National Cancer Institute

Planning for Long-Term Follow-Up and Health Risks Studies after Nuclear Accidents

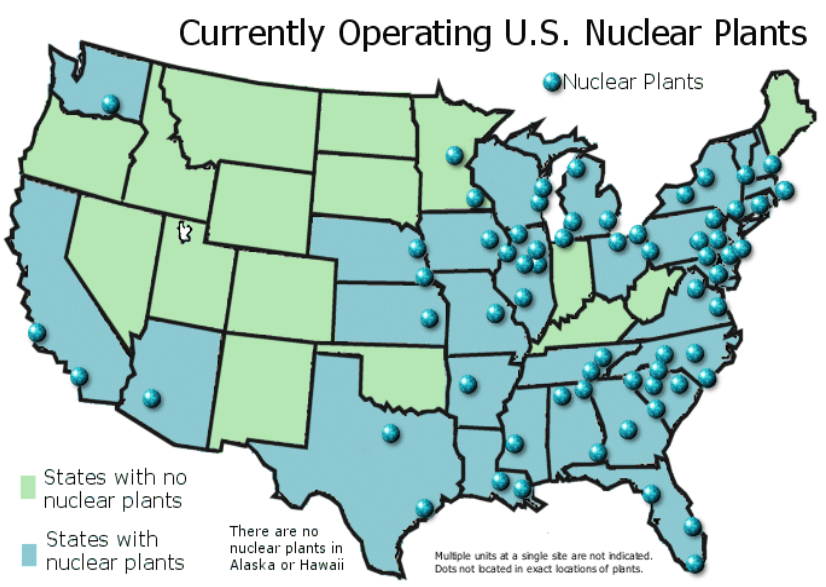
Martha S. Linet, M.D., MPH
Chief, Radiation Epidemiology Branch
National Cancer Institute

May 13, 2014

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Nuclear accidents



Fukushima Dai-ichi Plant after accident

Chernobyl Nuclear Plant after accident

Outline
Long-Term Follow-Up after Nuclear Accidents

- What is long-term follow-up?
- Why needed? Goals?
- When long-term follow-up may not be useful
- Who should be studied?
- Effective strategies for identifying the population to be studied
- Outcomes to study
- Exposure assessment strategies
- How to limit bias and confounding

What is Long-Term Follow-up?

- **Origin of 'long-term follow-up:' Clinical**
  - > **immediate clinical problem requiring attention**
  - > **short-term beneficial or adverse treatment effects**
  - > **'late' effects long after clinical problem addressed, *e.g.*, for cancer, effects after 5-year survival**
- **Observational epidemiological outcomes**
  - > **immediate effects associated with an exposure**
  - > **'late' effects from an exposure: months, years, decades**
- **Clinical and observational: late effects quantified as relative or absolute risks**

Why is Long-Term Follow-up Needed?

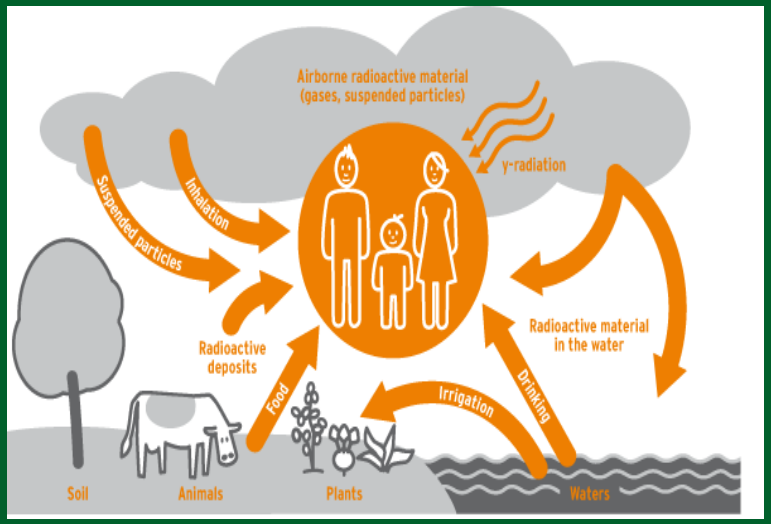
After a nuclear reactor accident, questions will be raised about health effects:

