

# International Dose Effect Alliance

November 2016 Workshop Proceedings



# IDEA

International **D**ose **E**ffect **A**lliance



# International Dose Effect Alliance

November 2016 Workshop Proceedings

3002009919

Final Report, March 2017

EPRI Project Manager  
D. Cool

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# ABSTRACT

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The Electric Power Research Institute (EPRI) Radiation Safety Program hosted a first-of-a-kind workshop on November 8–9, 2016, initiating the International Dose Effect Alliance (IDEA). IDEA provides a mechanism for organizations around the world to discuss low dose radiation research programs, priorities, and approaches. The workshop was designed to facilitate information exchange and collaboration on low dose radiation research programs; identify issues, areas of synergy, and opportunities for additional research; foster integrated, outcome-oriented approaches to resolving low dose risk; develop connections between programs conducting low dose radiation research; and facilitate discussions across countries and regions. More than 30 attendees from Japan, Canada, France, and the United States participated in the workshop discussions, including 20 presentations. The presentations represented a combination of program overviews, approaches to radiation research, and specific research outcomes and findings. The presentations and discussions identified opportunities to involve medical and chemical toxicology research in broader collaboration and a possible mechanism for organizing low dose radiation research using a qualitative adverse outcome pathway approach to identify specific areas of research needed to connect the results from radiation biology and epidemiology.

This report includes the presentations made during the workshop; provides insights on current activities in low dose research programs in Asia, Europe, and the Americas; and identifies areas of cooperation and possible collaboration. The specific results presented are useful in understanding both the complexity of the response to ionizing radiation and the different points of view in communications about radiation risk.

## **Keywords**

Adverse outcome pathway  
Epidemiology  
Low dose  
Radiation biology  
Radiation protection  
Radiation risk



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**PRIMARY AUDIENCE:** Radiation protection research program managers

**SECONDARY AUDIENCE:** Radiation protection managers and communications consultants

### **KEY RESEARCH QUESTION**

The International Dose Effect Alliance (IDEA) is a new EPRI initiative with a vision to provide an international platform for information exchange, discussion, cooperation, and collaboration in low dose ionizing radiation research. The initiative was created because there has been no established international platform to bring together the national and regional programs in Europe, Asia, and North America.

### **RESEARCH OVERVIEW**

The EPRI Radiation Safety Program hosted a first-of-a-kind workshop initiating IDEA to provide a mechanism for organizations around the world to discuss low dose radiation research programs, priorities, and approaches. The workshop was held in EPRI's offices in Charlotte, North Carolina, on November 9–10, 2016. More than 30 attendees from Japan, Canada, France, and the United States participated in the workshop discussions, including a total of 20 presentations. The workshop was designed to facilitate information exchange and collaboration on low dose radiation research programs; identify issues, areas of synergy, and opportunities for additional research; foster integrated, outcome-oriented approaches to resolving low dose risk; develop connections between programs conducting low dose radiation research; and facilitate discussions across countries and regions.

### **KEY FINDINGS**

- The research data seem to show both beneficial and detrimental effects of low dose radiation exposure in certain cells and tissues (Sections 6, 16, 19, and 21).
- The competing responses within the cell, tissue, organ, and organism form a complex pattern that has not, to date, allowed for an accurate quantitative assessment of risks at low doses or dose rates of ionizing radiation (Section 14).
- There is a need to move to a multidisciplinary approach to bring all of the information together, including contributions from outside the normal radiation research community, such as medical research and chemical toxicity research (Section 8).
- The research tends to be organized around particular topics rather than the possible steps in identifying the progression to harm for an individual. A new way of organizing research—along the lines of a qualitative adverse outcome pathway—could allow for the identification of gaps and consideration of a holistic view to answer the question of effects at low dose and dose rate (Section 12).

## **WHY THIS MATTERS**

The research on the health effects of low dose ionizing radiation takes many forms and covers a spectrum of topics. Although various regional platforms exist, a platform for discussion and collaboration at an international level will facilitate cooperation in research areas, establish agreement as to what research objectives will inform important regulatory outcomes, and leverage work across organizations. Recommendations, regulations, and communications that are informed by up-to-date scientific information will protect health and safety while minimizing unnecessary burden and contribute to public awareness and communication that recognizes radiation risk in the appropriate context.

## **HOW TO APPLY RESULTS**

This report contains the materials from the presentations made during the workshop; provides insights on current activities in low dose research programs in Asia, Europe, and the Americas; and identifies areas of cooperation and possible collaboration. Specific results presented are useful in understanding the complexity of the response to ionizing radiation as well as the different points of view in communications about radiation risk.

## **LEARNING AND ENGAGEMENT OPPORTUNITIES**

- EPRI's work in low-dose radiation effects includes the following:
  - Program on Technology Innovation: Evaluation of Updated Research on the Health Effects and Risks Associated with Low-Dose Ionizing Radiation (1019227)
  - Epidemiology and Mechanistic Effects of Radiation on the Lens of the Eye: Review and Scientific Appraisal of the Literature (3002003162)
  - Radiation Induced Cataracts: Science, Policy, and Impacts to Radiation Protection - June 2016 Workshop Proceedings (3002009113)
- National and international organizations interested in this report include those engaged in low dose radiation research, policy formulation, and development of regulations and guidance.
- Radiation protection managers and communication professionals will be interested in the current findings on contributors to radiation risk.

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# CONTENTS

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<b>ABSTRACT .....</b>	<b>V</b>
<b>EXECUTIVE SUMMARY .....</b>	<b>VII</b>
<b>1 EPRI WORKSHOP SUMMARY — NOVEMBER 9–10, 2016, CHARLOTTE, NORTH CAROLINA .....</b>	<b>1-1</b>
Introduction .....	1-1
International Dose Effect Alliance .....	1-1
Presentations .....	1-2
<b>2 EPRI WORKSHOP INTERNATIONAL DOSE EFFECT ALLIANCE .....</b>	<b>2-1</b>
<b>3 EPRI WORKSHOP WELCOME .....</b>	<b>3-1</b>
<b>4 MANAGING RISKS FROM LOW-DOSE RADIATION: HOW TO DECIDE .....</b>	<b>4-1</b>
<b>5 EPRI RADIATION SAFETY PROGRAM.....</b>	<b>5-1</b>
<b>6 RADIATION EFFECTS RESEARCH FOUNDATION CURRENT TOPICS AND FUTURE RESEARCH .....</b>	<b>6-1</b>
<b>7 LOW DOSE-RATE RESEARCH IN CRIEPI.....</b>	<b>7-1</b>
<b>8 LOW DOSE RADIATION RESEARCH IN EUROPE.....</b>	<b>8-1</b>
<b>9 CERTITUDE ATTITUDE: UNCERTAINTIES AND QUALITY IN RISK ESTIMATES FOR RADIATION-INDUCED DETRIMENT .....</b>	<b>9-1</b>
<b>10 THE ONE MILLION U.S. PERSONS STUDY OF LOW-DOSE RADIATION EFFECTS (MPS): DOSIMETRY ASPECTS .....</b>	<b>10-1</b>
<b>11 OVERVIEW OF THE UNITED STATES DEPARTMENT OF ENERGY RADIATION HEALTH STUDIES PROGRAMS.....</b>	<b>11-1</b>

---

<b>12 APPROACHES TO STUDYING THE BIOLOGICAL BASIS OF DOSE-RESPONSE .....</b>	<b>12-1</b>
<b>13 LOW DOSE RESEARCH AT CHALK RIVER LABORATORY.....</b>	<b>13-1</b>
<b>14 CELL/INTRACELLULAR COMMUNICATIONS: RELEVANCE AND POTENTIAL UTILITY TO CALCULATING INDIVIDUAL LOW DOSE RISKS .....</b>	<b>14-1</b>
<b>15 LOW DOSE RISKS – ANIMAL EXPERIMENTS.....</b>	<b>15-1</b>
<b>16 RESEARCH NEEDS IN THE LOW-DOSE RADIATION FIELD.....</b>	<b>16-1</b>
<b>17 INTERNATIONAL DOSE EFFECT ALLIANCE WORKSHOP: LOW DOSE EFFECTS RESEARCH – OPG’S PERSPECTIVE.....</b>	<b>17-1</b>
<b>18 LOW DOSE RESEARCH AT CANDU OWNERS GROUP .....</b>	<b>18-1</b>
<b>19 AFTER FUKUSHIMA: WHAT WE DID AND HOW WE SHOULD DO FOR THE FUTURE .....</b>	<b>19-1</b>
<b>20 LOW DOSE RESEARCH AT QST-NIRS .....</b>	<b>20-1</b>
<b>21 LIFELONG LOW DOES-RATE RADIATION INCREASES LIFESPAN OF AVERAGE DOGS AND EVEN MORE SO FOR SHORT-LIVED DOGS.....</b>	<b>21-1</b>

# 1

## **EPRI WORKSHOP SUMMARY — NOVEMBER 9–10, 2016, CHARLOTTE, NORTH CAROLINA**

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### **Introduction**

The Electric Power Research Institute (EPRI) Radiation Safety Program hosted a first-of-a-kind workshop initiating the International Dose Effect Alliance (IDEA) to provide a mechanism for organizations around the world to discuss low dose radiation research programs, priorities, and approaches. The initiative was created because there has been no established international platform to bring together the national and regional programs in Europe, Asia, and North America.

The workshop was held in EPRI's offices in Charlotte, North Carolina, on November 9–10, 2016. More than 30 attendees from Japan, Canada, France, and the United States participated in the workshop discussions, including 20 presentations. This publication provides a summary of the discussions, the presentations made during the workshop, and a list of attendees.

### **International Dose Effect Alliance**

IDEA is a new EPRI effort with a vision to provide an international platform for information exchange, discussion, cooperation, and collaboration in low dose ionizing radiation research. To realize this vision, the workshop in November 2016 was designed to accomplish the following:

- Facilitate information exchange and collaboration on low dose radiation research programs
- Identify issues, areas of synergy, and opportunities for additional research
- Foster integrated, outcome-oriented approaches to resolve low dose risk
- Develop connections between programs conducting low dose radiation research
- Facilitate discussions across countries and regions
- Organize collaborative forums for exchange of research priorities, strategies, programs, and results

The workshop was highly successful in achieving the preceding objectives. The presentations represented a combination of program overviews, approaches to radiation research, and some specific research outcomes and findings. With the discussions following each presentation, several conclusions were drawn, as follows:

- The research data seem to show both beneficial and detrimental effects of low dose radiation exposure in certain cells and tissues.
- The competing responses within the cell, tissue, organ, and organism form a complex pattern that has not, to date, allowed for an accurate quantitative assessment of risks at low doses or dose rates of ionizing radiation.
- There is a need to move to a multidisciplinary approach to bring all of the information together.
- There is clearly a need for worldwide discussions and the involvement of research organizations.
- Low dose radiation research tends to be organized around particular topics rather than the possible steps in identifying the progression to harm for an individual. A new way of organizing research—along the lines of a qualitative adverse outcome pathway—could allow for the identification of gaps and consideration of a holistic view to answer the question of effects at low dose and dose rate.

The workshop also identified two significant opportunities for expanding the collaboration of radiation research. The first of these opportunities is to involve the medical community in considerations and to look at medical cohorts where additional information can be drawn. Looking for effects in the context of medical treatment could likely draw considerably more funding. The second opportunity is to involve chemical toxicology and toxicity research activities and researchers. They have many of the same issues, just a different insult to the body.

Future workshops, anticipated to be conducted annually, will build on the initial discussions and seek to reach out to additional organizations so that progress can be made in more clearly understanding the implications of exposure to ionizing radiation.

## **Presentations**

The workshop was opened by Dr. Mike Howard, CEO, EPRI. His welcoming remarks outlined the EPRI mission of “Advancing safe, reliable, affordable, and environmentally responsible electricity for society through global collaboration, thought leadership, and science and technology innovation.” Dr. Howard then discussed the EPRI principles of independence, non-profit, and collaboration, drawing a clear connection between the IDEA workshop and the collaborative approach.

The keynote address was given by Mr. William Magwood IV, the Director General of the Nuclear Energy Agency of the Organization for Economic Co-operation and Development. He noted the importance of low dose radiation research, reminding attendees that current radiological protection policy adopts a linear nonthreshold approach in the absence of a clear scientific understanding; that approach has been criticized as being both not prudent enough and unnecessarily conservative. He concluded by noting that the challenge of improving our

scientific understanding of dose response is a vital enterprise that deserves more resources and attention, that scientific research objectives should address issues that impact stakeholder concerns, and that both radiation protection science and social science are needed in order to determine effective policies to manage risks.

Dr. Ohtsura Niwa, Director, Radiation Effects Research Foundation (RERF), Japan, reviewed current topics and future research at the Foundation. RERF work includes the Life Span Study with its epidemiological studies of people exposed to atomic bombs, those exposed in utero, and the F1 group of the children of those exposed. A subset of the population is the Adult Health Study, where clinical studies include physical exams, and donation of research bio-samples. Future research included promotion of epidemiology, mechanistic studies, and public communications.

Dr. Toshiyasu Iwasaki provided an overview of the work of the Central Research Institute of Electric Power Industry (CRIEPI) in Japan. CRIEPI has more than 25 years of experience in the field of low dose and low dose rate radiation research. Current aims and priorities include biological research to improve the radiation protection system, dose rate effects at very low dose rates, non-cancer effects at low dose rates, and individual sensitivities.

Dr. Jacques Repussard, President of the Multidisciplinary European Low Dose Initiative (MELODI), described the European strategy of research integration, key scientific challenges, and ideas for better international coordination. Within the European Union, closing key knowledge gaps is an ambitious target for radiation protection research and requires enhanced multidisciplinary; a holistic research strategy; and secure, stable, and excellence-based funding mechanisms. The EURATOM integration concept uses a set of research platforms that include MELODI, Alliance for environmental protection, NERIS for emergency preparedness, EURADOS for dosimetric calculations, and EURAMED for medical issues. Funds are provided through projects that meet the objectives of the platforms, with the current project being the Concert EJP (European Concerted Programme on Radiation Research: a European Joint Programme).

Dr. Lawrence Dauer, Memorial Sloan Kettering Cancer Center, discussed uncertainties and quality in risk estimates for radiation-induced detriment. After describing some fundamental concepts and an approach used to rank epidemiological research studies for methodological strengths and weaknesses, Dr. Dauer concluded that reports of estimates of risk from radiation exposure should always include a clear and thorough discussion of limitations of the data and realistic assessments of how those limitations might impact results.

Dr. André Bouville, U.S. National Cancer Institute (retired), provided a review of the dosimetry aspects supporting the “One Million U.S. Persons Study of Low-Dose Radiation Effects” (MPS). The MPS is examining various U.S. cohorts of workers, including the Department of Energy’s (DOE’s) Manhattan Project, Department of Defense atomic veterans, industrial radiographers, medical workers, and nuclear utility workers. Scientific Committee 6-9 of the National Council on Radiation Protection and Measurements is currently preparing a detailed report of guidelines to ensure consistency in the treatment of the dosimetry of various cohorts considered within the MPS, including the evaluation of uncertainty.

Dr. Isaf Al-Nabulsi, DOE Office of Health and Safety, provided an overview of the DOE Radiation Health Studies Programs. The program manages a portfolio of domestic and international health studies, including the U.S. support for RERF, the Russian Health Studies Program, and the Comprehensive Epidemiologic Data Resource. Dr. Al-Nabulsi also described the DOE Low Dose Program and legislative efforts intended to increase our understanding of low dose radiation effects.

Dr. Rory Conolly, U.S. Environmental Protection Agency (EPA), discussed approaches to studying the biological basis of dose response. In particular, the presentation focused on the evolution of studies looking at the mode of action, biologically based dose response, and adverse outcome pathway (AOP). An AOP approach, used within the EPA for various chemical hazards, attempts to lay out for a particular chemical and adverse outcome the sequential steps within a cell, organ, and organism that result in the effect of interest. He then described moving from a qualitative model to quantitative models. Dr. Conolly suggested that the AOP terminology helps by specifying the information needed to support regulatory decision making, including molecular initiating events, key events in the pathway, adverse outcomes for individuals, and adverse outcomes for populations.

Dr. Fred Beranek, Canadian Nuclear Laboratories (CNL), introduced workshop attendees to the low dose research being performed at Chalk River Laboratory in Canada. Radiobiology projects currently include low dose radiation effects, medical applications, and dosimetry. Within the area of low dose radiation effects are projects on the effects of low dose radiation on genes and cancer, a lifespan study comparing the toxicities of gamma and tritium beta radiations in mice, effects of low dose internal and external radiation on development of cancer, and effects of low dose radiation on the development of cardiovascular disease.

