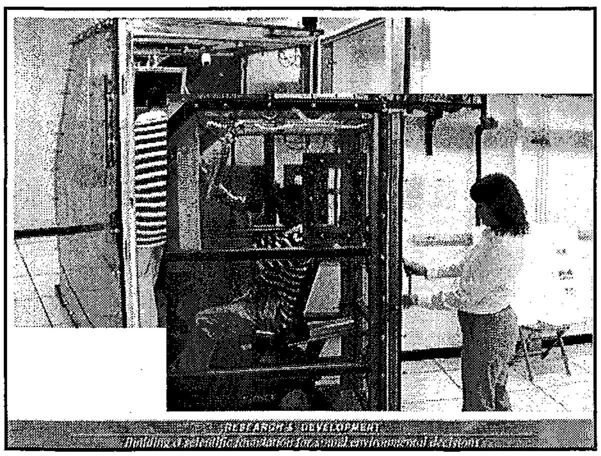
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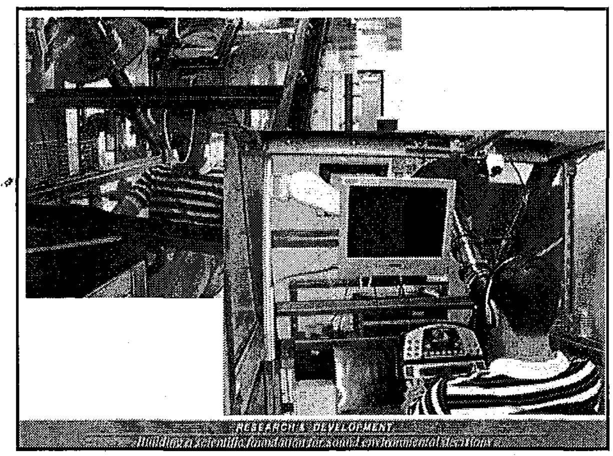
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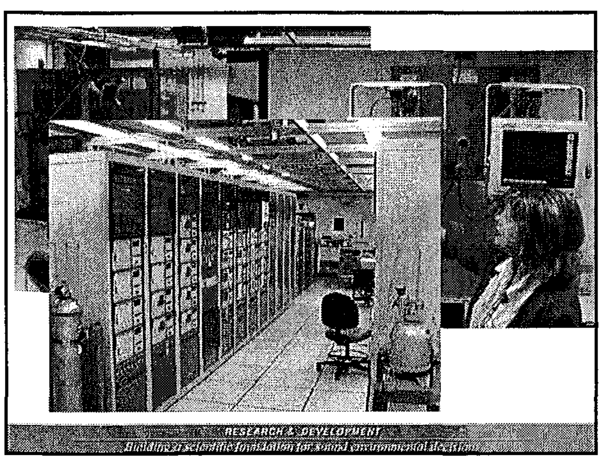
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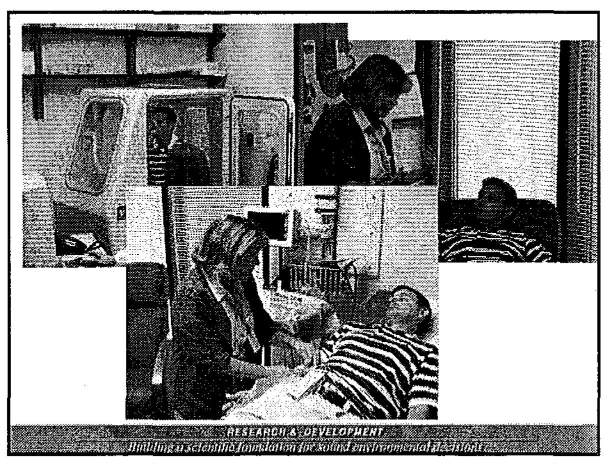
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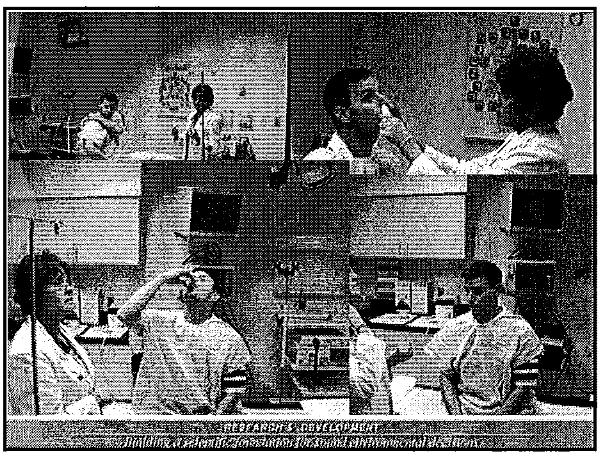
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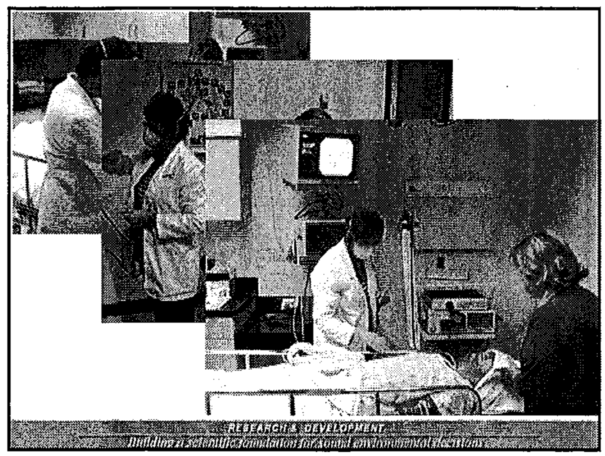
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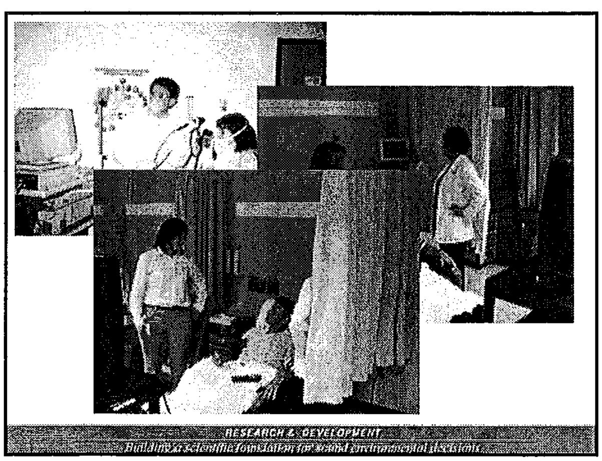
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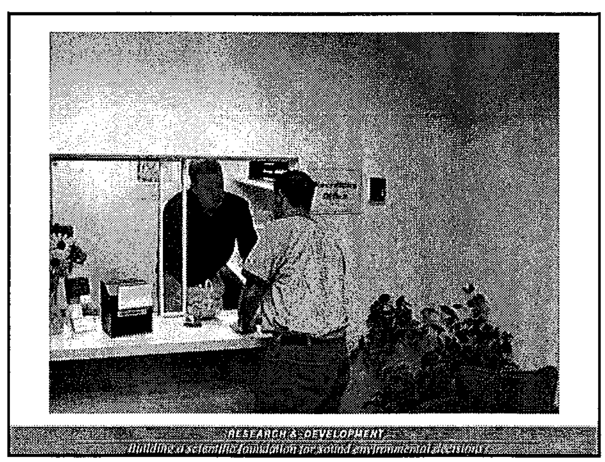
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A Day in the Life of a Typical CRUSTY Study Volunteer