1. **Immediately after the accident—What short-term adverse health effects should be expected?**

2. **Years after the accident—What were the actual and long-term health effects associated with the accident?**

Rationale for Long-Term Follow-up after Nuclear Accidents

- Address concerns of exposed population and general societal anxiety
- Provide important clinical and public health information
- Contribute to understanding of effects of low-dose radiation



When Long-Term Follow-up Will Be Most Useful

Features
Large exposed population
Wide range of radiation levels
Well-vetted protocol (with major scientific and stakeholder input)
High level of identification and recruitment of entire exposed population, with special attention to subgroups disproportionately affected by radiation exposure
Follow-up rates or participation levels very high
Complete ascertainment of disease outcomes of interest
High quality exposure assessment undertaken soon after accident
Bias and confounding are minimized

When Long-Term Follow-Up May Not be Useful

Features	Reasons Follow-up May Not be Useful
Small exposed population	Statistical power inadequate to estimate risks for rare outcomes (e.g., thyroid cancer)
Very low radiation levels	Regardless of population size, statistical power may be inadequate to detect small risks
Long follow-up (at least 10-20 years) not possible	Follow-up may end before onset of most radiation-related serious late effects
Follow-up rates or participation very low	Results may reflect bias
Confounding factors cannot be evaluated	Risk estimates may reflect findings associated with confounding, not radiation from the accident

Types of Long-Term Follow-up

- **Epidemiologic study**
  - > follow up of individual subjects for health effects
  - > estimate exposures of individual subjects
  - > assess observed risks of subjects vs an unexposed comparison group or general population
- **Risk projection study**
  - > predict types/numbers adverse health effects from epidemiologic studies in the literature
  - > utilize estimated average exposures in population groups
  - > assess predicted risks of subjects vs an unexposed group/ general population

Who Should be Studied?

- Nuclear plant workers
- Residentially proximate
- First responders
  - > emergency disaster workers (firemen, others)
  - > emergency responder health workers
- Clean-up workers
- Others

Important Considerations re Population to Include in Follow-up

- Populations disproportionately affected
  - children and fetuses *in utero*
  - pregnant/lactating women
  - parents of young children
  - patients with medical disorders associated with greater sensitivity to radiation
  - seriously ill or immunosuppressed patients
  - the elderly
- To estimate risks, must include population with a broad range of radiation exposures

Effective Strategies for Identifying Population to be Studied

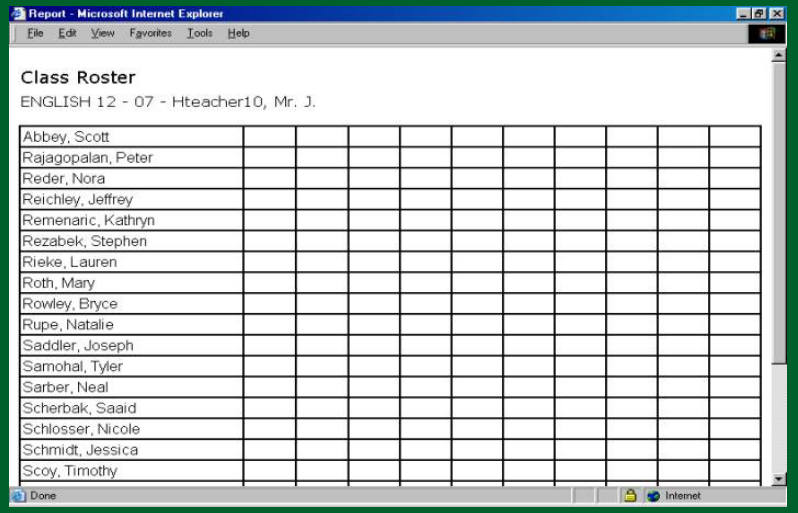
Short-Term Actions

- Triage & initial decontamination
- Protective pharmaceuticals
- Secure food, water, safety
- Evacuation and relocation per guidelines
- Criteria for entry/operations in hot zone