Dr. Jacqueline Williams, University of Rochester, described the relevance and potential utility of cell and intracellular communications to calculating individual low dose risks. Noting that there are many signal molecules both within the cell and the intracellular system that might be potential indicators of homeostatic imbalance, she expressed the view that a key question is how to narrow the signals of interest in critical systems associated with radiation-induced diseases. Dr. Williams concluded that animal models can verify gene and pathway involvement in radiation-induced disease. To be useful, these models should provide dose (persistence of signal) and threshold (loss of signal) information. There is a need to prioritize endpoints of interest and choose models that mimic human disease characteristics.

Dr. Gayle Woloschak, Feinberg School of Medicine, Northwestern University, discussed work with animal experiments and data to examine low dose risks. She noted that the reason to consider animal studies is that human data cannot answer all of the questions; to determine risk, there is a need to examine cellular studies, examine animal effects, examine animal population effects, and look for consistency in responses. Northwestern University has created a collection of data (JANUS) and tissue samples from materials made at different U.S. national laboratories during animal irradiation studies conducted between the 1950s and 1990s, and she noted that

EPRI has supported some of the efforts to make the data accessible. These include dog and mouse studies with both external beams and internal exposures. Dr. Woloschak then described the ongoing examination of the dose and dose rate effectiveness factor (DDREF) using animal data. Among the conclusions reached so far are the following:

- The inclusion of more animal mortality data showed that the Biological Effects of Ionizing Radiation (BEIR) VII report dose response model did not fit the observed data.
- DDREF estimates based on the curvature of acute exposure data were never significantly greater than 1.
- Estimates of DDREF using BEIR VII approaches and based on data that directly compared acute and protracted exposures were infinitely high (implying that low dose exposures are neutral with respect to carcinogenesis or life shortening).

Dr. Mohan Doss, Fox Chase Cancer Center, presented his views on research needs in the low dose radiation field. He suggested that the somatic mutation model might not be the primary cause of cancer, and that instead the suppression of the immune system might be a primary cause. Dr. Doss went on to report information from some studies where low dose whole-body radiation treatments performed as well as or better than chemotherapy. From this, he suggested the need for prospective studies to resolve the low dose rate cancer risk controversy, prospective studies to optimize cancer prevention from low dose radiation, clinical trials of low dose rate treatments for different types of cancers, and a study of lung cancer rates in residents of radon-mitigated homes, before and after mitigation, to determine the effect of residential radon on lung cancer.

Loc Nguyen, Ontario Power Generation (OPG), provided OPG's perspectives on low dose effect research. OPG, through the Candu Owners Group (COG), has ongoing projects to maintain the biological research facility at Chalk River National Laboratory, funding to educational institutions to carry out low dose research, and a mechanistic study using a mouse model to look at low dose radiation and cancer. Proposed projects include examining the relative biological effectiveness of tritiated water in inducing double strand breaks, effects of tritium exposure on the immune system and implications in breast and lung cancer development, and the biological and immunological effect of low dose radiation on aged populations.

Peter Ernst, COG, followed the OPG presentation with additional information on the COG program of low dose research. COG work is part of their Health, Safety and Environment area. Of note was the work with the National Science and Engineering Research Council Industrial Research Chairs, through which research at McMaster University has been funded for radiation biology and dosimetry.

Professor Masako Bando, Yukawa Institute, Kyoto University, described the views and concerns about radiation effects in Japan following the events at Fukushima. Her organization has worked with Japanese citizens and students on radiation units and radiation biology, supported multidisciplinary research meetings, and started research from the physical point of view on biological effects caused by low dose irradiation. A new project, based on the MELODI platform of research in Europe, has been started in Japan, called *JMELODI*. In addition, an effort has started to bring various research organizations together in a program called PLANET for multidisciplinary collaboration. Interest was expressed in connecting Japanese efforts through PLANET with the efforts of EPRI through IDEA for international collaboration.

Yutaka Yamada, National Institute of Radiological Sciences (NIRS) National Institutes for Quantum and Radiological Science and Technology (QST), provided an overview of low dose research at QST-NIRS. Their research plan for 2016–2022 includes development of a risk model based on epidemiology and animal studies, including radiation carcinogenesis experiments and mechanistic studies, construction of an animal experiment data archive (J-SHARE), and supporting the PLANET platform of experts previously cited herein. Their animal facility can house 11,000 mice and 3,000 rats, and work is underway looking at tumor types with different dose rates. The J-SHARE animal experiment archive is aimed to provide Japanese data and to collaborate with the JANUS database in the United States (Northwestern University) and the STORE database in Europe.

Dr. Jerry Cuttler, Elysium Industries, provided his perspectives on how lifelong, low dose rate radiation increased lifespan in dogs. He suggested that longevity is the best measure of health effects and presented data from several dog studies where the median lifespan of dogs was not reduced until approximately 700 mGy/year of exposure. He also presented a paper describing the treatment of Alzheimer's Disease with computed tomography (CT) scans, with a finding that 5 CT scans of 40 mGy each over a three-month period partially restored cognition memory, speech movement, and appetite in an Alzheimer's patient.

The IDEA workshop ended with a general discussion of issues and conclusions. There was general agreement of the usefulness of the workshop and a desire for the program to be continued. The next workshop is tentatively planned for December 12–14, 2017. There was also agreement that work should begin to develop an outline of research using the AOP approach. The objective would be to have a presentation at the next IDEA workshop and perhaps during the European Radiation Protection Week in 2017.

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## EPRI WORKSHOP INTERNATIONAL DOSE EFFECT ALLIANCE

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# EPRI Workshop International Dose Effect Alliance

**Donald A. Cool**  
Technical Executive

9 November 2016



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## Workshop Approach

- **Overviews of low dose research programs**
- **Research topics**
- **Discussion of opportunities for collaboration and insights for future activities**



# Agenda Day 1



8:00 Registration - Breakfast Available

## Session I

9:00 Welcome and Logistics: Dr. Donald A. Cool, EPRI

9:15 Welcome: Dr. Mike Howard, President and CEO, EPRI

9:30 Key Note: Mr. William D. Magwood IV, Director General, Nuclear Energy Agency

10:00 Introduction to EPRI Radiation Safety Program and IDEA: Dr. Donald A. Cool, Technical Executive, Radiation Safety, EPRI

10:30 Break

## Session II

11:00 Dr. Ohtsura Niwa, Director, Radiation Effects Research Foundation, Japan

11:30 Dr. Toshiyasu Iwasaki, Central Research Institute of Electric Power Industry, Japan

12:00 Dr. Jacques Repussard, Multidisciplinary European Low Dose Initiative, France

12:30 Lunch

3

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# Agenda Day 1



## Session III

1:30 Dr. Larry Dauer, Memorial Sloan Kettering Cancer Center (Via WebEx), Quality Assessment and Meta-Analysis

2:00 Dr. Andre Bouville, National Council on Radiation Protection and Measurements, Million Person Study Approach and Dosimetry

2:30 Dr. Isaf Al-Nabulsi, Senior Technical Advisor, Department of Energy

3:00 Mr Byoungil Lee, Korea Hydro and Nuclear Power/RHI, Korea

3:30 Break

## Session IV

4:00 Discussion: Approaches to International Collaboration

5:00 Closing

4

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## Agenda Day 2



8:00 Registration - Breakfast Available

### Session V

9:00 Dr. Rory B. Conolly, Environmental Protection Agency, Adverse Outcome Process

9:30 Dr. Fred Beranek, Canadian Nuclear Laboratories, Canada

10:00 Dr. Jacqueline Williams, University of Rochester, Cellular and Intracellular Communication

10:30 Break

### Session VI

11:00 Dr. Gayle Woloschak, Northwestern University

11:30 Dr. Mohan Doss, Fox Chase Cancer Center

12:00 Loc Nguyen, CHP, Ontario Power Generation, Canada

Peter Ernst, Candu Owners Group, Canada

12:30 Lunch

5

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## Agenda Day 2



### Session VII

1:30 Dr. Masako Bando, Researcher, Yukawa Institute for Theoretical Physics, Kyoto University, Japan

2:00 Dr. Yutaka Yamada, National Institute of Radiological Sciences, Japan

2:30 Dr. Jerry Cuttler, Elysium Industries

3:00 Break

### Session VIII

3:30 Discussion: Future Plans

5:00 Closing

6

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## Safety Message

Charlotte in the fall is beautiful with piles of the colorful leaves ... have fun ... but be careful cleaning them up!





# 3

## EPRI WORKSHOP WELCOME

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## EPRI Workshop Welcome

Mike Howard, Ph.D.  
EPRI CEO

International Dose Effect Alliance Workshop  
November 9, 2016

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- **Collaborative**
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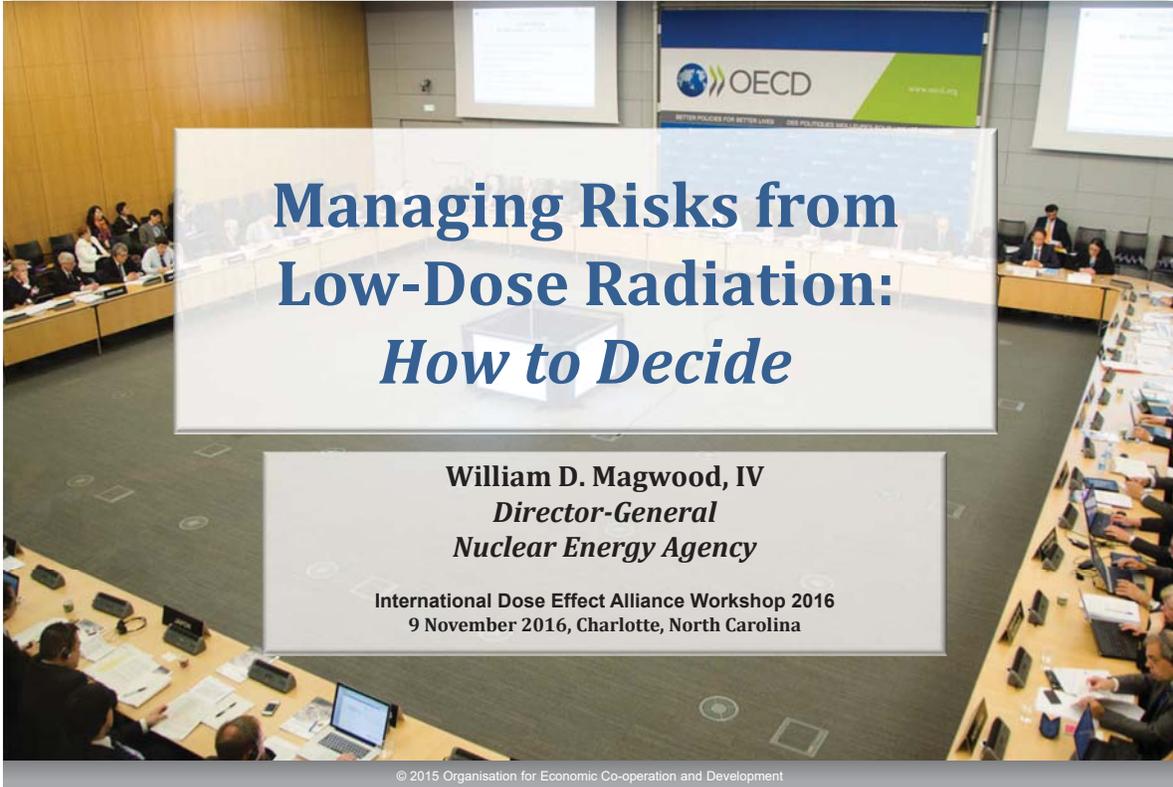


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# 4

## MANAGING RISKS FROM LOW-DOSE RADIATION: HOW TO DECIDE

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## Managing Risks from Low-Dose Radiation: *How to Decide*

**William D. Magwood, IV**  
*Director-General*  
*Nuclear Energy Agency*

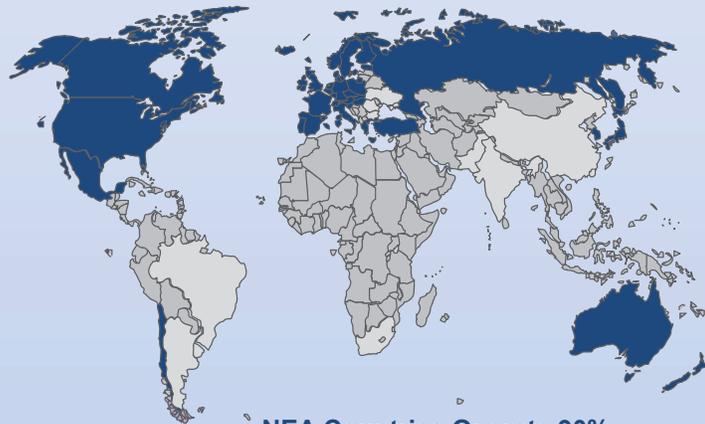
International Dose Effect Alliance Workshop 2016  
9 November 2016, Charlotte, North Carolina

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## NEA: Bringing Advanced Countries Together to Address Global Challenges

### The Role of the NEA is to:

- Foster international co-operation to develop the scientific, technological and legal bases required for nuclear and radiological safety.
- Develop authoritative assessments and forge common understandings on key issues as input to government decisions on nuclear technology policy
- Conduct multinational research into challenging scientific and technological issues.



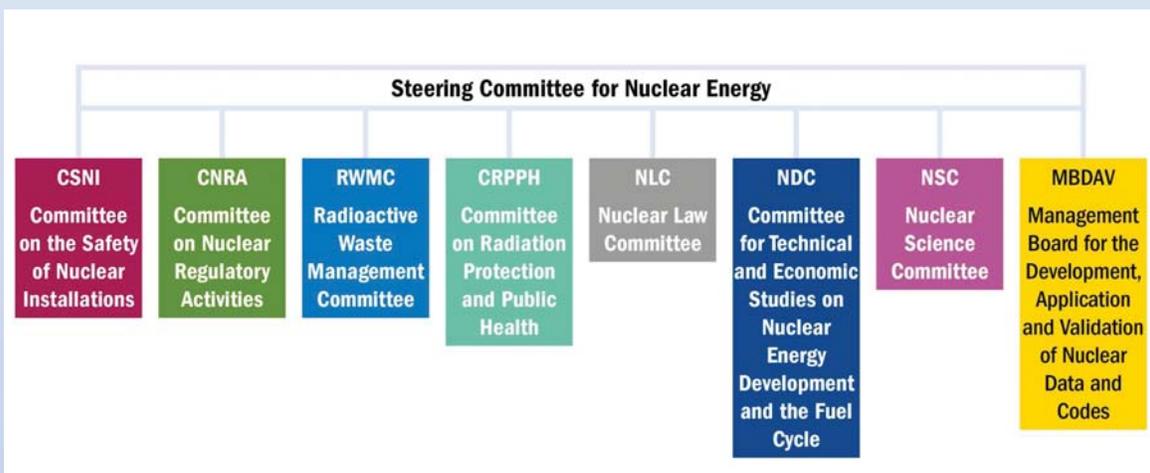
**NEA Countries Operate 90%  
of the World's Installed Nuclear Capacity**