- Present to the HSF at 8 am
- Medical assessment by the nursing staff
- Pre-exposure blood draw (typically about 80 mL)
- Placement of ECG electrodes for telemetry and holter monitor (heart rate variability, or HRV)
- 30 minute rest for pre-exposure HRV measurement
- Pre-exposure spirometry to assess lung function

A Day in the Life of a Typical CRUSTY Study Volunteer

- 2-hour particle or filtered air exposure with intermittent exercise
- Post-exposure spirometry, blood draw, and HRV
- Volunteers sent home for the night with the HRV monitor attached

A Day in the Life of a Typical CRUSTY Study Volunteer

- Volunteer returns to the HSF at 8 am the following morning
- 20-hr post-exposure blood draw, HRV, and spirometry
- Bronchoscopy procedure
- Post-bronchscopy recovery and observation
- Discharge the volunteer with payment and instructions for return if applicable

Dr. Graff discussed protocol preparation for conducting a controlled human exposure study at EPA's Human Studies Division. He offered three fundamental questions that should be answered: (1) What is the research question? (2) Who needs the data? (3) Why is the data needed? Protocol and consent forms from the IRB are needed. The major sections of the protocol should include the following: investigators and personnel; purpose and rationale; description of the study design, methods, and procedures; benefits to individuals or society; sample size calculations and methods of data analysis; confidentiality and data security, which is increasingly important under the HIPAA rules; and compensation. He added that the Human Studies Division has a standard set of payments and also tends to pay more as a greater number of entities are conducting these studies in Research Triangle Park. Dr. Graff stated that an external review, internal review prior to IRB submission, IRB review, and an internal review after IRB submission comprise a good protocol review. He then referred to a Westat recruiting contract that involved focused advertisement placement, which was dependent on the needs of the study. He indicated that some screening could occur through the telephone to verify study qualifications. Volunteers who passed the telephone screening were then scheduled to meet with the Westat recruiter for a more in-depth medical history screening.

With regard to informed consent, Dr. Graff stated that the consent forms should include a study purpose, reasons the volunteers should not participate, step-by-step description of the volunteer's participation, possible risks or discomforts, how privacy will be protected, what payment will be provided for participation, what will happen if a study-related injury occurs, questions about rights as a research subject, and how the samples collected will be stored. Consent forms should be written in layman's terms; both the volunteer and investigator should sign two consent forms (one for the study file and one that goes with the volunteer). It should be made clear that participation is voluntary and that the participant can withdraw from the study at any point. In addition, the volunteer should always be informed about new information gained from the study that might influence their willingness to continue to participate after enrollment.

Questions and Answers

An attendee asked how long it would be before cumulative exposures data would be made available. Dr. Devlin replied that ORD is preparing this, including regulations with regard to susceptible populations. Another attendee asked if there were any adverse events during the study. Dr. Devlin responded that there were no adverse events at the Human Studies Division in 30 years. It was learned that diabetics, however, were more susceptible to ozone, but there were no adverse effects among 5,000 volunteers. Another attendee inquired how many lives were saved from the new PM and ozone standards. Dr. Graff pointed out that 500,000 people are killed by particles world-wide, and 40,000 people are killed in car accidents alone in the United States. The public health benefits are compelling.

Protection of Human Subjects in EPA's Research and Non-Research Studies

September 28, 2005
Seattle, WA

The Power of Perception
A Broader View of Risk Communication

Alvin Chun
Director
Center for Risk Communication & Public Involvement
OSA, ORD, EPA, HQ
(415) 972-3720

Human Study Terms

- Human Studies
- Payment of Human Subjects
- Chemical Exposures Unknown
- Potentially High Exposures
- Low Income Subjects
- Potential Carcinogens
- Health Risks
- Confidentiality of Data

Translation into Plain Terms

• Govt Experiments	-	Human Studies
• Illegal Bribes	-	Payment of Human Subjects
• Scary	-	Chemical Exposures Unknown
• Death	-	Potentially High Exposures
• Helpless Victims	-	Low Income Subjects
• Horrific Deaths	-	Potential Carcinogens
• Dangerous	-	Health Risks
• Cover-Up	-	Confidentiality of Data

The "Story"

- There is an illegal top secret government experiment to kill innocent people.
- The government is covering up a mysterious and dangerous chemical that is causing cancer in people.

Outside Inquiries

- Why are you killing innocent people?
- Do you find that poor people are easier to trick and lure?
- This has the smell of a poorly planned conspiracy. We're getting different stories everytime we speak to your office. What else are you covering up?
- Why should we believe anything you say?
- You must be in the pocket of big business.
- Either you're lying or misleading people?

Some Answers

- We have no intentions of killing innocent poor people. You must be crazy!
- You can believe what you want but we have met all the regulations.
- All our studies have strong scientific justifications. I don't care what others have told you. We've gotten approvals from 3 IRB's as required by our regulations.

The New Story?

The Problems

- Studies and Good Intentions Aren't Always Viewed as Fact … But Perceptions Are
- We Can Create Perceptions Which Can Send the Wrong Message About Our Studies

Some Consequences

- (An organizational chart will be developed to illustrate how misperceptions can mobilize outside forces such as the media, advocacy groups and politicians to impact a study despite all the sound scientific and regulatory procedures that were followed.)

Some Solutions To Consider

- In addition to the science and regulatory requirements, think strategically about the potential perceptions and how they can influence outside parties.
- We work strategically with Management and Public Affairs to insure that a study is recognized as a solution to a problem.