Planning for long-term follow-up

Identifying the Population to Follow-up: Compile Complete Roster

- Compile a complete list of people exposed from:
  - > population registers
  - > hospital emergency & other hospital records
  - > rosters from response workers & volunteers
  - > school & business records
  - > voter registration lists
  - > outreach (public health & media campaigns)



Key Considerations in Launching a Long-Term Follow-up Study

Scientific	Ethics, Funding, Logistics
How to quickly and completely identify and recruit population?	Developing a protocol – obtaining scientific & stakeholder input
What outcomes to study? How to identify and validate outcomes?	Institutional Review Board (IRB) approvals; informed consent (explaining benefits & risks)
Methods to be used for exposure assessment?	Obtaining funding for a long-term follow-up and need for firewall between funders & study team
How to maximize participation and retain participation in long-term follow-up?	Length of time to develop protocol, obtain approvals, identify population, and conduct study
Strategies for evaluating potential confounders	Communications with stakeholders

Outcomes to Study

- **Cancers in young residents**
  - > thyroid cancer*
  - > leukemia*
  - > breast cancer
  - > lung, other solid tumors
- **Cancers in nuclear workers**
  - > leukemia
  - > radiogenic solid tumors
- **Non-cancer diseases**
  - > thyroid nodules & hypothyroidism in exposed and offspring
  - > cataracts
  - > ischemic heart disease, stroke
  - > pregnancy outcomes
  - > mental & psychological disorders

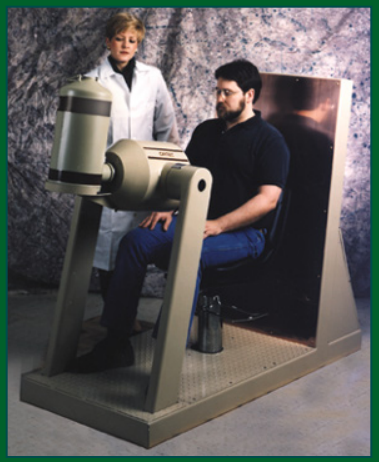
*Thyroid cancer and leukemia in offspring exposed *in utero*

Exposure Assessment Strategies:
As Soon As Possible After the Accident

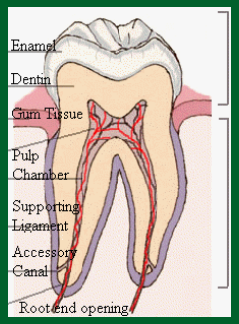
- Individual radiation measurements
  - > thyroid
  - > collect biological samples in subset (blood, urine)
- Physical measurements
- Interviews
  - > food intake (milk, leafy green vegetables)
  - > location (distance-, shielding-related)