## The NEA: 31 Countries Seeking Excellence in Nuclear Safety, Technology, and Policy

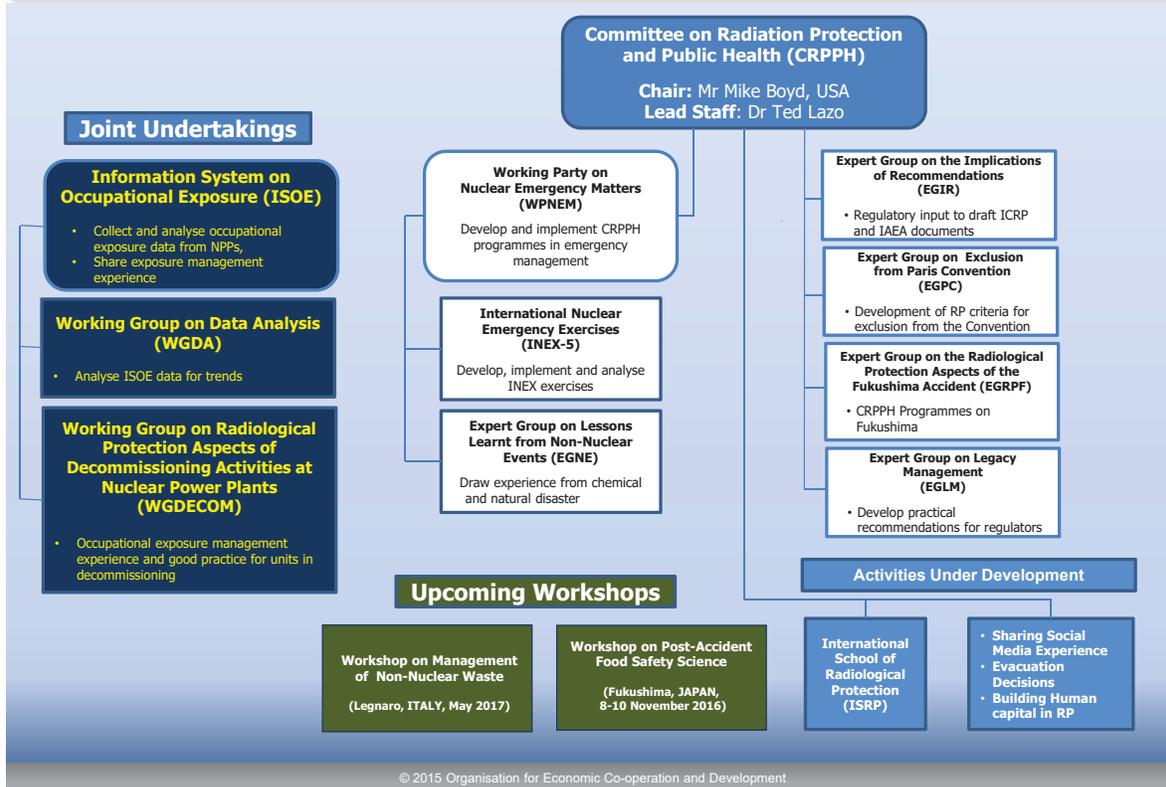
- 31 member countries w/ and wo/nuclear technology + key partners (e.g., China)
- 7 standing committees and 75 working parties and expert groups
- The NEA Data Bank - providing nuclear data, code, and verification services
- 21 international joint projects (e.g., the Halden Reactor Project in Norway)



## NEA Standing Committees



*The NEA's committees bring together top governmental officials and technical specialists from NEA member countries and strategic partners to solve difficult problems, establish best practices and to promote international collaboration.*



## Major NEA Separately Funded Activities

### NEA Serviced Organisations

- **Generation IV International Forum (GIF)** with the goal to improve sustainability (including effective fuel utilisation and minimisation of waste), economics, safety and reliability, proliferation resistance and physical protection.
- **Multinational Design Evaluation Programme (MDEP)** initiative by national safety authorities to leverage their resources and knowledge for new reactor design reviews.
- **International Framework for Nuclear Energy Cooperation (IFNEC)** forum for international discussion on wide array of nuclear topics involving both developed and emerging economies.

### 21 Major Joint Projects

(Involving countries from within and beyond NEA membership)

- **Nuclear safety research** and experimental data (e.g., thermal-hydraulics, fuel behaviour, severe accidents).
- **Nuclear safety databases** (e.g., fire, common-cause failures).
- **Nuclear science** (e.g., thermodynamics of advanced fuels).
- **Radioactive waste management** (e.g., thermochemical database).
- **Radiological protection** (e.g., occupational exposure).
- **Halden Reactor Project** (fuels and materials, human factors research, etc.)

## Safety Regulation and Science

- **There has been considerable research regarding the health risks from ionising radiation**
- **But at low levels of exposure (50 - 100 mSv), the scientific evidence is inconclusive**
- **How much regulation is “enough” is a judgement, and uncertainty regarding the risks below 50 - 100 mSv makes this more difficult**

**This makes regulatory  
policymaking an inexact science**

## Radiological Safety Policy

- **Radiological protection policy around the world generally adopts the LNT philosophy**
  - Any radiation exposure carries risk
  - Radiological protection evolves toward minimizing exposures with some consideration of social, economic, and beneficial use taken into account
- **Is the resulting approach:**
  - Not prudent enough?
  - Appropriately balanced?
  - Unnecessarily conservative?

## Examples of Policy Questions Impacted By Scientific Uncertainty

- How should occupational and public doses be regulated?
- How should risks from medical exposure be controlled?
- How different are the risks to children?
- How should radioactive waste disposal be regulated?
- How should emergency response be regulated?
- How should decommissioning standards be set?
- How should post-accident recovery be regulated?

## Key Topics for Scientific Investigation

- Identifying the biological pathway(s) from cancerous cells to healthy cells
- Explaining of how radiation initiates or accelerates the process in which cells becoming cancerous
- Determining whether the effects of chronic exposure differ from acute exposure
- Finding the bio-markers for radiation-induced cancer
- Determining whether there is a threshold below which there is no risk of radiation-induced cancer



## Until the Science is Definitive, A Multi-Disciplinary Approach is Needed

- Determining the appropriate level of risk from a radiological activity is both a scientific and a societal process
- Decision-makers and RP experts must be conscious of stakeholder concerns
- Public consultation must be an integral part of decision-making
- Technical judgement must be informed—but not determined—by social norms and expectations

**Radiological protection and social science must be applied in concert to determine the appropriate responses to each risk**

## Fukushima Stakeholder Dialogues *A Good Model for Engagement*

**NEA supported 12 dialogue sessions organised by ICRP between 2011 and 2015, with stakeholders from affected areas of Fukushima Prefecture**

- Addressed many stakeholder concerns regarding radiological protection and social disruption
- Included input from RP technical experts and social scientists, jointly addressing stakeholder concerns
- Affected individuals participating in the Dialogues developed more positive images of their future



## Building Trust in Decisionmaking: *NEA Forum on Stakeholder Confidence (FSC)*

- Established in 2000 to analyse and support stakeholder interaction and public participation in decision-making
- 10 “national workshops” conducted thus far – most recently in September in Berne, Switzerland
- Issued Publications such as “*Local Communities’ Expectations and Demands on Monitoring and the Preservation of Records, Knowledge and Memory of a Deep Geologic Repository*”
- Emphasises transparency, stepwise decision-making, and an open partnership approach between all interested parties



## Other NEA Activities

- **Villigen Workshops (1998, 2001, 2003)**
  - *Key message:* We must integrate RP aspects into societal decisions, rather than integrating societal aspects into RP decisions
- **Chernobyl Response (1987 - 2006)**
  - *Key message:* RP expertise should be at the service of stakeholders
- **Science and Values Workshops (2008, 2009, 2011, 2012)**
  - *Key message:* Decisions are informed by science, but are driven by social values

## Closing Messages

- **The challenge of improving our scientific understanding of dose response is a vital enterprise which deserves more resources and attention**
- **Scientific research objectives should address issues that impact stakeholder concerns**
- **Dialogue should deepen among policy makers, regulators, industry and the public**
- **RP science and social science are both needed in order to determine effective policies to manage risks**

## Thank you for your attention



More information @ [www.oecd-nea.org](http://www.oecd-nea.org)  
All NEA reports are available for download free of charge.

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# 5

## EPRI RADIATION SAFETY PROGRAM

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# EPRI Radiation Safety Program

**Donald A. Cool**  
Technical Executive

9 November 2016



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## EPRI's Principles

### **Independent**

Objective, scientifically based results address reliability, efficiency, affordability, health, safety and the environment

### **Nonprofit**

Chartered to serve the public benefit

### **Collaborative**

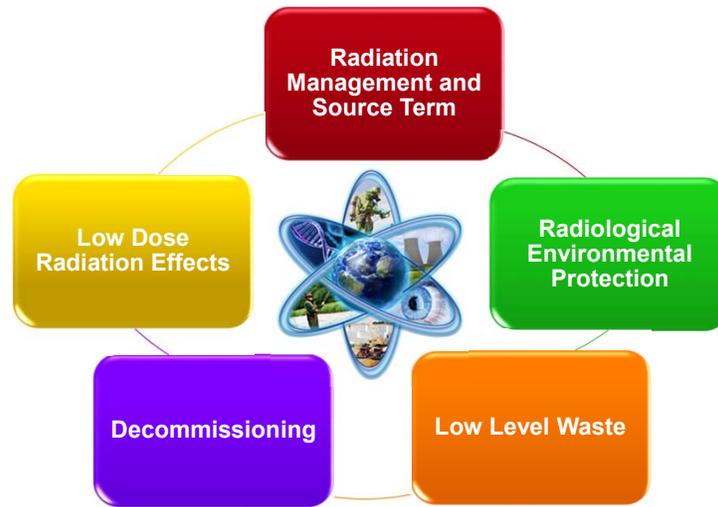
Bring together scientists, engineers, academic researchers, industry experts

Founded 1972

Major offices: Palo Alto, CA; Charlotte, NC; Knoxville, TN



# EPRI Radiation Safety Program



**Enhance Radiation Safety for Workers and the Public**

3

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## Radiation Safety Research Focus Areas

**ALARA Strategies and Technologies**

- Combines source term reduction technologies with typical dose reduction tools and work planning improvements to provide a comprehensive strategy for reducing dose to workers.

**Radioactivity Generation and Control (Source Term Reduction) – Joint w/Chem.**

- Understanding radioactivity and radiation field generation and transport processes and tools/technologies to improve control of radioactivity.

**Radiation Safety Guidance**

- Development and maintenance of guidelines, guides and sourcebooks for radiation protection, source term reduction, radiological environmental protection (which includes groundwater), and low level waste.

**Radiation Measurements and Dosimetry for Workers and Public**

- Investigates advanced radiation detection and monitoring technologies for site and environmental monitoring purposes. In addition, more accurate dose calculation methodologies will be investigated to improve the quantification of the dose to workers and the public

**Effluent and Radwaste Minimization**

- Investigates effluent (gaseous, liquid), groundwater remediation, and radwaste minimization technologies and management strategies. Also evaluates the impact to effluent and radwaste programs from changes in plant design or operational factors.

**Optimized Worker Protection**

**Integration of Industrial and Radiological Safety**

- Includes research related to the development of technologies and strategies that better meet the needs for an integrated approach to worker protection – radiological and industrial hazards.

**Benchmarking and Trending (Fundamental)**

- Maintenance of databases for the Standard Radiation Monitoring Programs (SRMP/BRAC) and the industry low level waste benchmarking database, RadBench™.

**Low Dose Radiation Health Effects**

- Investigates health effects from exposure to ionizing radiation to inform the development of radiation safety standards, radiation protection practices, and communication of risks to workers and the public.

**Decommissioning Technology and Strategy**

- Investigates technologies and strategies to facilitate the development and execution of a safe, efficient, and cost-effective decommissioning program.

4

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# EPRI Radiation Safety – Technical Strategy Groups



## TSG Membership

- 3-Yr Commitment Basis (in addition to RS Base)

## Offers

- Knowledge transfer
- Influence on research direction
- Benchmark of emergent issues
- Surveys of practices
- Independent assessment one (1) per membership period
- Access to
  - Deliverables
  - Collaboration SharePoint
  - Webcasts
  - Workshops

## Interactive & Collaborative Peer Groups

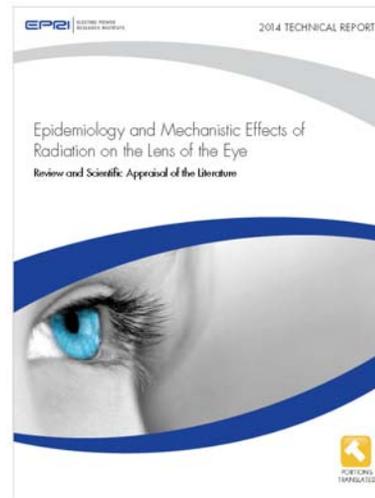
5

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## Deliverable Types

- Technical Reports
- Technical Updates
- Key Issue Review
- Publication Summary
- Comment Summary



6

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## Why is Low Dose Risk Important?

- Low Dose radiation risk is a **fundamental, global issue** which impacts everything from dose limits to public perceptions
- Protection policies apply conservative and precautionary approaches due to not knowing the dose – effect relationship ➔ Reduce Uncertainty

Dialogue continues....

- ICRP task groups on DDREF, Effective Dose, Detriment ...
- NCRP recommendations under development
- EPA regulation changes being considered



**Goal: Reduce uncertainties in risk estimates to inform standards**

7

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## EPRI Low Dose Program Objectives

- **Develop a technical basis for more accurate and biologically plausible radiation health risk models and interpretations**
  - Analyze existing epidemiological and animal databases for information to improve estimates of risk
  - Comprehensive review of existing, influential studies
  - Synthesize research into an integrated picture
- **Support dialogue and collaboration amongst research organizations**
- **Create products to address current issues and activities**

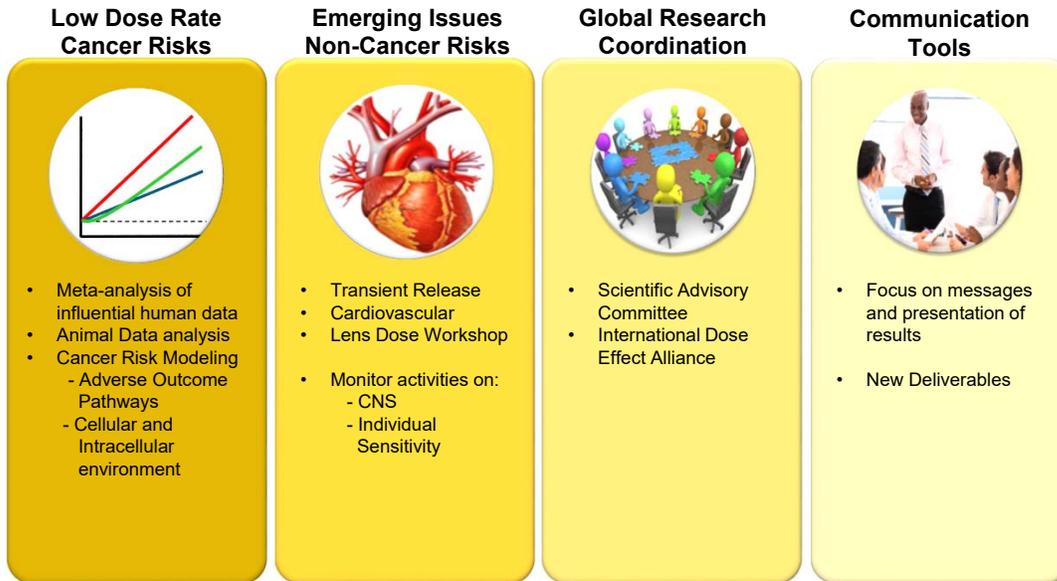


8

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## EPRI Low Dose Program Research 2016 – 2019



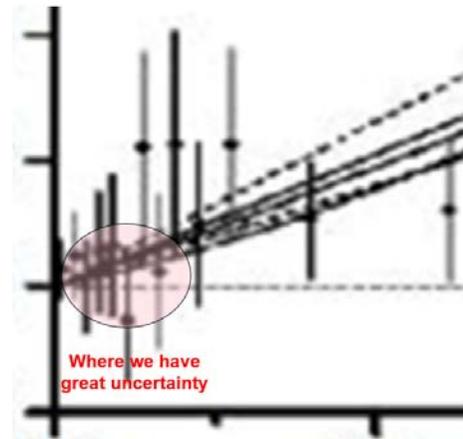
9

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## Value of Low Dose Research

- Reduce Uncertainty
- Connect cause and effects
- Explain relationships
- Risk Inform approaches
- Provide credible input to regulations, guidance, programs, communications

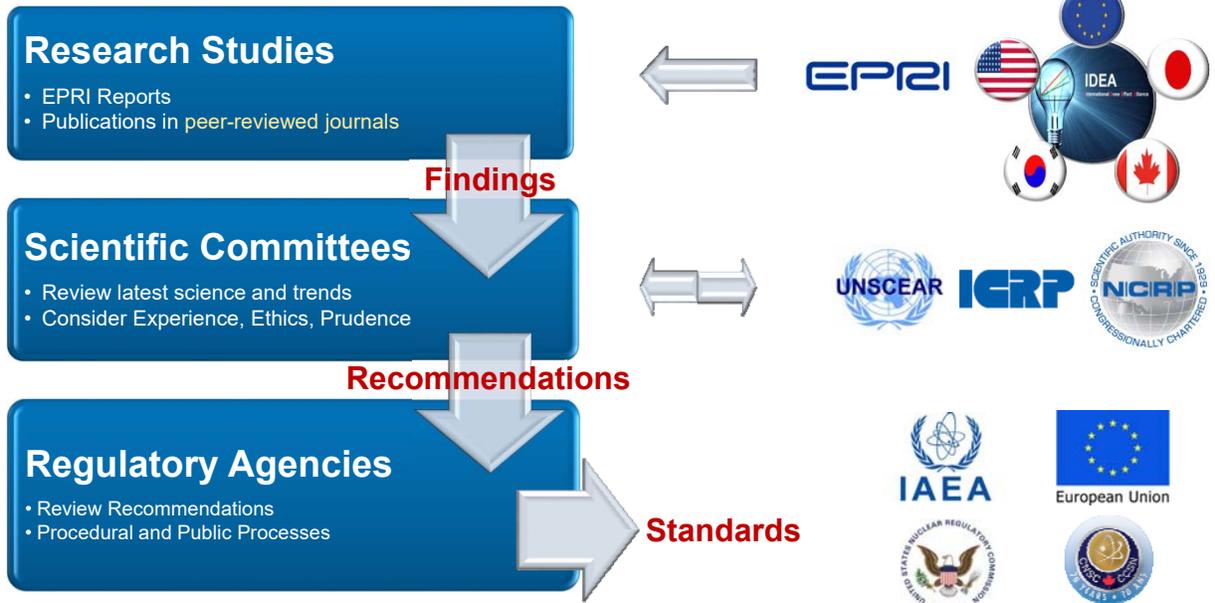


Reduced uncertainty → risk informed radiation protection

10

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11

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## International Dose Effect Alliance (IDEA)

### Background:

- Research on effects of ionizing radiation is occurring in many countries throughout the world.
- There are currently no established international mechanisms for discussing and collaborating on low dose radiation research priorities, strategies, programs, or results.
- A forum is needed to facilitate collaboration and cooperation.