Some Strategic Steps to Consider

- Get the word out about the problem and how the proposed study is trying to help
- Be open to outside concerns and address them before advancing the study
- Insure that people inside the Agency know the facts and where they can get them
- Appoint a point of contact to insure consistency

The Power of Perception: A Broader Perspective on Risk Communication
Alvin Chun, ORD, Office of the Administrator

Dr. Bruce Macler, Region 9, introduced Capt. Alvin Chun. Capt. Chun pointed out that throughout this workshop, he has been watching and listening to the attendees. His perception of the group was that attendees were careful, caring, very articulate, and honest people. It was clear that much work went into organizing the workshop. He asked everyone to think about the workshop title, "Human Studies by EPA" and commented that the public would perceive this wording to be a negative thing. The public's perception of the federal government, especially of EPA, is generally negative. Those in government are often perceived as bureaucratic, lazy, secretive, and wasteful. The title was reworked to "Protection of Human Subjects in EPA's Research and Non-Research Studies" because of fear that someone out in the public would find out about this workshop. He added that there is a misperception between the public, EPA, and other attendees. He discussed how human study terms could be translated into plain terms. For example, the term "human studies" can be translated as government experiments. "Payment of human subjects" can be translated as illegal bribes; "chemical exposures unknown" as scary; "potentially high exposures" as death; and so on. The "story" then becomes that there is an illegal top secret government experiment to kill innocent people, and that the government is covering up a mysterious and dangerous chemical that is causing cancer in people. He showed how interpretations such as these give wrongful and inaccurate perceptions of human studies. As a result, there are a lot of questions that arise such as: Why are you killing innocent people? Do you find that poor people are easier to trick and lure to these studies? What else are you covering up? Why should we believe anything you say? Some of the answers then are that "we have no intentions of killing innocent poor people"; "you can believe what you want, but we have met all the regulations"; "all of our studies have strong scientific justifications, and we've gotten approvals from three IRB's as required by our regulations." Although studies and good intentions are not always viewed as fact, perceptions are viewed as such.

Capt. Chun added that perceptions could be created that send the wrong message about the studies. Some of the solutions that can be considered in averting this would be to think strategically about the potential perceptions and how they can influence outside parties. Also, working strategically with management and public affairs can help to ensure that a study is recognized as a solution to a problem. Strategic steps could include: getting the word out about the problem and how the proposed study is trying to help; being open to outside concerns and addressing them before advancing the study; ensuring that people inside the Agency know the facts and where they can get them; and appointing a point of contact to ensure consistency. He advised everyone on being aware of the power of perception in the things they do and in the things they write. Human studies are hard to define. Empathy and openness are important to the public when communicating on this topic. In addition, it would be a good idea to let people know of a problem early on so as to earn their trust. Capt. Chun suggested the development of a brochure to explain human studies.

Questions and Answers

A suggestion was made for more information to be disseminated to soften the public's perception of EPA. A question was asked on how to motivate people to get a more positive reaction. Capt.

Chun suggested creating doubt about a current situation, which would be dependent on establishing trust. An attendee asked what to do if the information still is not accepted. EPA has to listen to what the public is saying. The human subjects issue goes to the heart of the public's values. If the public hears that something is negative on the television, then they will believe it no matter what EPA says about it. Capt. Chun suggested establishing good relationships, acknowledging peoples' concerns, being open with the facts, and negotiating with the public if their values are different. A comment was made that, from a scientific viewpoint, it is hard to share the facts with the public. Another attendee asked what could be done to change the perceptions within EPA. Capt. Chun observed that most people experience many disruptions during the day and are distracted with other tasks, which makes it harder to focus on changing perceptions. Staff in the Regions, however, have more control of their time, so they might be capable of promoting change.

Day Four

Additional Safeguards for Vulnerable Subjects

September 29, 2005

David Forster
Western Institutional Review Board

Vulnerable Subjects – Definition

"Vulnerable" was not the best word choice for use in the 1981 NIH and FDA regulations

Webster's –

1. Capable of being physically wounded
2. Open to attack or damage

Vulnerable Subjects – Historical Use of Term

- "The special considerations that should be given to children and infants are, first, that they are particularly vulnerable and helpless and therefore call for more consideration than other groups."
- Human Guinea Pigs, M.H. Pappworth, 1967.

Vulnerable Subjects – Historical Use of Concept

- Dr. Robert Marston, in a speech at University of Virginia on November 10, 1972, addressed the concept of individuals with "limited civil freedom," and called for better protections for them.
- This included "prisoners, residents of institutions for the mentally retarded and mentally ill, and minors."
- Hastings Center Report 3(2): 1-4, Apr 1973.

Vulnerable Subjects – Historical Use of Term

"Vulnerable" is not used in:

- The Nuremberg Code,
- The Declaration of Helsinki (until 2000 version),
- 1974 NIH regulations on subject protection, or
- The Belmont Report.

- Used in the 1981 NIH and FDA regulations.

Vulnerable Subjects – The Belmont Report

The Belmont Report addressed the concept of vulnerability as part of the principle of Respect for Persons:

"Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection."

Belmont Report quote

- "Not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated."

Elements of Autonomy

Capacity

Voluntariness

Freedom from the control or influence of others.

Vulnerable Subjects

(Have Actual or Potential Limitations on Autonomy)

Lack of Capacity
- Children
- Mentally Disabled
- Temporary
- Fluctuating

Limits on Voluntariness
(potential for control, coercion, undue influence, or manipulation)
- Fatal or Incurable Disease
- Emergency Situations
- Hierarchical Social Structure
- Economically Disadvantaged
- Educationally Disadvantaged
- Marginalized Social Groups

Definitions

- Control - Physical restraints.
- Coercion - Use of a credible threat of harm or force to control another.
- Undue Influence - Misuse of a position of confidence or power to lead another to make a decision he would not otherwise have made.
- Manipulation - Deliberate management of conditions or information in such a way as to lead another to make a decision he would not otherwise have made. Examples of information manipulation include lying, withholding information, and exaggeration.

Constant Considerations about Vulnerability

- Within any population of vulnerable subjects, individuals will have different levels of vulnerability.
- The level of vulnerability of an individual may change due to changes in capacity or in conditions affecting voluntariness.
- The IRB considers a hypothetical group of subjects, whereas the investigator interacts with actual subjects.

HHS Regulation 45 CFR 46.111(b) - Definition of Vulnerable Subjects

"When some or all of the subjects, such as children, prisoners, pregnant women, handicapped or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence [,] additional safeguards have been included in the study to protect the rights and welfare of these subjects."

ICH 1.61 - Definition of Vulnerable Subjects

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate.

ICH 1.61 - Definition of Vulnerable Subjects (cont.)

Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention.

ICH 1.61 - Definition of Vulnerable Subjects (cont.)

Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

Children

- Wide range of capacity depending on age.
- Potential for control, coercion, undue influence, or manipulation by parents, guardians, or investigator.
- Are automatically vulnerable by regulation.