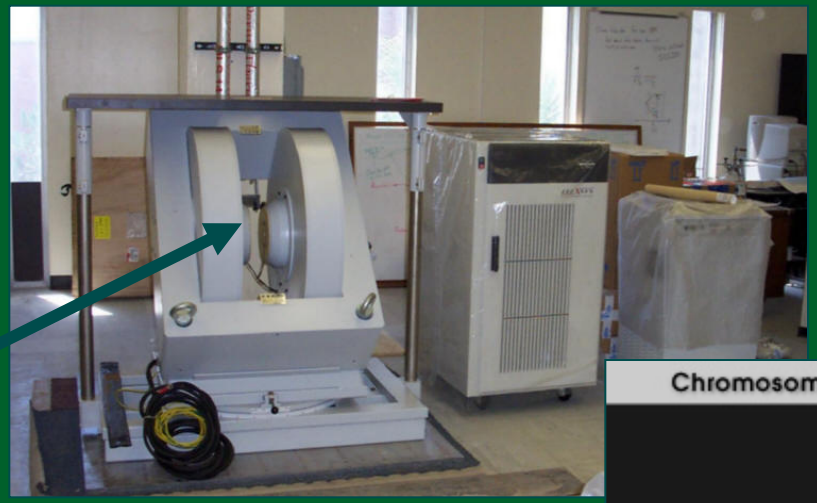
Other Later Physical and Biological Dosimetry Useful for Dose Estimation

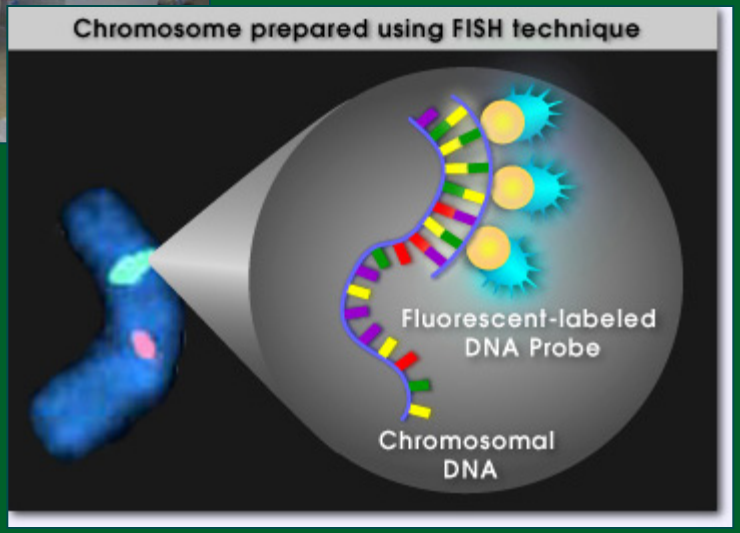
Gamma emissions from the lungs or whole-body



EPR signal from tooth enamel







Chromosome aberrations in lymphocytes

How to Limit Bias and Confounding

- **Limit bias:**
  - > Compile complete exposed population
  - > Seek high participation from all exposure groups
  - > Utilize appropriate comparison
  - > Obtain expert assistance with exposure measures

- **Limit confounding:**
  - > Obtain detailed information about potential confounders (particularly other sources of radiation such as medical radiation as well as reproductive factors, smoking, and others

- **Consider effect modifiers:**
  - > Age at exposure, sex, ethnic group, attained age

Scientific Benefit of Long-Term Follow-Up Studies

- There is limited understanding of:
  - > lifetime cancer risks associated with low-dose radiation, including protracted exposures
  - > cancer risks according to age at initial exposure, gender, race, or ethnic group
  - > other potential radiation-related risk modifiers (smoking, other lifestyle or reproductive factors, environmental exposures, others)
  - > mechanisms of radiation carcinogenesis
- Knowledge is even more limited for other radiation-related outcomes

Summary

- **Long-term follow-up after nuclear accidents can address population concerns if:**
  - **> the population is at high risk, adequate in size to detect key outcomes, with a range of radiation levels, and followed sufficiently long**
  - **> high-quality epidemiologic follow-up and exposure assessment methods are used**
  - **> bias and confounding are minimized**

- **Long-term follow-up may not be useful if:**
  - **> populations are too small**
  - **> radiation levels are very low**
  - **> follow-up is too short to detect late effects**
  - **> bias and confounding are not minimized**

If planning long-term follow-up…
DON'T WAIT TO:

- create complete population roster
- collect individual-based radiation measurements
- develop & administer questionnaire to obtain data to estimate radiation exposure