Canadian Nuclear Laboratories

Laboratoires Nucléaires Canadiens

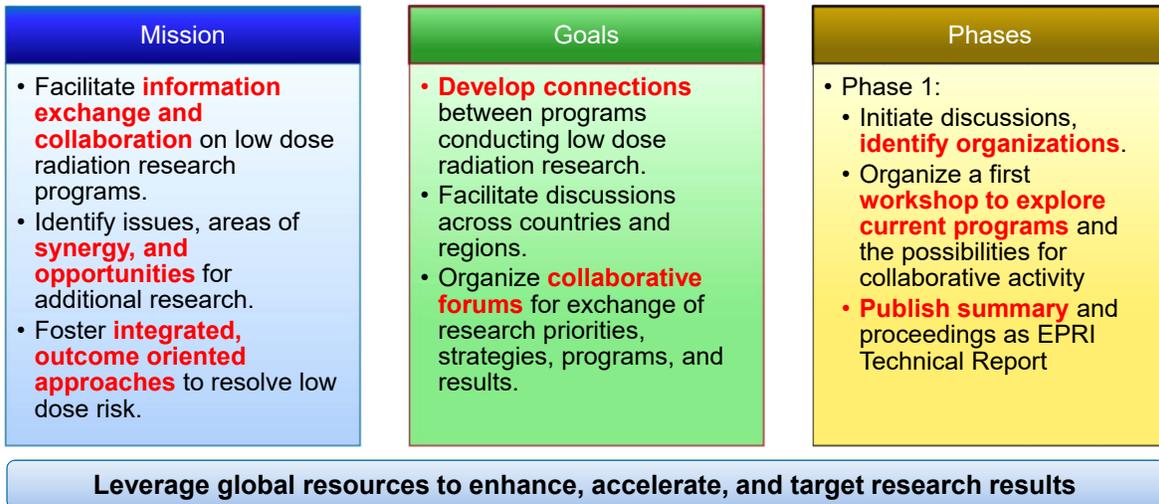
12

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## IDEA Vision

International platform for information exchange, discussion, cooperation, and collaboration in low dose radiation research



13

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14

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# 6

## RADIATION EFFECTS RESEARCH FOUNDATION CURRENT TOPICS AND FUTURE RESEARCH

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# Radiation Effects Research Foundation

## Current topics and future research

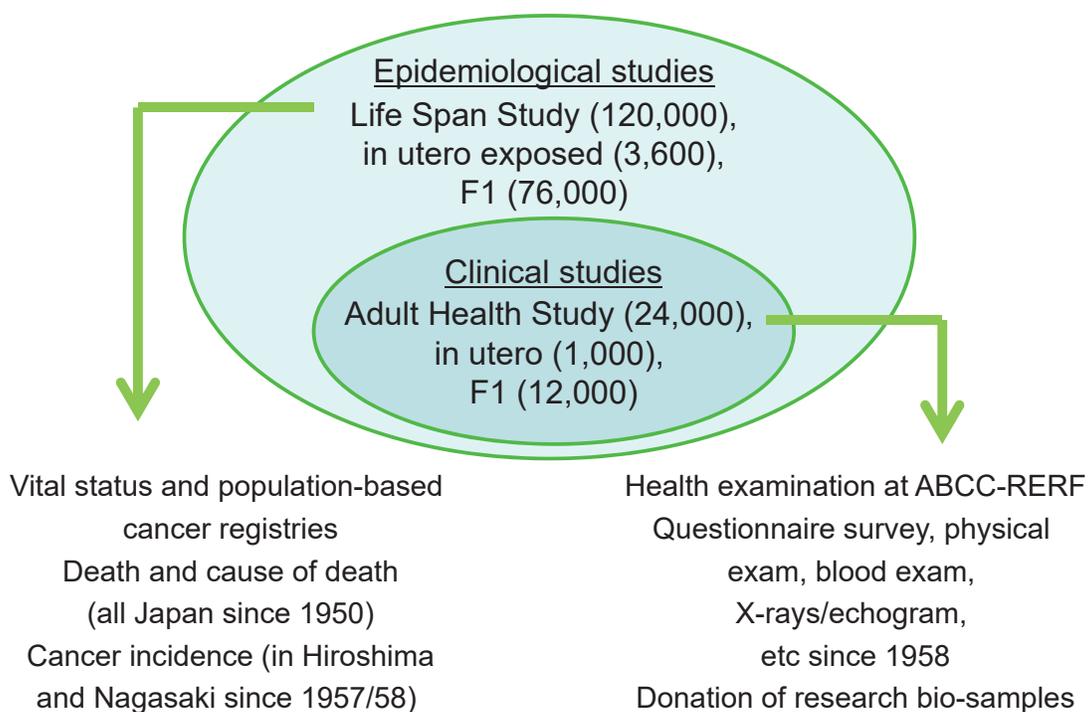
by Ohtsura Niwa @ EPRI

November 09, 2016

Current topics and future studies of radiation health effects at RERF

1. Hereditary effects and its future
2. Somatic effects such as cancer and non cancer
3. Age dependency of radiation carcinogenesis with specific emphasis on in utero exposures
4. Use of biosamples
5. Future of RERF research

## 0. Overview of RERRF Research Design Life Span Study (LSS) and Adult Health Study (AHS)



## 1. Old (but new) studies on hereditary effects

indicator	number	duration	results
UPO	77,000	1948-1954	no effect
Sex ratio	140,000	1948-1966	no ef
Chromosome mutation	16,000	1967-1985	no effect
Biochemical changes	23,000	1975-1984	no effect
Perinatal death	80,000	1946 – now	no effect
Cancer	76,000	1950 – now	no effect

Until now, no discernable effect was found

Effect of radiation is small enough not to be detected in a population of  $\approx 70,000$

Similar lack of effect was found for F1 born to the childhood cancer survivors

Genome analyses are planned for the F1/parents trios

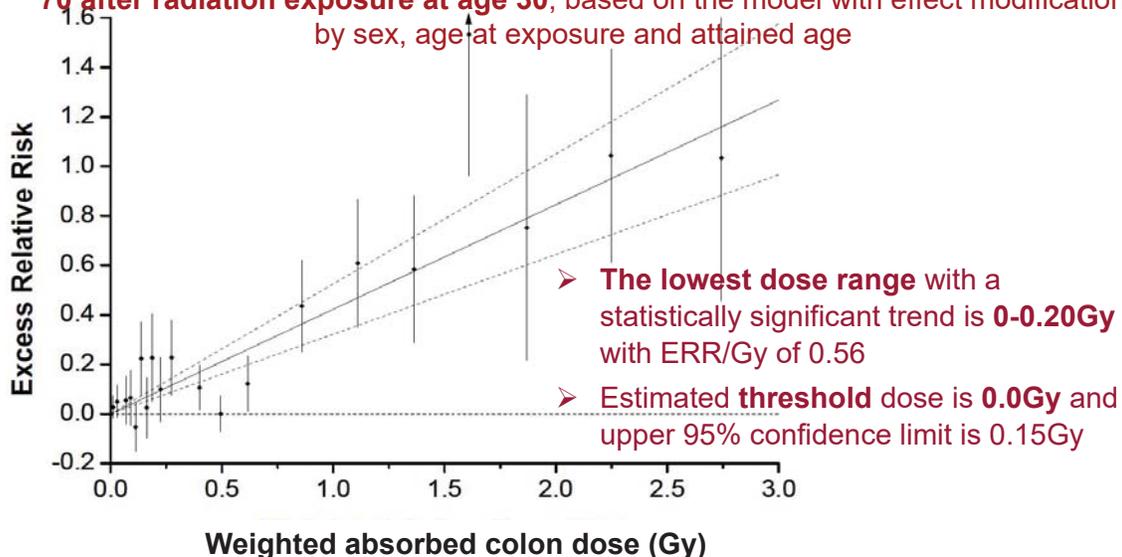
Experimental analyses of F1 mice are ongoing at RERF

3

## 2. Somatic effects: cancer epidemiology

### LNT for solid cancer from LSS, 1950-2003

- The **linear (L) model** ( $ERR = \beta d$ ) provides the best fit over the full-dose range
- **ERR/Gy=0.42** (95%CI: 0.32, 0.53) for the gender-averaged risk estimates **at age 70 after radiation exposure at age 30**, based on the model with effect modification by sex, age-at exposure and attained age



## Comparison of Linear and LQ ERR Models



- Dose response is consistent with linear for women
- Dose response is not consistent with linear for men

Grant et al, *submitted*  
5

## Further considerations

Linearity of radiation dose response is a logical outcome

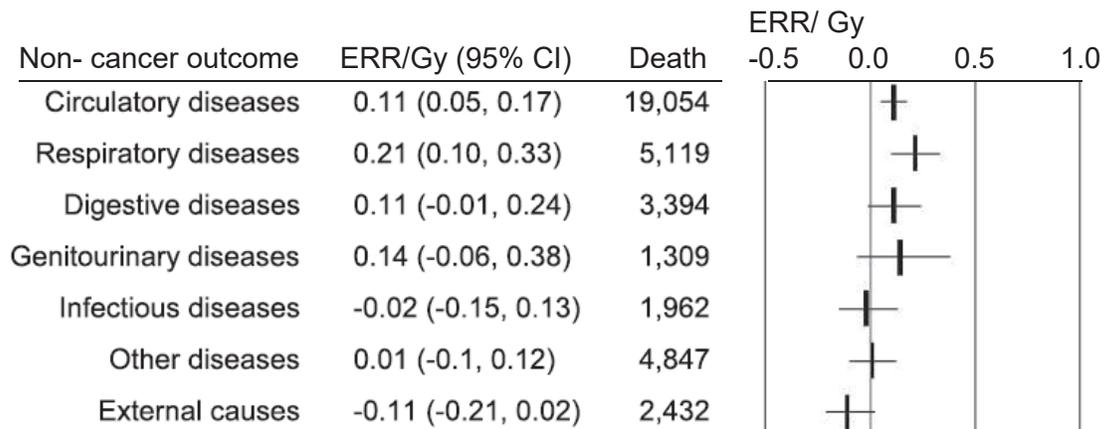
of multi-hit model in which radiation contribute one hit

→ So, other models to be considered?

BEIR VII calculation of DDREF based on the LQ model to be redone with the new data.

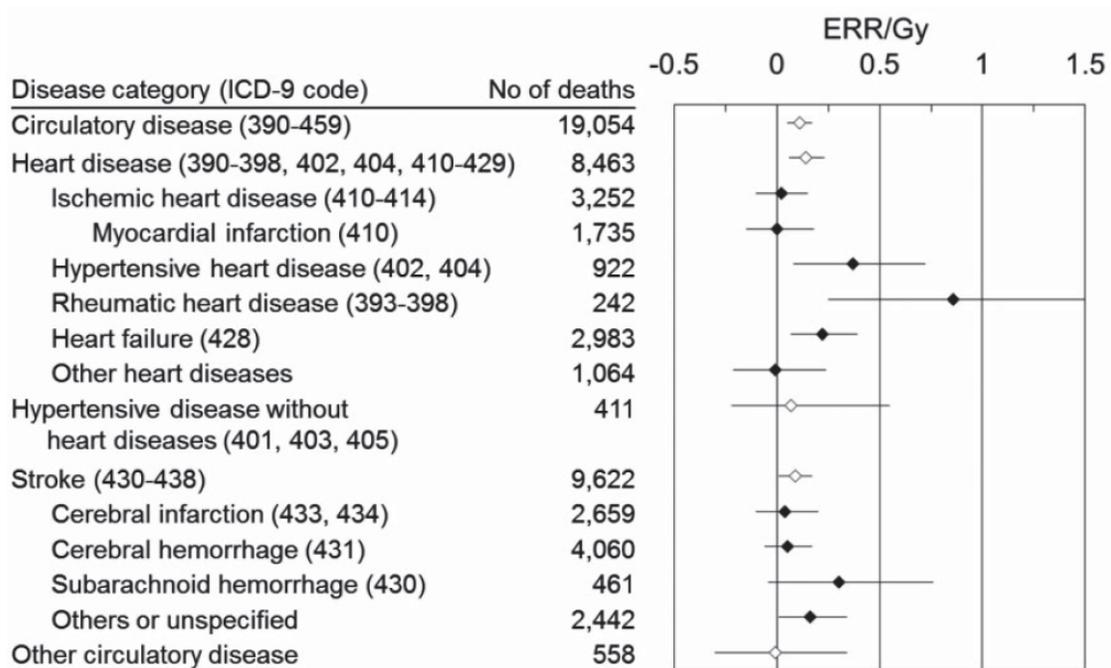
Fragility of theoretically based DDREF calculation

## 2. Somatic effects: non-cancer



Ozasa, Simizu et al. 2012

## Somatic effects: non-cancer



Ozasa, Ann ICRP, 2016

## Lessons to be learned from the survivor data

Increase in CVD was observed among the survivor  
This increase is mediated through hypertension rather than atherosclerosis  
Increased risk of rheumatic heart disease may be a secondary association, among proximal survivors  
Experimental approaches to elucidate the mechanism is based on the atherosclerosis mediated model

### 3. Age dependency: cancer risk of in utero exposures

#### A-bomb study

In utero exposed survivors had no childhood leukemia  
For the solid cancer, follow-up of 1958 -1999 indicated similar/ lower incidence than childhood exposed of  
ERR = 1/ Gy

#### OSCC

OSCC demonstrated extremely high incidence of 50/Gy for both childhood leukemia and cancer

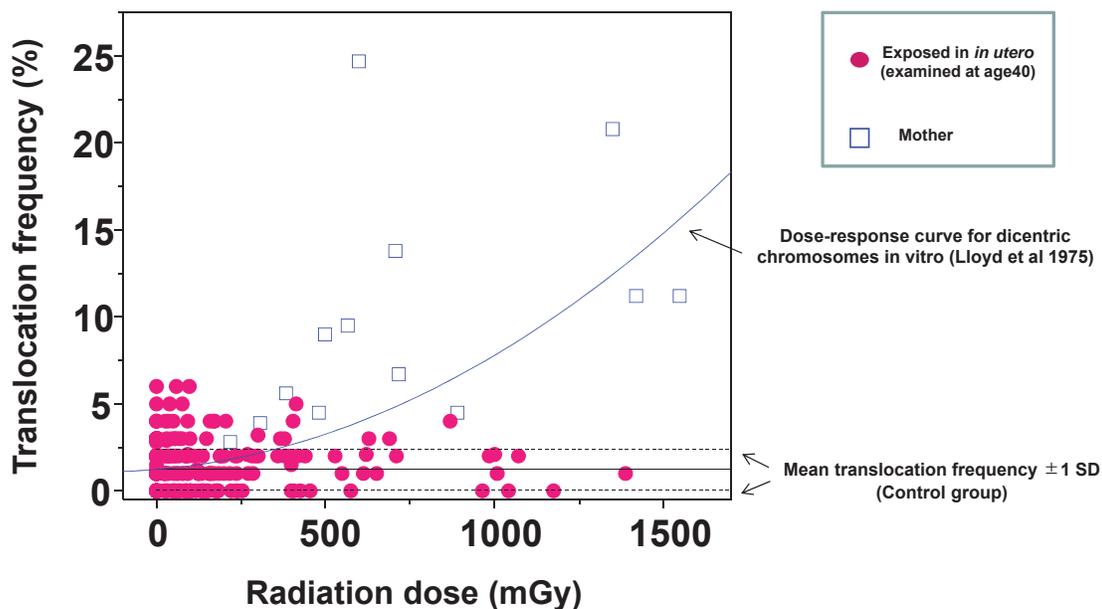


#### Mouse study

Experimental mouse studies demonstrate low or null cancer risk of in utero exposures

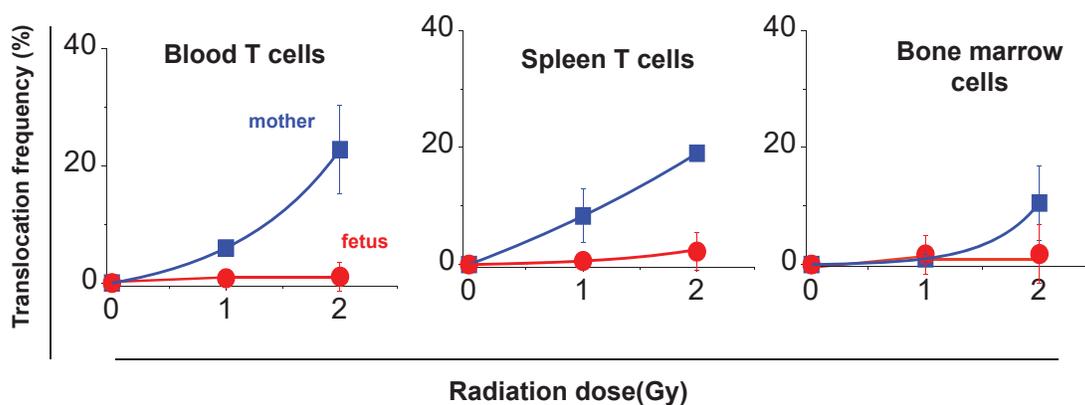


## Translocation frequency in blood lymphocytes is not elevated in the *in utero* exposed survivors



Ohtaki et al, Rad Res, 161: 373-379 (2004) 5

Similar lack of a dose response was also observed for in utero exposed **mouse hemato-lymphoid cells**.