Embryos and Fetuses

- Absolutely no capacity.
- Complete control by mother.
- Pregnant women and fetuses are automatically vulnerable by regulation.

Mentally Disabled

- Problems with capacity, continuous or fluctuating.
- Often institutionalized or hospitalized.
- Often economically disadvantaged.
- Often educationally disadvantaged.
- Often have limited access to medical care.
- Potential for control, coercion, undue influence, or manipulation.
- Many suffer from incurable diseases.

Emergency Situations

- Possible problems with capacity.
- Potential for control, coercion, undue influence, or manipulation.
- Limits on voluntariness due to time constraints.
- Institutional setting.

Hierarchical Social Structure

- Potential for control, coercion, undue influence, or manipulation.
- Examples include: Prisoners, military personnel, employees, students, hospitalized patients, and residents of nursing homes and other medical institutions.
- Prisoners are automatically vulnerable by regulation.

Educationally Disadvantaged

- May have limitations on understanding.
- May be illiterate.
- Potential for undue influence or manipulation.

Economically Disadvantaged

- May enroll in research in order to receive treatment.
- May enroll in research solely for compensation (for example, Phase I drug studies).
- Often educationally disadvantaged in addition.
- Potential for undue influence or manipulation.

Marginalized Social Groups

- Have little social power.
- Often not granted full access to social institutions, such as the legal system.
- Potential for control, coercion, undue influence, or manipulation.
- Many possible sources - disease, race, poverty, etc.

Individuals with Fatal Disease

- May take very high risks in desperation for cure.
- Potential for undue influence or manipulation.
- May be problems with capacity, permanent or temporary, caused by disease or drugs.
- Vulnerability magnified in dying subjects.

Individuals with Incurable Disease

- May take very high risks in desperation for cure.
- Potential for undue influence or manipulation.
- May be problems with capacity, permanent or temporary, caused by disease or drugs.

What are additional safeguards for vulnerable subjects?

- Regulations – "When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects." 46.111(b)

What are additional safeguards for vulnerable subjects?

- The subpart A regulations do not provide a definition.
- However, subparts B, C, and D do provide examples.
- Congress tasked the National Commission with writing reports on research with pregnant women, prisoners, children, and the institutionalized mentally disabled.
- The first three reports are the basis for subparts B, C, and D of the NIH regulations (45 CFR 46).

21 CFR 50/45 CFR 46 - Subpart D

§50.51/46.404 Clinical Investigations not involving greater than minimal risk.

Any clinical investigation . . . in which no greater than minimal risk to children is presented may involve children as subjects only if the IRB finds and documents that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians as set forth in §50.55/§46.408.

21 CFR 50/45 CFR 46 - Subpart D

- **Additional Protections for Children Involved as Subjects in Research**
- Source: 48 FR 9818, March 8, 1983, unless otherwise noted.

21 CFR 50/45 CFR 46 - Subpart D

§50.52 /46.404 Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.

Any clinical investigation . . . in which more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, may involve children as subjects only if the IRB finds and documents that:

21 CFR 50/45 CFR 46 - Subpart D

(a) the risk is justified by the anticipated benefit to the subjects;

(b) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

(c) adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in 50.55.

21 CFR 50/45 CFR 46 - Subpart D

§50.53/46.404 Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

Any clinical investigation . . . in which more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is not likely to contribute to the well-being of the subject, may involve children as subjects only if the IRB finds and documents that:

21 CFR 50/45 CFR 46 - Subpart D

(a) the risk represents a minor increase over minimal risk;

(b) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

(c) the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(d) adequate provisions are made for soliciting assent of the children and permission of their parents or guardians as set forth in 50.55/46.408.

21 CFR 50/45 CFR 46 - Subpart D

§50.54/46.407 Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

If an IRB does not believe that a clinical investigation . . . involving children meets the requirements of §50.51, §50.52, or §50.53, the clinical investigation may proceed only if:

(a) The IRB finds that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

21 CFR 50/45 CFR 46 - Subpart D

(b) The Commissioner of Food and Drugs, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:

(1) that the research in fact satisfies the conditions of §50.51, §50.52, or §50.53, as applicable, or

(2) that the following conditions are met:

21 CFR 50/45 CFR 46 - Subpart D

(i) The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) The clinical investigation will be conducted in accordance with sound ethical principles; and

(iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in 50.55.

21 CFR 50/45 CFR 46 - Subpart D

- **50.55/46.408 Requirements for permission by parents or guardians and for assent by children.**

21 CFR 50/45 CFR 46 - Subpart D

- 50.56/46.409 Wards.

(a) Children who are wards of the state or any other agency, institution, or entity can be included in research approved under §46.406 or §46.407 only if such research is:

(1) Related to their status as wards; or

(2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

21 CFR 50/45 CFR 46 - Subpart D

(b) If the research is approved under paragraph (a) of this section, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis.

45 CFR 46 - Subpart B

Additional Protections for Pregnant Women, Human Fetuses, and Neonates Involved in Research

(Revised November 13, 2001, FR 56775)

45 CFR 46 - Subpart B

- Pregnant women or fetuses may be involved in research if all of the following conditions are met:

(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

45 CFR 46 - Subpart B

(b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

45 CFR 46 - Subpart B

(h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

(i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

(j) Individuals engaged in the research will have no part in determining the viability of a neonate.

45 CFR 46 - Subpart C

Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

45 CFR 46 - Subpart C

- §46.302 Purpose.
- Inasmuch as prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research, it is the purpose of this subpart to provide additional safeguards for the protection of prisoners involved in activities to which this subpart is applicable.

45 CFR 46 - Subpart C

- §46.304 Composition of Institutional Review Boards where prisoners are involved.

(a) A majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board.

(b) At least one member of the Board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity.

45 CFR 46 - Subpart C

- §46.305 Additional duties of the Institutional Review Boards where prisoners are involved.

(a) In addition to all other responsibilities prescribed for Institutional Review Boards under this part, the Board shall review research covered by this subpart and approve such research only if it finds that:

(1) The research under review represents one of the categories of research permissible under §46.306(a)(2);

45 CFR 46 - Subpart C

(2) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;

45 CFR 46 - Subpart C

(3) The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;

(4) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners.

Conclusion

- The use of additional safeguards provide extra protections for vulnerable subjects.
- They serve a paternalistic function, and administratively limit the choices open to subjects, investigators, IRBs, and agencies.
- in other words, they cut off some of the possible branches of choice in a decision-making tree.

Thursday, September 29, 2005 (Day Four)

AM Moderators: Alicia Alto and Suzanne Wuerthele

Special Protections for Children, Fetus, Elderly, Lower Socioeconomic Groups, English as a Second Language Groups

David Forster, Western IRB and University of Washington

Mr. Forster began his presentation with identifying that the Western IRB was a "for-profit" agency, with 80 percent of the board members not on staff. The Western IRB has completed many reviews for other institutions (e.g., Johns Hopkins University), and the reviews were primarily for medical research. In addition, there are approximately 20-30 private IRBs (out of a total of 4,000) in comparison to university IRBs. Mr. Forster expressed that in referring to vulnerable subjects, the term "vulnerable" was not the best choice of word to use in the 1981 NIH and FDA regulations. In the historical use of the term "vulnerable subjects," it meant that children and infants are particularly vulnerable and need more consideration than other groups. Vulnerable subjects also can be regarded as human guinea pigs (M.H. Pappworth, *Human Guinea Pigs*, 1967). In a speech at the University of Virginia in 1972, Dr. Robert Marston addressed the concept of individuals with "limited civil freedom" and called for better protection of them. This included prisoners, residents of institutions for the mentally retarded and mentally ill, and minors (see *Hastings Center Report* 1973;3(2):1-4). The term "vulnerable" is not used in the Nuremberg Code, Declaration of Helsinki, 1974 NIH regulations on subject protection, or the *Belmont Report*. It was used, however, in the 1981 NIH and FDA regulations. Mr. Forster added that the *Belmont Report* addressed the concept of vulnerability as part of the principle of Respect of Persons: "Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection." Vulnerable subjects have actual or potential limitations on autonomy. Those that lack capacity are children and the mentally disabled. Limits on voluntariness include a fatal or incurable disease, emergency situations, hierarchical social structure, economically disadvantaged, educationally disadvantaged, and marginalized social groups.

Mr. Forster stated that there are constant considerations about vulnerability, and individuals will have different levels of vulnerability. The level of vulnerability of an individual may change because of changes in capacity or in conditions affecting voluntariness. The IRB considers a hypothetical group of subjects, whereas the investigator interacts with the actual subjects. The definition of vulnerable subjects according to DHHS Regulation 45CFR 46.111(b) states that "when some or all of the subjects, such as children, prisoners, pregnant women, handicapped or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of these subjects." As an additional safeguard for vulnerable subjects, Congress has asked that reports be written on the impacts of research with pregnant women, prisoners, children, and the institutionalized mentally disabled. Also, clinical investigations cannot involve more than minimal risk to vulnerable subjects, and only if the IRB finds and documents that adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as listed in 21CFR50 and 45CFR46, Subpart D.

Those studies that involve greater than minimal risk and no direct benefit to individual subjects, but are likely to provide generalizable knowledge about the subject's disorder or condition, can be conducted only if the IRB finds and documents that the risk is a minor increase over minimal risk, and the intervention or procedure involves experiences that are commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations. Children who are wards of the state or any other agency, institution, or entity can be included in research approved under CFR 46.406 or 46.607 if the research is related to their status as wards or if conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards. The regulation also states that the IRB will require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or *in loco parentis*. Pregnant women or fetuses may be involved in research if "preclinical studies, including those on pregnant animals, and clinical studies, including those on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses." No inducements, monetary or otherwise, will be offered to terminate a pregnancy and those engaged in the research will have no part in determining the viability of a neonate. In the case of prisoners as vulnerable subjects, 45CFR46 Subpart C states that additional safeguards should be taken for the protection of prisoners involved in research activities. The use of additional safeguards must provide extra protections for vulnerable subjects and serve to limit the choices open to subjects, investigators, IRBs, and agencies.

Questions and Answers

A question was asked whether there was a national IRB group. Mr. Forster replied that ARENA is a national group that holds meetings at which larger IRBs attend. The smaller IRBs, he added, do not attend because they do not have enough funds to send people to these meetings. In general, the IRBs think that there should be more regional IRBs; however, during the past 5 years, there has been more talk about national IRBs or central IRBs. Another question was asked about the financial outlook for the Western IRB and other "for-profit" IRBs. Mr. Forster responded that the for-profit IRBs charge on a fee-for-service basis. When some institutions began closing, these IRBs were facing a more serious problem, but the situation has been improving. The problem now is teasing out the costs of an IRB. With regard to informed consent, an attendee asked if there was any reason not to provide information when conducting research. Mr. Forster stated that the informed consent process should be followed closely and that people should be told all the information they need to make an informed decision. He pointed out that it is standard practice to use deception, and that at times many ethical issues arise. A question was asked regarding how the Common Rule, 40CFR46 (EPA counterpart), the *Belmont Report*, and other documents or reports fit together. Mr. Forster pointed out that these items are Part A of the NIH regulations, which is comprised of pieces added by various agencies. Another question was asked about whether the FDA screens the ethics of the research studies. Mr. Forster added that the FDA is now thinking about eliminating the Helsinki regulations and adopting more ethical considerations. A comment was made regarding the fact that EPA has not adopted all of the subparts of the NIH regulations, but that hopefully, Dr. Preuss would affect some change in this respect. Another comment was added that EPA Regions might be conducting research that may involve human subjects but not what would be considered HSR. It is important to distinguish between HSR and public health practice. Mr. Forster added that it is a

difficult distinction to make but should be made with the help of an IRB. A question was asked if an accreditation process was starting to take place for IRBs. Mr. Forster replied that the accreditation process began about 3 years ago, but it was an expensive process. Eventually, he added, all IRBs will be accredited.

Overview of the Proposed Third Party Rule
Anne Lindsay, EPA Office of Pesticides Programs

Dr. Wuerthele introduced Ms. Lindsay, Deputy Director of the Office of Pesticides Programs (OPP). Ms. Lindsay pointed out that she spent her entire EPA career in the pesticides program; she is a policy person, not a researcher or scientist. She stated that OPP makes decisions about whether pesticides should enter, remain, or be removed from the market. OPP does not commission research and essentially is not a scientific research organization. She added that in the future, however, opportunities might exist to collaborate and develop better ways of doing things. OPP is involved in conducting third-party studies. She discussed some of the key elements of a new proposed rule published in the *Federal Register* on September 12 that provides the strongest protections for human subjects proposed by the federal government, including a categorical ban on any new testing of pesticides that involves intentional dosing of pregnant women or children. She referred participants to the following Web site for the full proposal and related materials: http://www.epa.gov/oppfead1/guidance/human-test.htm. Ms. Lindsay described some of the many types of HSR activities with pesticides. She explained that many human studies involve collecting data on people who are exposed to pesticides in their daily activities (e.g., pesticides loaders and applicators). Approximately 22 third-party toxicity studies that cover about 14 different pesticides have been submitted to EPA. These studies were submitted between 1967 and 2004, the majority of which were generated between 1996 and 2004. Nineteen of the studies were intended to identify or quantify the toxic effects of a pesticide. These studies do not involve intentional exposure. Other examples of human studies that do not involve intentional exposure include epidemiologic studies, analyses of accidents or incidents, and monitoring and observational studies. There are, however, many types of intentional dosing studies such as studies to test the effectiveness of mosquito repellents. Dermal absorption studies can involve a small amount of chemical being placed on the skin of a human volunteer and researchers determining how much of the chemical is absorbed and how quickly it infiltrates the individual's blood, urine, or excrement. This type of absorption study can be very important in assessing a pesticide's risk in an occupational setting. In addition, there are intentional dosing studies to identify or measure toxic effects in humans in which volunteers receive small but increasing doses of a chemical to ascertain the dose that causes a threshold adverse reaction. She added that the majority of human studies on pesticides received by OPP come from observational studies of exposure; most of these studies do not involve intentional dosing or exposure but rather collect data from subjects engaged in normal daily activities.