Nakano et al, Rad Res, 167:693-702 (2007)

## Carcinogenic risk of in utero exposures

Epidemiology: Conflicting data between OSCC and RERF

Basic science: [Mouse experiments](#) favor low risks for in utero exposures, depend on the tissue

Mechanistic consideration: lack of chromosome aberration for in utero exposed survivors favors the low sensitivity to leukemogenesis

[Stem cell competition](#) to eliminate unfit stem cells during perinatal stages may be the mechanism (see ICRP Pub 131)

More story on stem cell competition will be discussed by Dr. Iwasaki of CRIEPI

## 4. RERF Biosamples

Archive consists of a mix of biosamples collected from individuals within various cohorts over extended time frames:

1. Serum	approx.	490,000
2. Plasma	approx.	100,000
3. Lymphocyte	approx.	130,000
4. Urine	approx.	110,000
5. Paraffin embedded tissues	approx.	700,000
6. Prepared slides	approx.	1,400,000
7. Others		

# Automated Bio-repository (-80°C BioStore II)



## 5. Future of RERF research

Promotion of epidemiology, mechanistic studies and public communications

Epidemiology: Continue to produce top ranking data

A-bomb survivors would disappear in 2030

→ A complete set of data base in 2030

Basic science: Promotion of mechanistic studies, firstly on hereditary effects and then carcinogenesis

Data base and bio-samples:

Creation of Research Resource Center  
open to researchers in the world

Relation to the society:

Establish more intimate relations with each  
members of survivors, F1, and public  
Dissemination of knowledge on radiation  
health effects to general public



# 7

## LOW DOSE-RATE RESEARCH IN CRIEPI

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IDEA Workshop 2016  
9<sup>th</sup> November 2016, Charlotte

# Low dose-RATE research in CRIEPI

Toshiyasu IWASAKI

Radiation Safety Research Center,  
Central Research Institute of Electric Power Industry (CRIEPI),  
Tokyo, JAPAN



## Central Research Institute of Electric Power Industry



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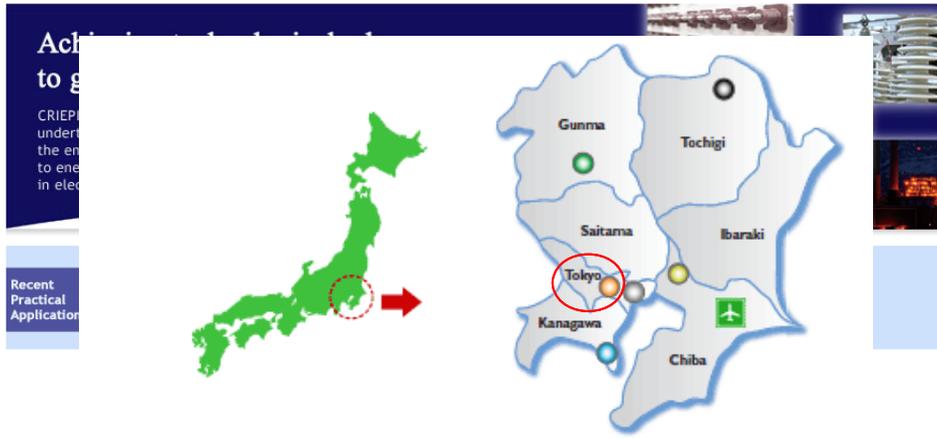
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## History of low dose/low dose-rate radiation research activities in CRIEPI

- 1987~ Pilot study on radiation hormesis
- 1988~ Research project on radiation hormesis
- 1998 Long-term low dose rate irradiation facility
- 2000 Low Dose Radiation Research Center
- 2003~ Research project on biological effects of low dose radiation  
Abandon 'hormesis' finally
- 2007 Radiation Safety Research Center  
(biology + health physics)  
Low dose microbeam X-ray irradiation facility
- 2009~ Research projects on  
"mechanisms of low dose-RATE radiation effects"  
and "rationalization of radiation protection methods"

More than 25 years' experience in the field  
of low dose and low dose-rate radiation research



## Unique facilities in CRIEPI



Long-term low dose rate  
irradiation facility

- Source: Cs-137  $\gamma$ -ray
- Dose rate: 0.3 ~ 3 mGy/hr



Microbeam  
X-ray irradiation facility

- X-ray: 1.49 keV Aluminum K-shell X-rays
- Beam size: less than 2  $\mu\text{m}$  in diameter
- Beam intensity: 0.1 Gy/min ~ 5 Gy/min



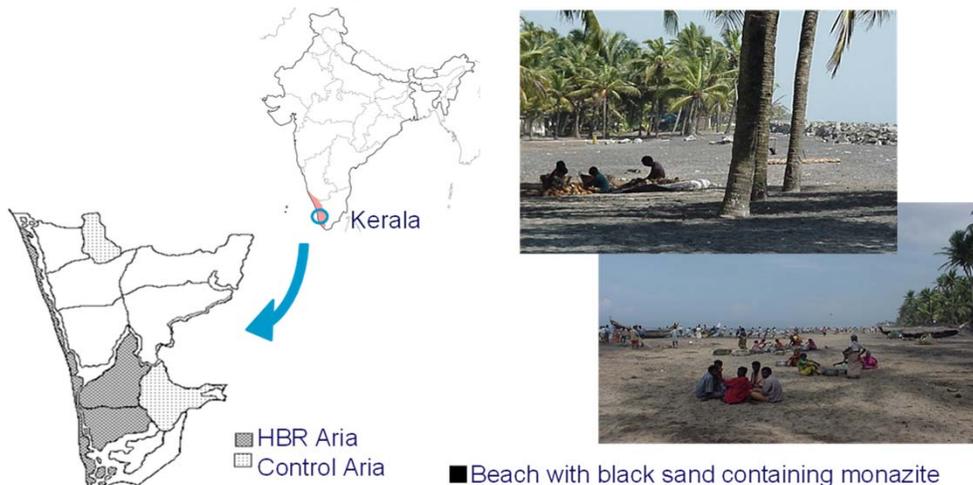
## Aims and research priorities in RSC

### ■ Main Aim

- Biological research to improve RP system
  - ✓ Pick up issues which can cause big change in RP system
    - Except for medical exposure situations
    - ×Acute, ○ chronic, (very) low dose-rate exposure situations
- Research priorities
  1. Dose-**rate** effects at very low dose-rate
    - ×Dose response at low dose (less significant after ICRP Pub 99)
  2. Non-cancer effect (at low dose-**rate**)
    - Circulatory disease
    - ×Cataract (no impact on detriment issues)
  3. Individual sensitivities
    - Age→NIRS in Japan
    - Genetic background of sensitivities at low dose-rate

## Support epidemiological study in high natural background areas

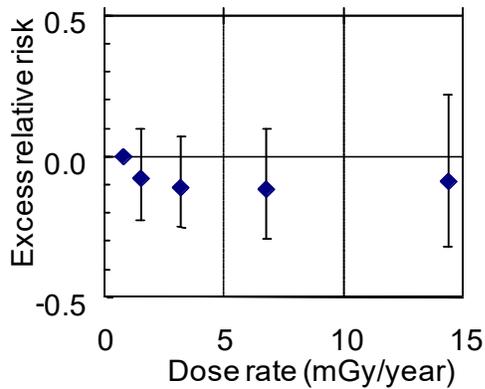
### ■ Cohort in Karunagappally, Kerala, India



## Epidemiological data at low dose-rate

### ■ Kerala cohort study

- No increase of cancer risk at less than ~20 mGy/year

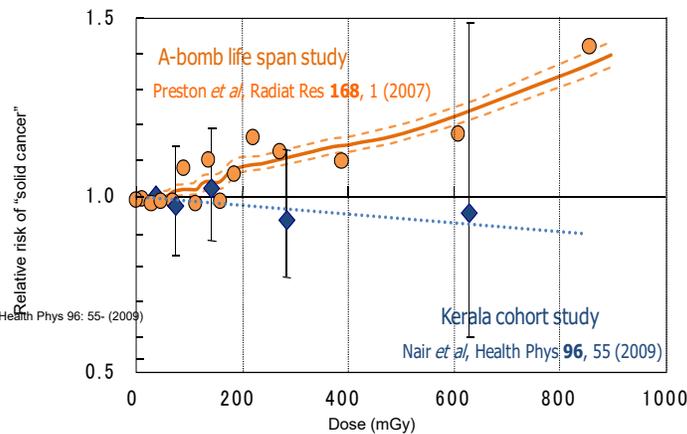


From Nair et al. Health Phys 96: 55- (2009)

## Epidemiological data at low dose-rate

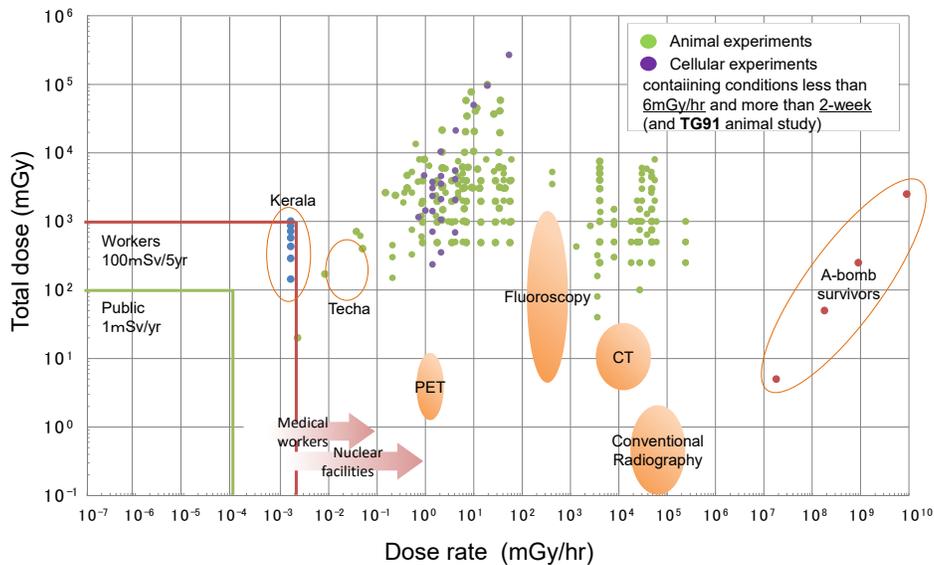
### ■ Kerala cohort study

- No increase of cancer risk at less than ~20 mGy/year

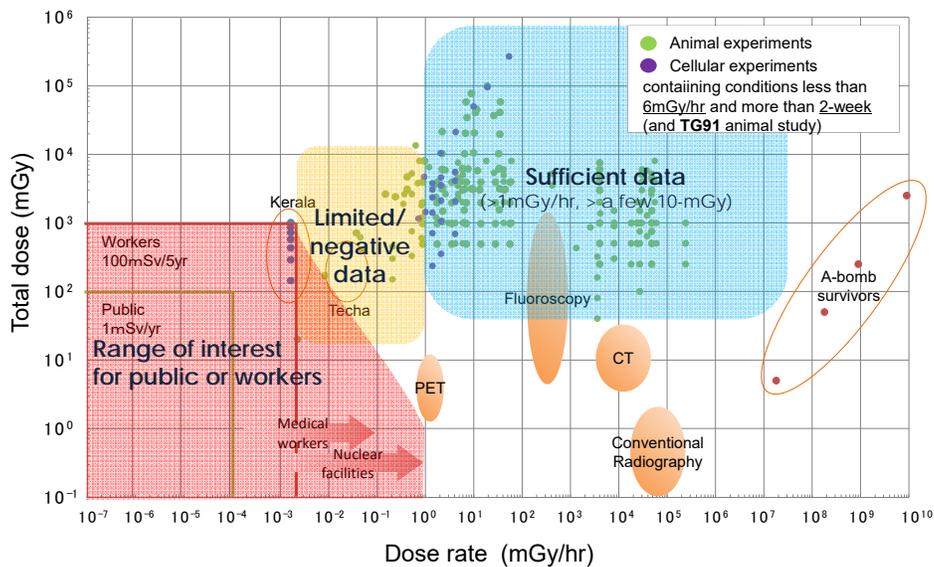


From Nair et al. Health Phys 96: 55- (2009)

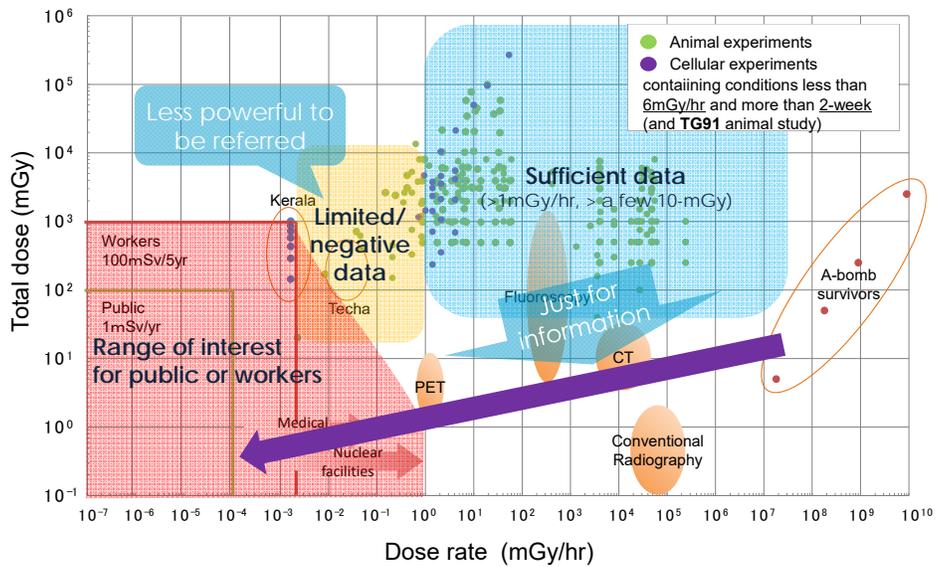
## Dose/dose-rate of interest and studied for biological experiments



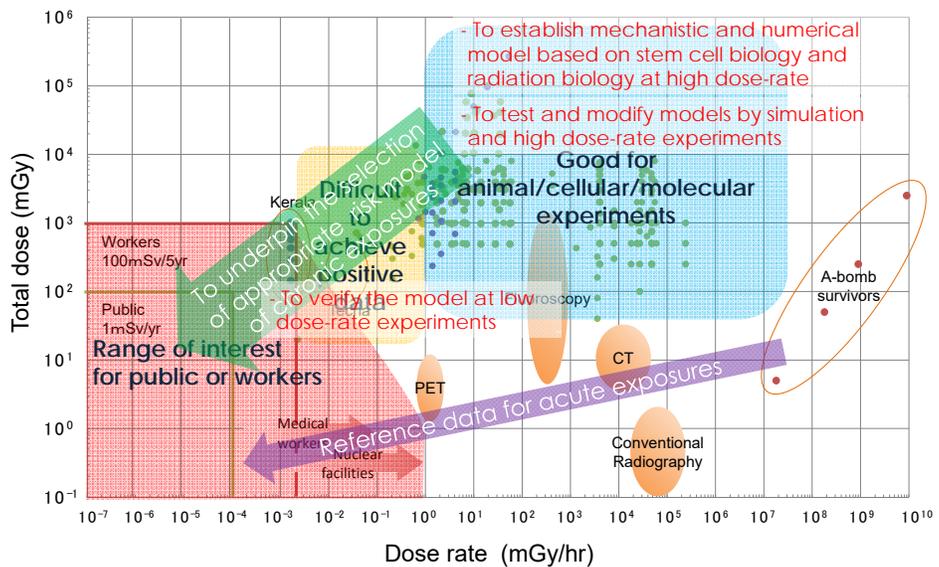
## Current status of low dose/low dose-rate biological research



# Current status of extrapolation



# Desirable approach



## Research activities in CRIEPI

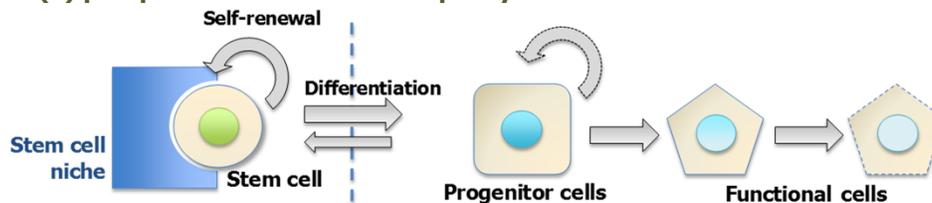
- Dose-rate effects on radiation carcinogenesis
  - Accumulativeness of radiation damage at tissue level
    - ✓ Turnover and competition of tissue stem cells (TSCs) as suggested in ICRP Pub 131 (2012)
  - X-ray microbeam as mimicking low fluence irradiation
- Non-cancer effects
  - Cardiovascular disease at low dose-rate
- Individual sensitivity
  - Genetic background of IS at low dose-rate (2017~)

## Accumulativeness of radiation effects

- Tissue stem cell (TSC) turnover
  - Mutation has been assumed to be accumulated in TSC in radiation induced carcinogenesis
  - TSCs are maintained as a pool with turnover

Stem cell has,

- (1) Long-term self-renewal capacity, and
- (2) pluripotent differentiation capacity



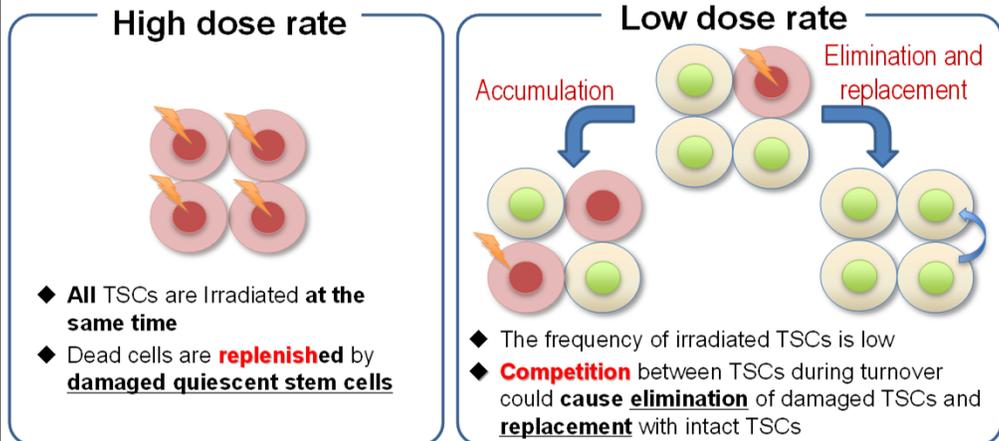
Modified from Prof Niwa's slide at 2<sup>nd</sup> MELODI WS

## ICRP Stem Cell report (Pub 131)

- 3 levels of QC systems in a body *(ibid 3.3.2.)*
  - Molecular level
    - ✓ DNA repair
      - Operate mainly within a few days after irradiation
  - Cellular level
    - ✓ Apoptosis
  - Tissue level
    - ✓ Competition
      - Slow process requiring **weeks and/or months**

## Tissue level considerations at very low dose-rate

Low dose rate = spatially/temporally dispersed

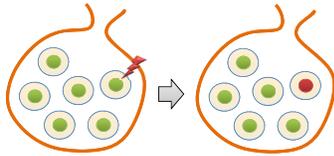


This elimination theory lowers the linear term. ... possibility for a DREF value larger than unity, as in the case of the current DDREF ... (ICRP pub 131)

# Stochastic modeling of competition in stem cell pool

## (1) Hit event

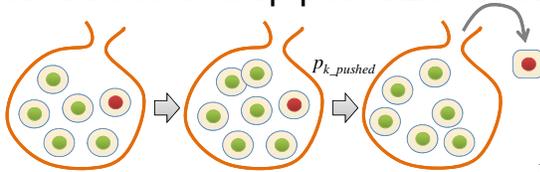
A cell is hit in a frequency of  $H$ .



$N$  : number of cells  
 $H$  : hit rate  
 $T$  : turnover rate  
 $x$  : strength in competition  
 $x=1$  (normal cell)  
 $x=x_d$  (damaged cell)

## (2) Turnover event

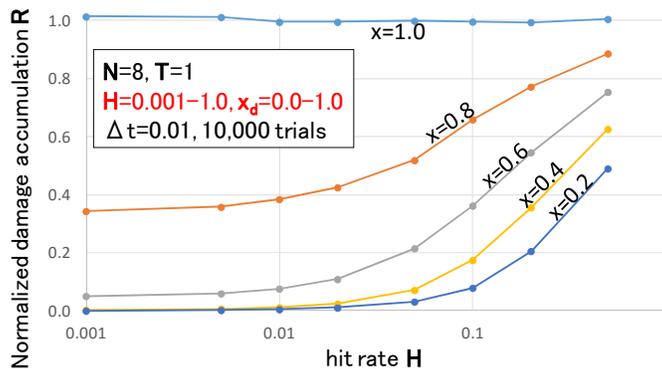
A cell reproduces in a frequency of  $T$ , and one cell is pushed out to keep pool size constant.



$$P_{k\_pushed} = \frac{1}{x_k} \bigg/ \sum_{i=1}^{N+1} \frac{1}{x_i}$$

# Results of numerical simulation (1)

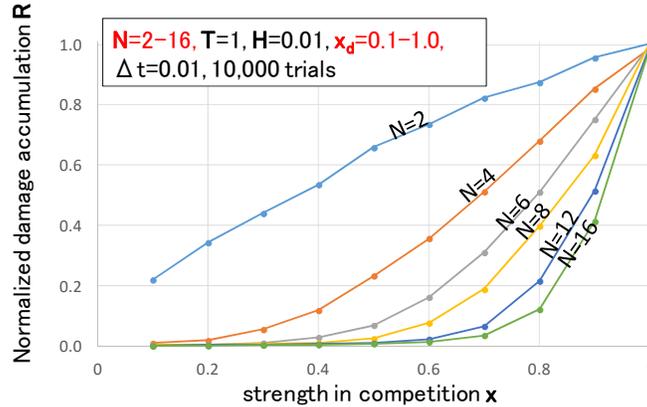
## Impact of hit rate $H$ (~ dose-rate)



When the hit rate  $H$  was lower enough than the turnover rate  $T$ , the stem cell pool was more likely to suppress damage accumulation (equivalent to dose-rate effect in this model).

## Results of numerical simulation (2)

### Impact of size of stem cell pool N



When the size of stem cell pool N was large, the damage accumulation could be suppressed even if the strength in competition of the damaged cell  $x_d$  is not so much small.

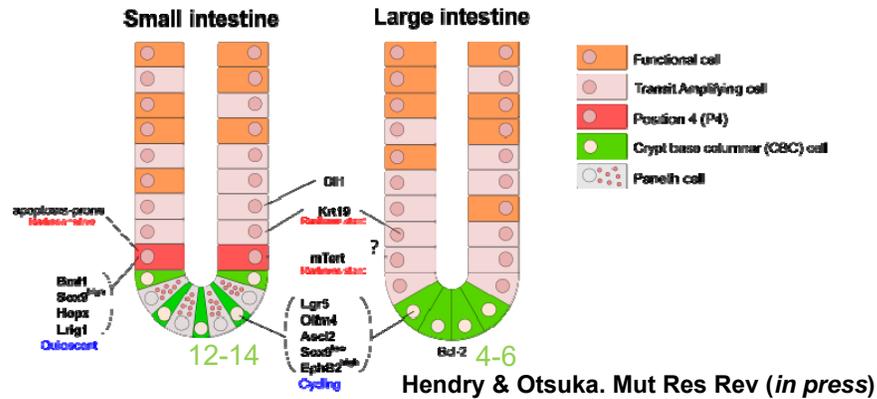
### From the simple numerical model ...

1. **Damage accumulation** in stem cell pool was **suppressed at low dose-rate** with considering little competition.
2. Important parameters which contribute to the dose-rate effect was strength in competition, turnover rate, and size of stem cell pool.

# Biological approach: Intestinal stem cells as cell of origin in cancer

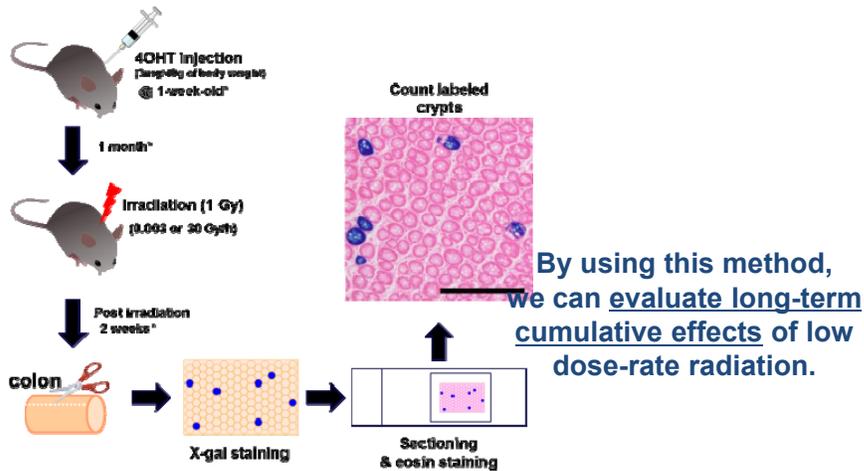
## ■ Intestine

- Well characterized
- Risk relevant ( $w_T$  for colon = 0.12)



## Animal experimental system

*Lgr5-EGFP-Cre<sup>ERT2</sup>*

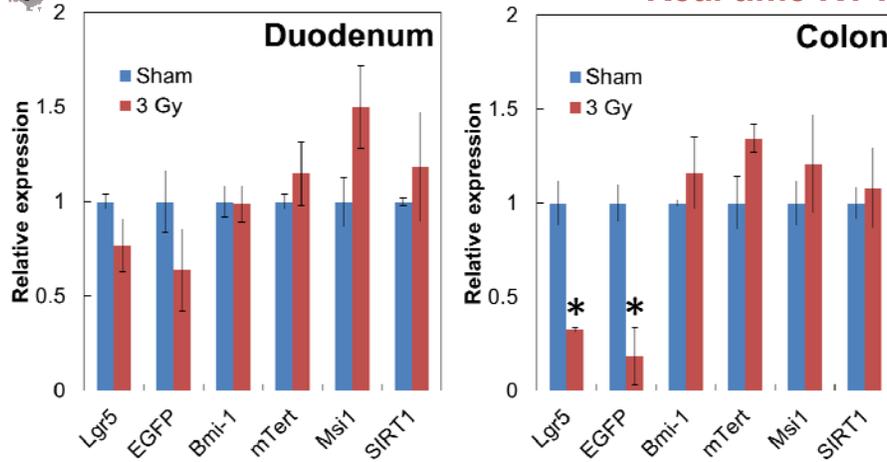


Otsuka & Iwasaki. *J Radiat Res* (2015)

# Radiosensitivity of intestinal stem cells



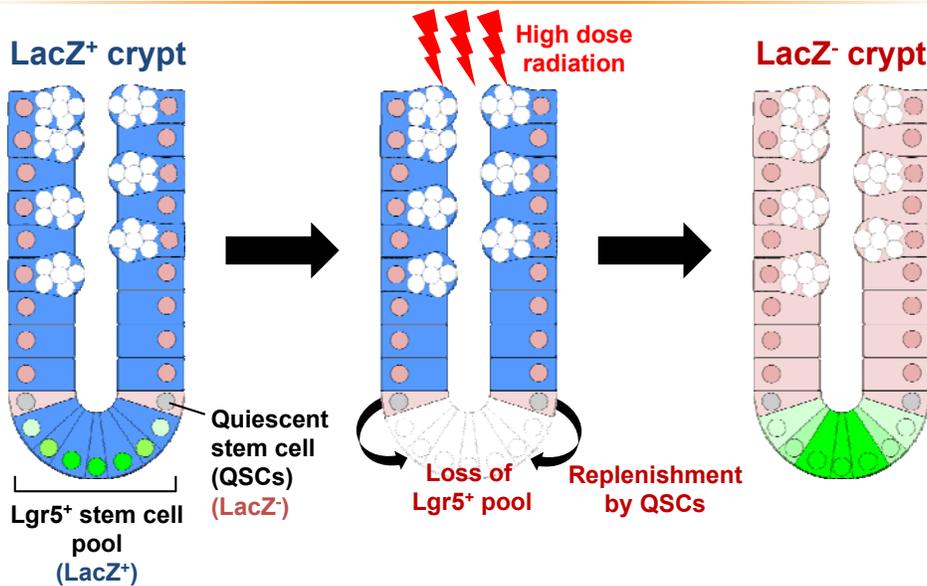
Otsuka K (unpublished data)  
Real time RT-PCR



- Whole tissues were harvested 24h after X-ray irradiation
- All expression levels were normalized by its *Gapdh* expression

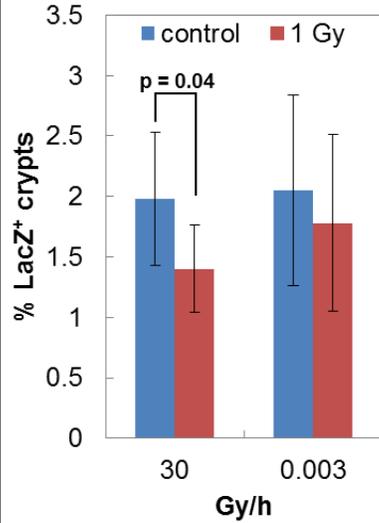


# Quantitative evaluation of Lgr5<sup>+</sup> replenishment



## Dose-rate effects on Lgr5<sup>+</sup> replenishment

Otsuka *et al.* J Radiat Res (in press)



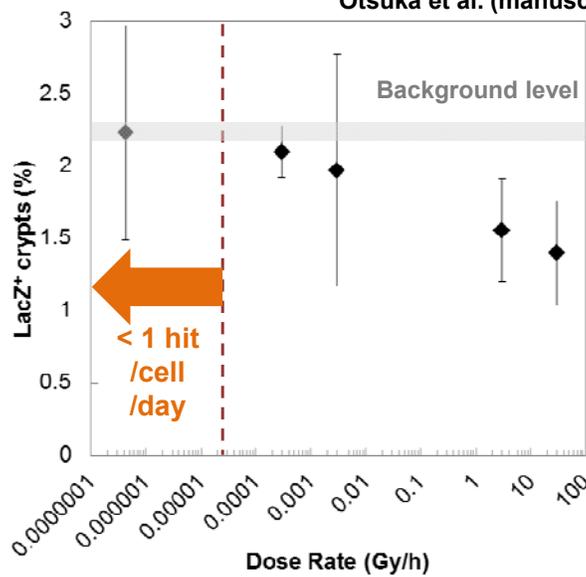
Low dose rate irradiation facility @ CRIEPI

CRIEPI

CRIEPI

## Dose-rate effects on Lgr5<sup>+</sup> replenishment

Otsuka *et al.* (manuscript in preparation)

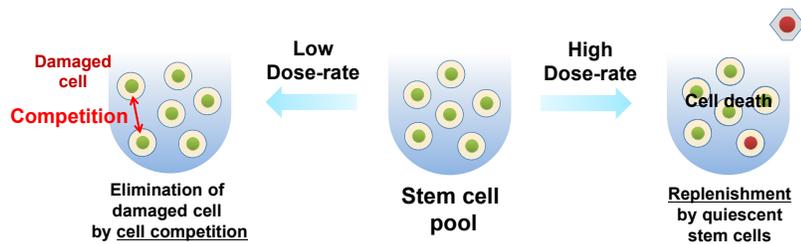


CRIEPI

CRIEPI

## Summary of biological approach

1. Some parameters extracted from modeling approach can be confirmed by biological approach.
2. Colonic Lgr5<sup>+</sup> stem are radiosensitive enough to detect the effects of low dose/dose-rate radiation.
3. There may be a dose-rate limit to induce the replenishment of Lgr5<sup>+</sup> cells by quiescent stem cells.