Ms. Lindsay provided an overview of the Common Rule and EPA's codification at 40CFR26. She defined first-, second-, and third-party research. She explained that HSR conducted by a federal Common Rule agency is "first-party" research. Research conducted by others with the support of a federal Common Rule agency is "second-party" research. Research conducted by others with no support from any federal Common Rule agency is considered "third-party" research. EPA's Common Rule applies to all of EPA's first- and second-party research. EPA's proposed rule would extend the Common Rule to certain regulated third-party research. EPA's proposed regulation is to protect the welfare of human research participants by setting rigorous standards to guide how new human research is performed and by defining criteria to judge the acceptability of the results once such research is completed. Human subjects must be treated ethically and be fully informed of potential risks. The main focus of EPA's proposed new

regulation is intentional dosing human studies for pesticides conducted by private researchers without federal government support (i.e., by third parties).

Ms. Lindsay summarized the substance of EPA's proposed rule. She indicated that the regulation would establish stringent and enforceable standards for ethical conduct of research involving intentional dosing of humans with pesticides. The proposal, she added, is based on the 2004 report of the National Academy of Sciences (NAS) and contains even more protective measures than those recommended by the NAS and goes beyond the requirements of EPA's FY06 Appropriations Act. The proposed rule, which was signed by the President of the United States on August 2, 2005, prohibits conducting new third-party intentional dosing studies on pregnant women or children under current pesticide laws. This rule is consistent with the Appropriations Act forbidding the use of pregnant women, infants, or children as subjects and applies to all intentional dosing studies, not just toxicity studies, and to all substances, not just pesticides. The proposed rule makes no exceptions, either for EPA or for regulated third parties. In addition, the proposed rule also forbids EPA from relying on studies that involve intentional dosing of pregnant women or children in its pesticide decision-making, whether they are based on the results from new or old intentional dosing studies. By extending the Common Rule to third parties who conduct intentional dosing studies intended for submission to EPA, people who volunteer for third-party intentional dosing pesticide studies will be treated ethically, potential risks will be fully disclosed to them, and every effort will be made to minimize any additional risks.

Ms. Lindsay pointed out that although third-party intentional dosing HSR studies with pesticides currently are not required to undergo any external review, EPA is proposing to establish an HSRB to review study protocols before the research is conducted and the reports after the research have been completed. Every new intentional dosing study for a pesticide will undergo ethical review by a local IRB and then by EPA staff and the HSRB. Recommendations from all three groups regarding the scientific and ethical aspects of the proposed research will be provided to investigators before a study begins. The 90-day comment period on the proposed rule, as required by the Appropriations Act, will end in early December. A final rule is due within 180 days of enactment, which will be the end of January. OPP has begun discontinuing reliance on third-party intentional dosing human toxicity studies. OPP would like the proposed rule to be approved by February 2006. She emphasized the value of public input.

Questions and Answers

A comment was made that the OPP program was very rigorous in its review of human studies data. The question was asked whether human studies would follow the same standards as animal studies. Ms. Lindsay replied that human studies are performed incorporating the highest scientific standards; otherwise, they would not be ethical to conduct. She added that the early critics of the proposed rule view this as a loophole that would encourage people to violate the standards in the Rule. She did not think that decisionmakers in the Agency would want to be in a position where they knew that there was a piece of reliable data showing a need for better protective regulatory action but that it was forbidden to use it according to the Rule. Some think this is wrong. Another question arose regarding whether OPP receives data from pregnant women and children non-intentional dosing studies. Ms. Lindsay could not recall ever receiving

such a study. One comment being considered in the proposed Rule is whether the coverage should be broadened to include non-intentional dosing studies. There are related ethical questions that probably should be included in the Rule. Another question was asked whether the pesticides data and human studies data are readily available. Ms. Lindsay stated that the best pesticides data are available and that most or all of the human studies data can be made available through a FOIA request. A question was asked regarding the fate of data collected on pregnant women and if such a study would be regarded as unethical. Ms. Lindsay replied that the study would have to go through the HSRB and would need large public input to decide how the data should be used. An attendee asked whether a categorical ban would be placed on such a study. Ms. Lindsay indicated that a categorical ban would be placed on the conduct of data use only, not on the study. A question was asked whether there were any plans to address classification of a harmful substance. Ms. Lindsay replied that the Agency needs to hold more discussions on this topic. Additionally, she stated that the struggle would be to find an effective way to use the proposed Rule.

Where To Go for Help—Overview
Jean Zodrow, EPA Region 10

Dr. Lorenzana referred the attendees to the List of Resources in Appendix A. Other materials are available on QuickPlace. She added that there definitely would be follow up after this meeting. She then referred to the next presentation, which would be given by the four discussion leaders on their group's recommendations. She added that for those involved in the planning group, there would be a conference call meeting in 2 weeks. At that time, the first priority would be to review the recommendations and decide how to consolidate the recommendations.

Draft Recommendations and Proposed Next Steps

The following recommendations were compiled by attendees at the end of the workshop:

- Create a culture where the protection of human subjects in EPA-conducted or -funded studies (whether the studies are HSR or public health practice) is the number one priority.

- Increase management's focus/attention on HSR by: (1) having workshop participants brief their DRAs, (2) inviting Peter Preuss to brief DRAs and RAs on HSR requirements, (3) identifying HSR on SCOUT, and (4) developing a briefing strategy for upper management.

- Develop and implement interim guidance and policy for Regions as national efforts evolve.

- Identify a Human Subjects Officer and associated advisory board in each Region.

- Have the Regional Human Subjects Officer make the final regional determination as to whether a study is HSR or public health practice. Dr. Roger Cortesi (ORD/NCER) and Dr. Rick Hermann (ORD/NHEERL-Human Research Protocol Office Director) are available for consultation.

- Create a National Human Subjects Officer Council led by a Agency Human Subjects Research Review Official that is composed of Human Subjects Officers from each Region and National Program Offices to maintain consistency and communication across the Agency and to inform with new developments on HSR; develop national guidance and policy for HSR; identify additional tracking needs for the existing system that includes query capability; and develop an Agency-wide human subjects training plan and program.

- Make changes to IGMS to reflect the HSR determination and approval process, including: (1) enhancing awareness of HSR and its requirements relevant to the EPA Grants Program by coordinating with the 12 Regional Grants Management Officers; (2) reconciling grant funding timelines with the HSR approval process and making potential grantees aware of IRB review comments prior to funding approval; (3) defining HSR and public health practice on grant solicitation (perhaps in consultation with NCER) and request the grantee to meet specific requirements if the study is HSR; (4) incorporating HSR training for all Project Officers; (5) creating a tracking system for grants that are either HSR or public health

practice; (6) considering provisional grant awards prior to HSR approval; and (7) modifying Question 14 in IGMS that asks whether human subjects are involved to include a corollary question as to whether the study is HSR. If the answer to that question is "yes", require approval by the Agency's Human Subjects Research Review Official (Peter Preuss). If "no" to research, require attachment of the regional decision memo.

- Create a tracking system that is accessible to the Regions on the progress of decisions with respect to the status of a study within the Human Subjects Research Review Official's review process.

- Develop Agency written guidance, Web site, and list of references and subject experts for public input and comment in the *Federal Register*.

- Develop a straw proposal for the new Human Subjects Research Review Official generated by the workshop and finalized by the workshop planning group.

- Suggest that EPA create its own IRB, which would be accredited and consist of members who are not EPA employees or persons from the regulated community. Also, possibly suggest that IRBs used by the Agency be accredited.

- Identify and publicize consequences for noncompliance of EPA Order 1000.17, change 1A, (40CFR Part 26) Policies and Procedures for the Protection of Human Subjects in Research Conducted or Supported by EPA.

- Review and provide comments on the Proposed Rule for Third Party Studies as these comments could influence workshop recommendations.

- Ensure regional participation on the future workgroup that will be determining specifics involved with implementing the recommendation provided within the Proposed Rule for Third Party Studies for the creation of a Human Subjects Review Board.

- Set up a conference call with Lee Tyner (OGC) to address legal concerns and questions that were developed by the workshop planning group.

- Have workshop co-leads Patti Tyler and Roseanne Lorenzana develop a workshop recommendation package.

Ms. Tyler and Dr. Lorenzana agreed to follow up with the recommendations made as a result of this workshop and adjourned the meeting. Dr. Lorenzana asked attendees to contact her via e-mail if they had more questions after the workshop.

Appendix A

List of Resources

Protection of Human Subjects in EPA's Research and Non-Research Studies

LIST OF RESOURCES

Pre-Meeting Materials Available on Quickplace and OSP Intranet:

1. Code of Federal Regulations, TITLE 45 PUBLIC WELFARE DEPARTMENT OF HEALTH AND HUMAN SERVICES PART 46 PROTECTION OF HUMAN SUBJECTS (Note: Focus on Subpart A since this is the text of the "Common Rule," which EPA adopted as 40 CFR 26)
2. EPA Order 1000.17, Change A1, POLICY AND PROCEDURES ON PROTECTION OF HUMAN RESEARCH SUBJECTS IN EPA CONDUCTED OR SUPPORTED RESEARCH
3. HSR Activities Exempt From IRB Review 40 CFR 26.101(b)(1)-(6)
4. Both seminar slide presentations (Peter Preuss and Rick Hermann/Rebecca Calderon)
5. NHEERL Human Research Policy
6. NHEERL Human Research Guidance, July 2005
7. NERL - Policy and Procedures Guidance for Obtaining Approval of NERL Studies Involving Human Subjects, Human Material, or Human Data
8. Public Health Practice vs. Research: A Report for Public Health Practitioners Including Cases and Guidance for Making Distinctions (Johns Hopkins, May 2004). (www.epa.gov/oppfead1/guidance/human-test.htm)
9. Guidelines for Defining Public Health Research and Public Health Non-Research (CDC Document)
10. Federal Register Notice - Advanced Notice of Proposed Rulemaking on 3rd Party Intentional Dosing Studies
11. CDC-ATSDR Protection of Human Subject Procedures
12. NAS Report: Intentional Human Dosing Studies for Regulatory Purposes, Scientific and Ethical Issues (VERY LONG DOCUMENT) (http://books.nap.edu/catalog/10927.html)
13. The Belmont Report (http://ohsr.od.nih.gov/guidelines/belmont.html)
14. Pesticide Testing on Human Subjects: Weighing Benefits and Risks. *Environmental Health Perspectives*, V. 113(7), pp.813-817, 2005.
15. Review of Procedures for Protecting Human Subjects in Recent Clinical Studies of Pesticides. *Regulatory Toxicology and Pharmacology*, 2003 Oct;38(2):210-23.

Other:

1. Andrew Schneider and David McCumber. An Air That Kills: How the Asbestos Poisoning of Libby, Montana, Uncovered a National Scandal.

Contacts for Determining Exemptions Covered Under the Paperwork Reduction Act:

1. Barbara Pace, Office of Cross-Cutting Law Issues
2. Rick Westlund, Office of Environmental Information
3. Peter Preuss, Office of Research and Development, National Center for Environmental Assessment
4. Roger Cortesi, Office of Research and Development, National Center for Environmental Research
5. Richard Hermann, National Health and Environmental Effects Research Laboratory, Human Studies Division
6. Lee Tyner, Office of General Counsel, EPA Headquarters

Helpful Links:

http://www.primr.org/

http://www.hhs.gov/ohrp/

http://www.epastudies.org

OHRP Human Subject Assurance Training
(http://ohrp-ed.od.nih.gov/CBTs/Assurance/login.asp)

Federalwide Assurances (http://www.hhs.gov/ohrp/assurances/assurances_index.html)

CITI Training Program (https://www.citiprogram.org/default.asp)