Then, “competition” ?

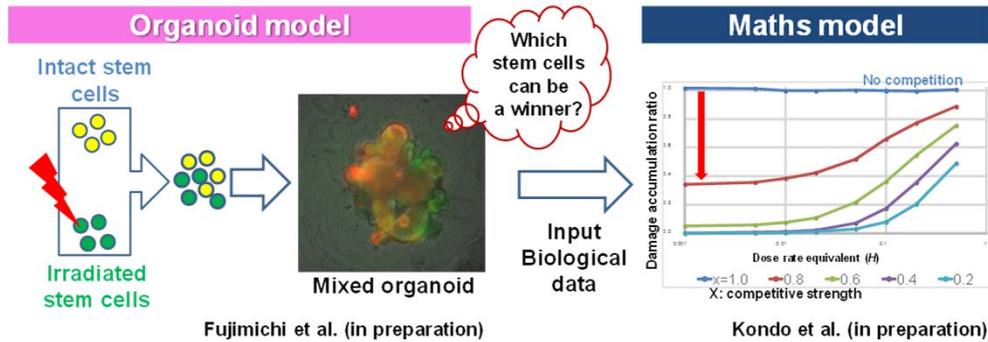
## Organoid culture from isolated stem cells

- High efficient organoid formation from single intestinal stem cell



## Organoid model for 'competition'

- How to evaluate for the presence of 'stem cell competition'



## Non-cancer effects

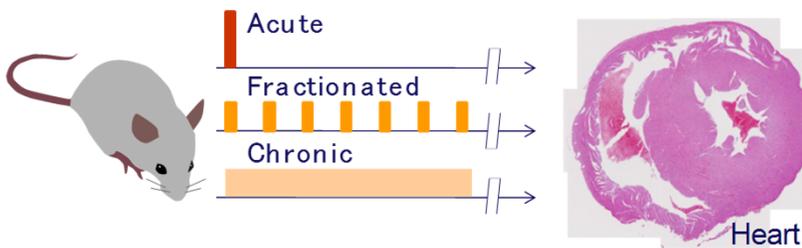
### Cardiovascular disease (CVD)

To elucidate causality at low dose and low dose-rate

- ✓ Under the recognition that underpinning evidence on dose-rate effect would be key issue for RP

#### Experimental research

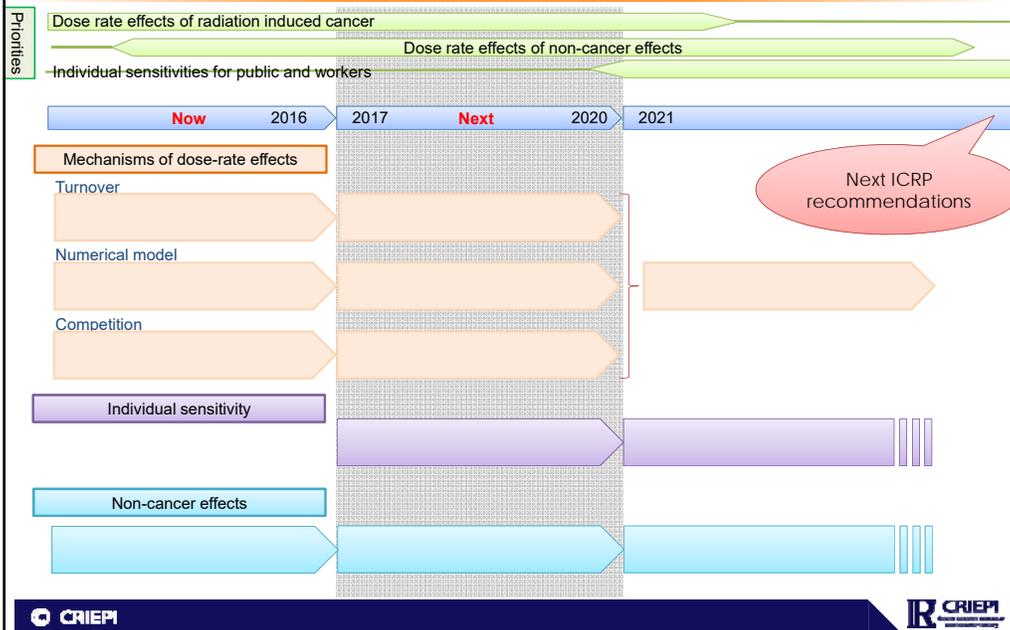
- ✓ Search for indices for low dose radiation damages which could be retained and have causal relationship to CVD
  - By histological analysis after acute/fractionated/chronic exposure



## Next period of research plan (2017-20)

- Dose-rate effects on radiation carcinogenesis
  - Quantitative analysis of stem cell competition
    - ✓ With combining modeling approach
  - To establish mechanistic and numerical model of dose-rate effects with considering competition
- Non-cancer effects
  - Identification and Analysis of surrogate biomarkers in heart or vessels which show different response to fractionated and chronic exposures
- Individual sensitivity
  - Preliminary evaluation of genetic background for different responses among human primary cells

## Research plan in CRIEPI



Interface to outer 'system's  
(ICRP, MELODI, ...)

We are not alone!



- Information sharing, opinion transmission
- Identification of issues for RP research
- Priority setting, roadmap, rolling
- Education and training
- Support of NRC activities

# 8

## LOW DOSE RADIATION RESEARCH IN EUROPE

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# Low dose radiation research in Europe

Jacques Repussard  
President of MELODI

Charlotte (NC), November 2016



## Contents

- The European strategy of research integration
- Key scientific challenges, as seen from Europe
- Towards better international coordination
- Conclusion



## Contents

- The European strategy of research integration
- Key scientific challenges as seen from Europe
- Towards better international coordination
- Conclusion



## The HLEG Report in 2010

This report on low dose research problematic commissioned by EURATOM (available on internet) led to a new policy response, aiming at the objective of resolving the scientific and societal challenges through better « integration » of european R&D capabilities along a shared strategy.



## Knowledge gaps invite doubts about the robustness of the European radiation protection system for low dose/dose rate exposures

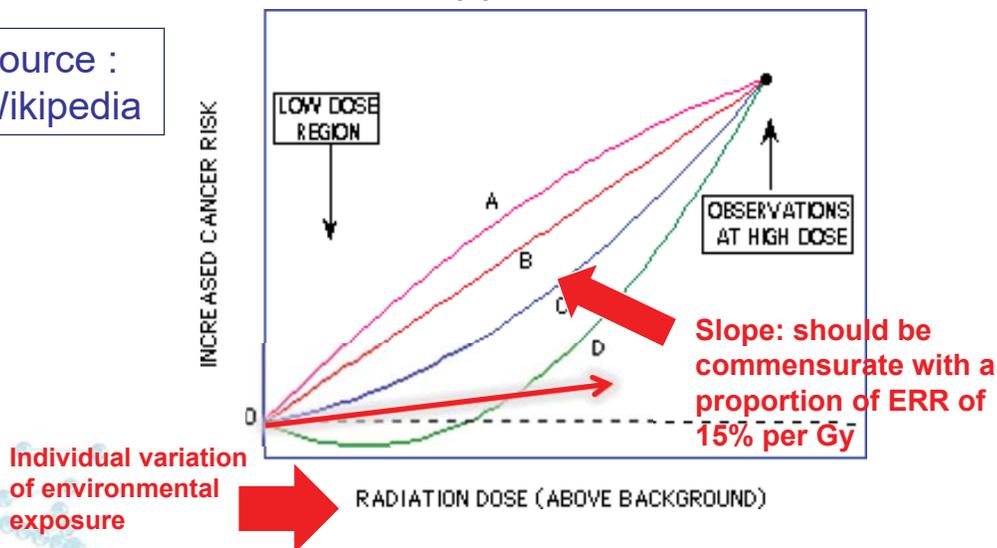
- The LNT-precaution-based regulatory system leads to **confusion in perception** of the relative significance of health risks at low dose/dose rate exposures,
- **Poor judgement** outside the professional sphere about the hierarchy, prevalence and prevention of radiological risks can lead to inadequate risk management decisions,
- Unresolved operational issues of radiation protection optimisation, in the **medical field**: individual sensitivity, damage to healthy tissues subsequent to radiotherapy, particularly with advanced protocols, and for **space travel**.

5



An example of misleading information : The usual dose /risk curve slope invites to see an ERR of approx 100%...

Source :  
Wikipedia



6

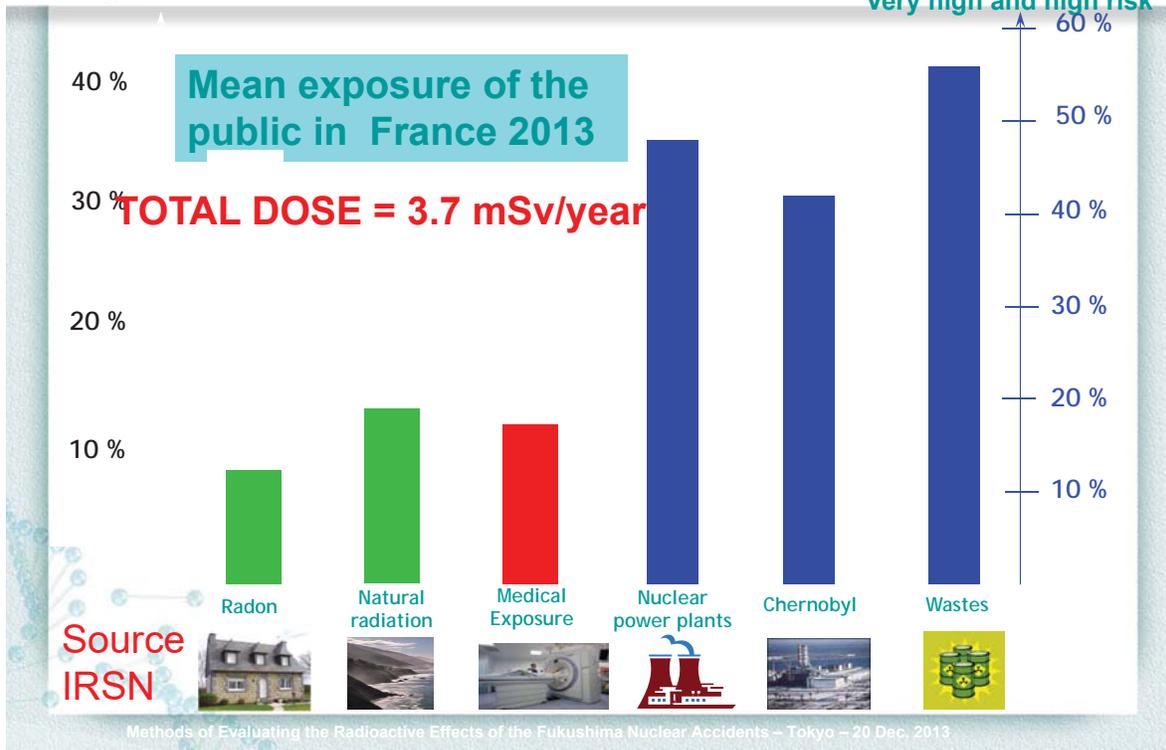


# Radiation risk as perceived by the French public

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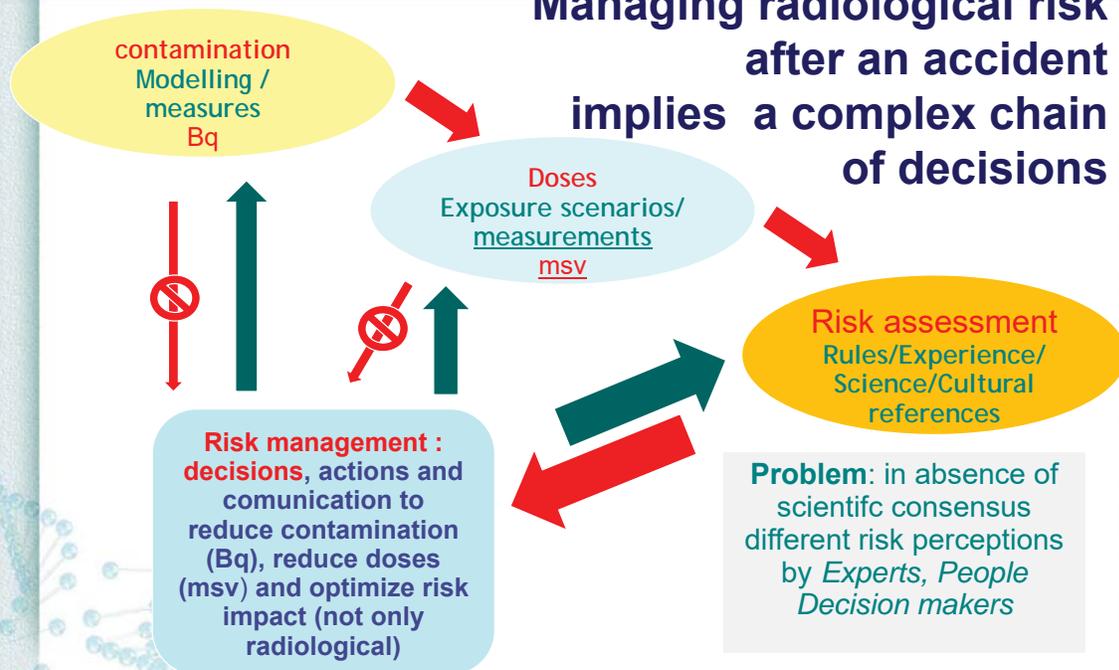
% answers :  
Very high and high risk



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## Managing radiological risk after an accident implies a complex chain of decisions





## 4 key EU policy objectives

Closing key knowledge gaps is an ambitious target for RP research which requires to:

- Enhance multidisciplinary (e.g. epidemiology, physics and radiobiology)
- Develop a holistic research strategy
- Secure stable and excellence based funding mechanisms
- Include societal aspects in the R&D scope



## The EURATOM integration concept : platforms + projects

Platforms	MELODI	Alliance	Neris	Eurados	EURAMED
DoReMi	—				
Comet		—			
Prepare			—		
OPERRA	—	—	—	—	- - - -
Concert EJP	—	—	—	—	- - - -
EURATOM Call 2016	—			—	—



**MELODI**

Multidisciplinary European Low Dose Initiative

## **The missions of R&D Platforms: promote integration, develop strategic research agendas and roadmaps in order to:**

- Improve the radiation protection system for low dose / dose rate exposures (MELODI)
- Better understand the behaviour and effects of radionuclides in the environment and on ecosystems (Alliance)
- Improve radiological preparedness for large scale pollutions (NERIS)
- Provide excellence in radiation measurements techniques and related dose estimations (EURADOS)
- Optimize the use of radiations for medical applications (EURAMED)
- Help society in its interaction with radiation risk (*European Stakeholder Forum (a joint Platforms project)*)



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## **The inclusion of medical research partners**