Contacts for Help with Human Subjects Research Issues

ISSUE	NAME	PHONE	E-Mail
Determining if a study is human subjects research	Peter Preuss Roger Cortessi	301-564-3322 202-343-9813	preuss.peter@epa.gov cortesi.roger@epa.gov
Determining if a study is exempt from IRB review	Peter Preuss Roger Cortessi	301-564-3322 202-343-9813	preuss.peter@epa.gov cortesi.roger@epa.gov
Human subjects research versus public health practice	Roger Cortessi	202-343-9813	cortesi.roger@epa.gov
Information on IRBs and submitting a grant proposal	Helen McGough	206-543-0098	hmcgough@u.washington.edu
Information on submitting a human subjects research protocol	Richard Hermann	919-966-6217	hermann.richard@epa.gov
NHEERL Human Research Guidance	Richard Hermann Rebecca Calderon	919-966-6217 919-966-0617	hermann.richard@epa.gov calderon.rebecca@epa.gov
EPA Grants Management	See Regional list of GM contacts on p.3		
Communications and Public Involvement	Due to the sensitivity of this topic, all media and public communications should be go through Ann Brown, Office of Research and Development, 919-541-7818, brown.ann@epa.gov. At the same time be sure to inform your regional public affairs office. Assure that all EPA parties that should be informed are informed.		
Ethical considerations for vulnerable subjects	David Forster	360-252-2428	dforster@wirb.com
Proposed Third Party Rule	Anne Lindsay	703-305-7090	lindsay.anne@epa.gov
Research Study Protocols -Epidemiological studies -Clinical Studies	Rebecca Calderon Danelle Lobdell Bob Devlin Don Graff	919-966-0617 919-843-4434 919-966-6255 919-843-5155	calderon.rebecca@epa.gov lobdell.danelle@epa.gov devlin.robert@epa.gov graff.don@epa.gov
Legal responsibilities of project officer in human subject research	Lee Tyner	202-564-5524	tyner.lee@epa.gov
Office of Children's Health Protection	Michael Firestone Devon Payne-Sturges	202-564-2199 202-564-2706	firestone.michael@epa.gov payne-sturges.devon@epa.gov

Office of Pesticide Programs	**Regional Contacts for Human Subjects Research Issues**		y.anne@epa.gov
Region	**Name**	**Phone**	**E-mail**
Region 1	Rick Sugatt	617-918-1415	sugatt.rick@epa.gov
Region 2	Roland Hemmett	732-321-6755	hemmett.roland@epa.gov
Region 3	Ronald Landy	410-305-2757	landy.ronald@epa.gov
Region 4	Tom Baugh	404-562-8275	baugh.thomasl@epa.gov
Region 5	Gilberto Alvarez	312-886-6143	alvarez.gilberto@epa.gov
Region 6	Jeffrey Riley	214-665-8542	riley.jeffrey@epa.gov
Region 7	Brenda Groskinsky	913-551-7188	groskinsky.brenda@epa.gov
Region 8	Patti Tyler	303-818-3130	tyler.patti@epa.gov
Region 9	Bruce Macler	415-972-3569	macler.bruce@epa.gov
Region 10	Roseanne Lorenzana	206-553-8002	lorenzana.roseanne@epa.gov

Find the Grant Regional Office Near You

Region 1 (CT, MA, ME, NH, RI, VT) Grants and Funding in New England - http://www.epa.gov/region01/grants/index.html

community funding sources and environmental education grants program. Pam Ringhoff 617-918-1912

Region 2 (NJ, NY, Puerto Rico, Virgin Islands) Grants - http://www.epa.gov/region02/grants/

grants available to the Region 2 community including current issues, application kits, community grants and FAQs. Roch Baamonde 212-637-3401

Region 3 (DE, DC, MD, VA, PA, WV) Grants and Funding in the Mid-Atlantic States - http://www.epa.gov/region03/grants/index.htm

general grant information and water financing information. Kathleen Blinebury 215-814-5395

Region 4 (AL, FL, GA, KY, MS, NC, SC, TN) Grant Assistance - http://www.epa.gov/region4/financial/index.html

grant information and information managing your EPA assistance agreement. Ed Springer 404-562-8410

Region 5 (IL, IN, MI, MN, OH, WI) Funding Sources: http://www.epa.gov/region5/business/index.htm#financial

- information on grant funding available in Region 5. Sharon Green 312-353-5661

Region 6 (AR, LA, OK, NM, TX) Grants and Funding http://yosemite.epa.gov/r6/r6w3c2.nsf/WebGrant?OpenView&Start=1&Count=130

- information about grants, funding and procurement and also minority and women business enterprise information. Hattie Brown 214-665-7423

Region 7 (IA, KS, MO, NE) Regional Grants Information - http://www.epa.gov/region7/economics/index.htm

regional and national grant information as well as forms and guidelines. Karen Sherrill 9130551-7461

Region 8 (CO, MT, ND, SD, UT, WY) Grants and Financial Assistance - http://www.epa.gov/region8/community_resources/grants/grants.html

information covering grants available in Region 8. Wayne Anthofer 303-312-6305

Region 9 (AZ, CA, HI, NV, American Samoa, Guam) Funding Sources - http://www.epa.gov/region09/funding/index.html

information on Region 9's continuing program and project grants. Carolyn Truong 415-972-3663

Region 10 (AK, ID, OR, WA) Grants - http://yosemite.epa.gov/R10/HOMEPAGE.NSF/webpage/Grants

information on grants available in Region 10. Armina K. Nolan 206-553-0530

Headquarters - Grants Administration Division (202) 564-5325 (E.S.T. 8:00 a.m. - 4:00 p.m., Monday thru Friday) Betty Utterback or Mildred Lee

Websites for additional information:

General HSR information:
http://www.hhs.gov/ohrp/

Human subjects research flow charts to assist with decision making
http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm#c1

Common Rule:
http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm

Ethics training through CITI:
https://www.citiprogram.org/default.asp

HIPPA privacy act information
http://www.hhs.gov/ocr/hipaa/

Approved federal wide assurances for IRBs
http://ohrp.cit.nih.gov/search/asearch.asp#ASUR

Registration of an IRB
http://www.hhs.gov/ohrp/assurances/

IRB Guidebook
http://www.hhs.gov/ohrp/irb/irb_guidebook.htm

Informed consent requirements and documents
http://www.hhs.gov/ohrp/policy/index.html#informed

Use of another institution's IRB
http://www.hhs.gov/ohrp/humansubjects/guidance/irb-rely.htm

Special protections for children as research subjects
http://www.hhs.gov/ohrp/children/

Expedited IRB review
http://www.hhs.gov/ohrp/humansubjects/guidance/expedited98.htm

Appendix B

Participants List

Protection of Human Subjects in EPA's Research and Non-Research Studies

Silver Cloud Hotel - Broadway
1100 Broadway
Seattle, WA 98122

September 26 – 29, 2005

Participants List

Alicia Aalto
U.S. Environmental Protection Agency

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Patricia Cirone
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Roger Cortesi
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Dana Davoli
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Robert Devlin
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David Forster
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Armina Nolan
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Vivian Turner
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Jeanmarie Zodrow
U.S. Environmental Protection Agency