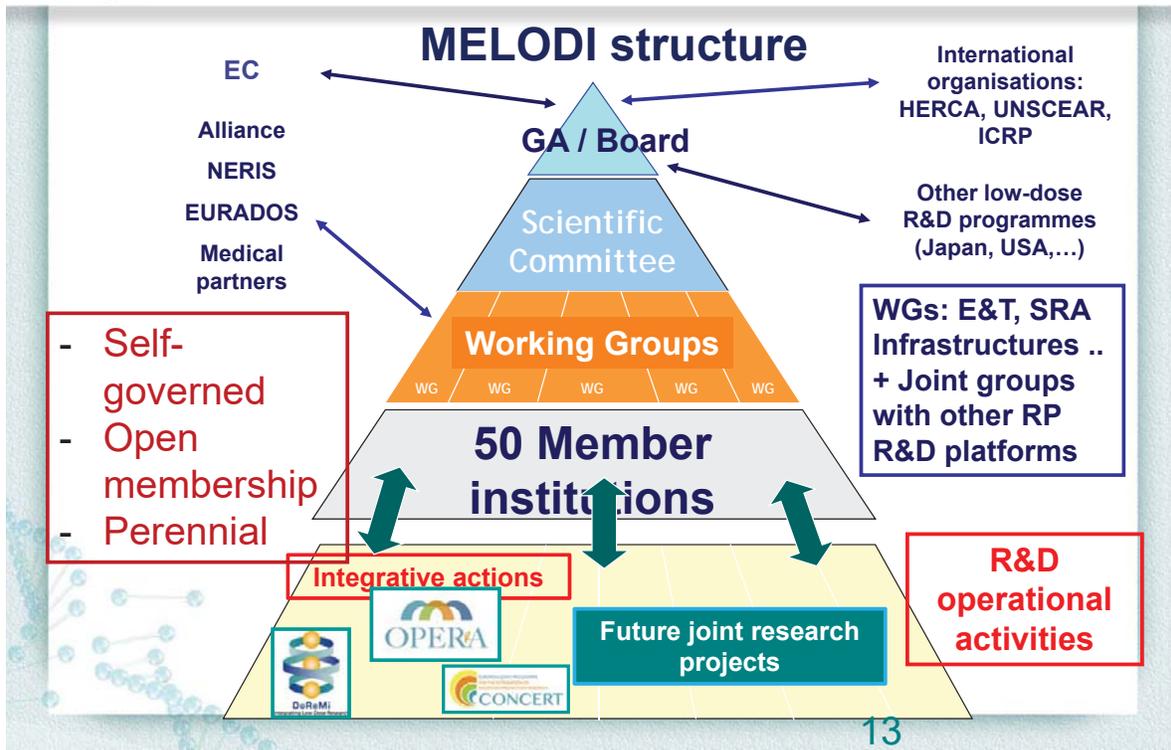
- **MOU Signed in 2014 between: MELODI, EURADOS, and 5 major European medical professional associations , notified to the European Commission**
- **Signatories commit to cooperate to promote integration and efficiency of European radiation protection research, to maintain and use common infrastructures and to promote scientific E&T**
- **This protocol led the creation of EURAMED in 2016, a new platform operating in close interaction with MELODI and EURADOS, bringing together the EURATOM and medical research capabilities.**



# MELODI: an example of a european R&D associative platform

MELODI

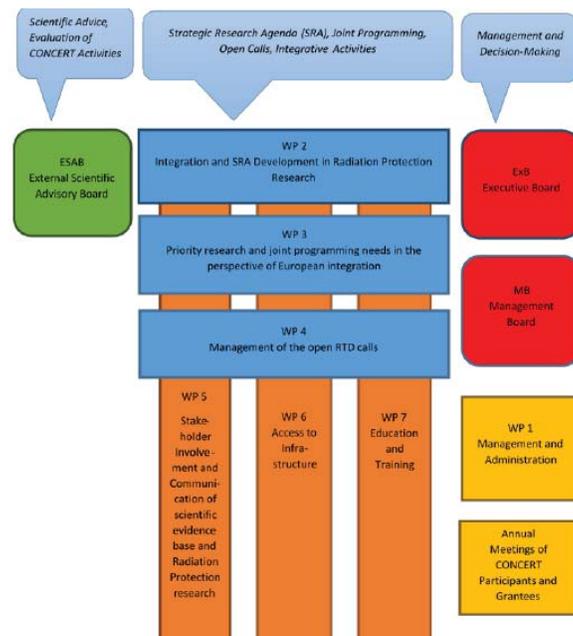
Multidisciplinary European Low Dose Initiative



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## The latest EURATOM project: EP CONCERT



# CONCERT EJP

European Concerted Programme on Radiation Protection Research a European Joint Programme

- Supporting integration
- Funding research
- 27M€ over 5 years



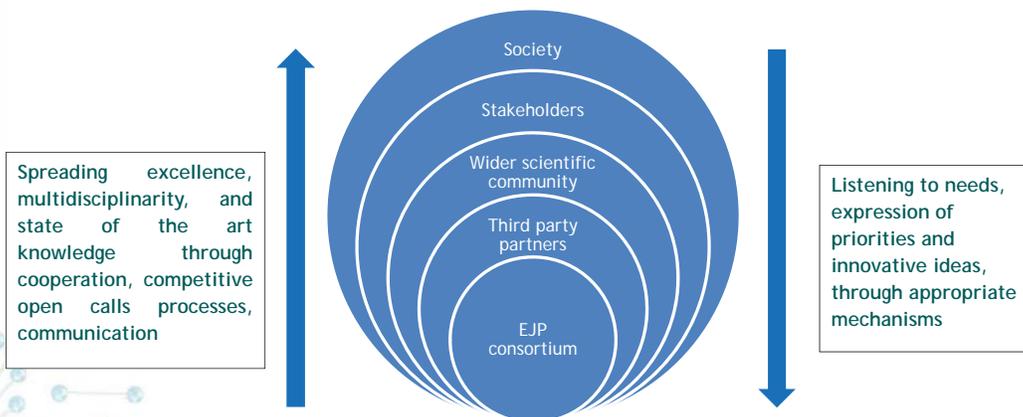
## CONCERT Funding Scheme

- 70% EURATOM + 30% National co-fund by the EJP Partners (in total around 27 M€)
- 60% (16M€) for two CONCERT open research calls (2016 and 2017)
- 30% (8M€) for CONCERT integrative activities (R&D Roadmapping, joint programming, stakeholder engagement, access to research infrastructure, E&T)
- 10% (3M€) for administration and management

15



## CONCERT: an innovative two way street to integration



16



## Platforms + Projects:

- Medium/long term strategy continuity
- Open and multidisciplinary Scientific community
- Consensus building capability
- Stakeholder interaction
- Funding based on competition and excellence
- Publicly available results
- EU Policy supporting long term strategy

17



## Contents

- The European strategy of research integration
- Scientific challenges as seen from Europe  
(based on EURATOM DoReMi results @)
- Towards better international coordination
- Conclusion

@ see report

18



## **Cancer risk: understanding reasons for and effects of observed non linearities in low dose/dose rate radiation responses**

- in the expression of genes and proteins as well as in the profiles of regulating miRNAs,
- in the induction, signaling and repair of radiation-induced DNA damage,
- in the dose rate dependency of the induction of senescence in endothelial cells of the cardiovascular system,
- in the setup of pro – and anti-inflammatory immune responses.



## **And beyond cancer risk, a need to further understand:**

- Factors and mechanisms for individual radiation sensitivity and susceptibility to the induction of cancers,
- radiation induced effects on the immune system, and their variations depending on dose rate, dose, and fractionation of dose,
- mechanisms involved in non-cancer effects (with or without threshold?), particularly cardiovascular, eye lens opacities and neurological effects.



## Development of validated bio-markers and optimisation of radiological research cohorts

- **review and validation of new molecular biomarkers for :**
  - biological dosimetry purposes (eg: H2AX, 53BP1, FTXR, 8-oxo dGua)
  - indicators for biological effects such as telomere-FISH, Raman spectroscopy), for characterizing IR exposure, metabolic changes and pathological changes (different types of cancers and non-cancer pathologies),
  - individual sensitivity and susceptibility
- **Optimisation of epidemiological cohorts and of bio-sample information quality and open availability**

21



## Contents

- The European strategy of research integration
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Conclusion

22



## International scientific cooperation for low dose effects is so far mainly organised downstream of R&D (UNSCEAR, ICRP,...)

With exceptions:

- Japan/US lifespan ABomb cohorts follow up
- Post Chernobyl research
- EURATOM research programs
- Post Fukushima research

23



## Potential benefits from increasing R&D cooperation upstream

- Optimisation of use of rare resources,
- Propagation of excellence and multidisciplinary,
- Acceleration of downstream processes towards radiation protection doctrine establishment (ex: medical care, long distance space travel, rad-waste management, post-accident situations)

24



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# Possible arrangement

## A trilateral MOU ? (Europe, USA+, Japan+)

- Mutual information (SRA's, R&D calls)
- Visiting scientists and access to key infrastructures
- Open data and stakeholder consultation policy
- Coordinated thematic consensus conferences
- Co-funded R&D initiatives
- Rotating coordination secretariat **(need to identify potential signatories !)**

25



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## Paris, October 10/12 2017: an opportunity to finalise an international low dose R&D cooperation arrangement



Claire Coustals  
ICRP Chair



Jacques Dupuisard  
MELODI Chair



Jean Christophe Weil  
IRSN Director General

IT IS A GREAT PLEASURE for us to officially announce that ICRP, MELODI and IRSN are together organising an exceptional combined international event in Paris - France (Disney Business Center) on October 10-12<sup>th</sup>, 2017.

FOR ICRP it will be the 4<sup>th</sup> International Symposium on the System of Radiological Protection.

FOR MELODI, it will be the 9<sup>th</sup> European Workshop on Low Dose Ionizing Radiation Risk Research, in the context of the European Radiological Protection Week, which brings together all partners of the European research platforms: MELODI, EURADOS (dosimetry), NERIS (emergency and recovery preparedness), ALLIANCE (radioecology) and EURAMED (medical radiological protection).

FOR IRSN, the responsibility to host this scientific event and to contribute with our expertise and means to the organization.

THIS COMBINED EVENT will offer the opportunity for professionals, experts and researchers worldwide to discuss their respective concerns and the current challenges facing all areas of radiological protection, as well as the way forward through new research, updating doctrines, or better interactions with stakeholders.

WE EXPRESS OUR THANKS to our French and European colleagues, who are already dedicating time and efforts to help us organise this scientific event, and to all supporting organisations for making it possible.

Please join us in Paris.  
Save the date in your agenda!

### Preliminary program

#### Programme of the Joint ICRP/ERPW sessions:

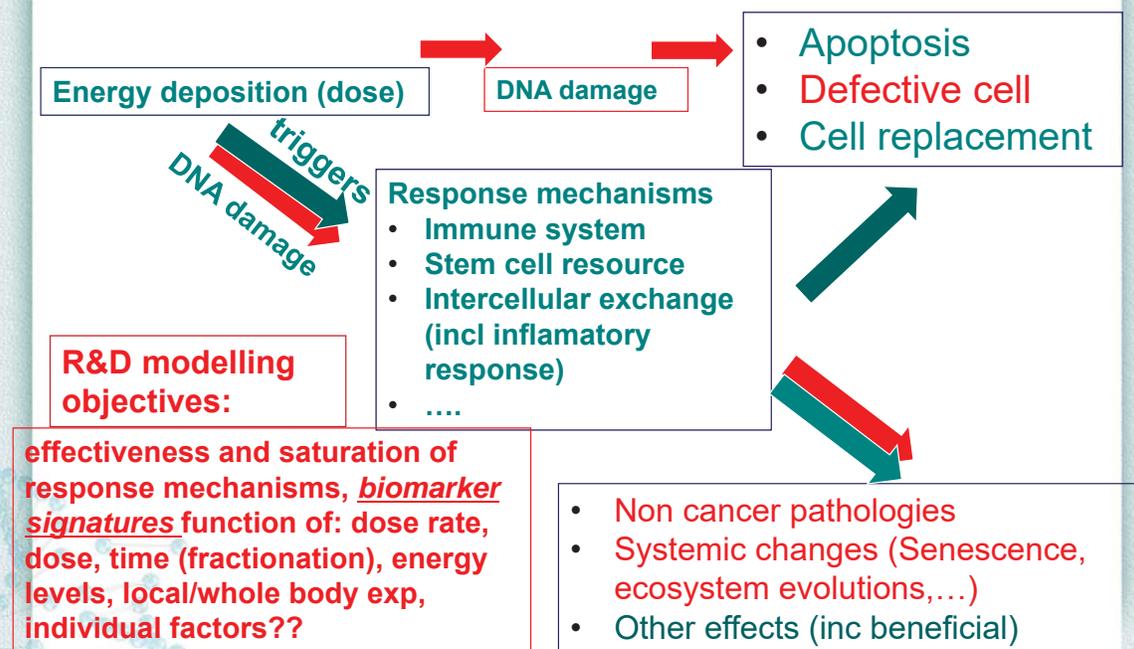
- ▲ Effects, Risks, and Detriment at Low Dose and Low Dose-Rate  
(in collaboration with MELODI)
- ▲ Advances in Dose Coefficients  
(in collaboration with EURADOS)
- ▲ Advanced Radiotherapy: Benefits and Radiation Protection due to Developments in Imaging, New Technologies, and Stratification  
(in collaboration with EURAMED)
- ▲ Post-Accident Recovery  
(in collaboration with NERIS)
- ▲ Integrated Protection of People and the Environment  
(in collaboration with ALLIANCE)

#### Programme of the ERPW sessions :

- ▲ Recent scientific advances in radiation biology and pathology, epidemiology, dosimetry, radioecology, medical applications of ionizing radiation and emergency preparedness and response
- ▲ Call for abstracts
- ▲ Strategic Research agendas (SRA) and European Road Map



# Thank you for your attention





## Modelling and Biomarkers of response mechanisms « efficiency »

Of major potential importance for:

- Radiation protection of populations (and ecosystems) at very low dose rates (waste management, post accident doctrines: food, relocation, communication with individuals and stakeholders)
- Radiation protection of patients and workers (internal doses)
- Medical research in general (radiation used as a marker for assessing key biological response mechanisms to stress, and not only risk).

29



## An international open/shared framework to:

- Consolidate data accessible repositories (radiobiology + epidemiology)
- Adopt a Charter for open and quality assured data
- Set up an open and sustainable multicentric modelling infrastructure,
- Promote radiobiology/physics R&D beyond risk related issues, and guarantee the independance of research (attract new talents),
- Discuss results in open consensus conferences

30

# 9

## CERTITUDE ATTITUDE: UNCERTAINTIES AND QUALITY IN RISK ESTIMATES FOR RADIATION- INDUCED DETRIMENT

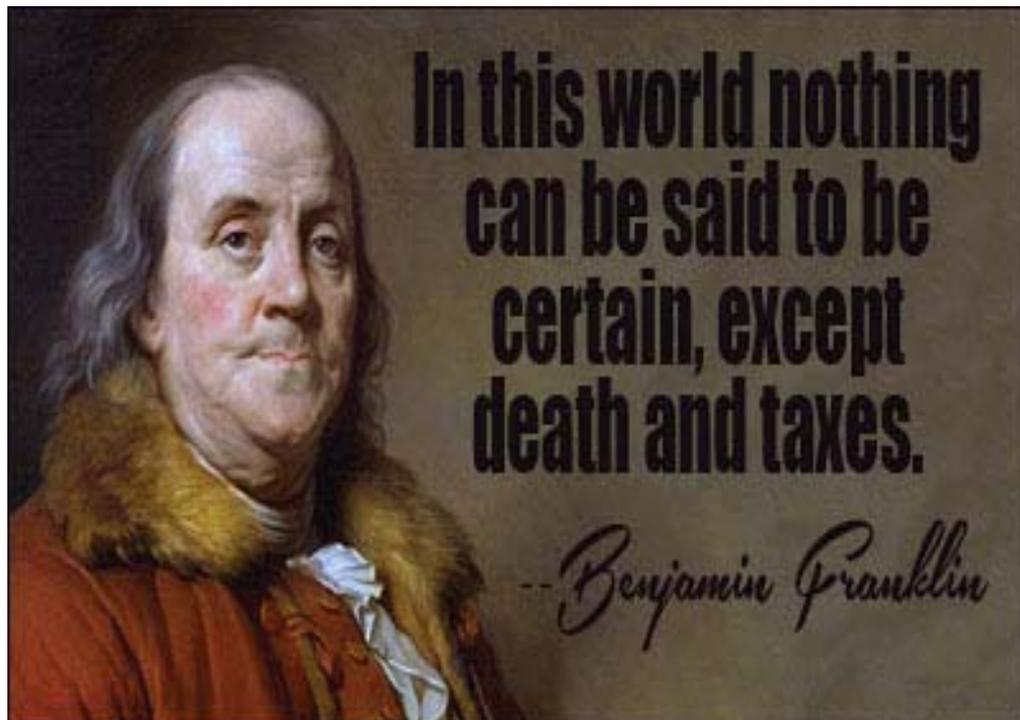
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Cancer Center

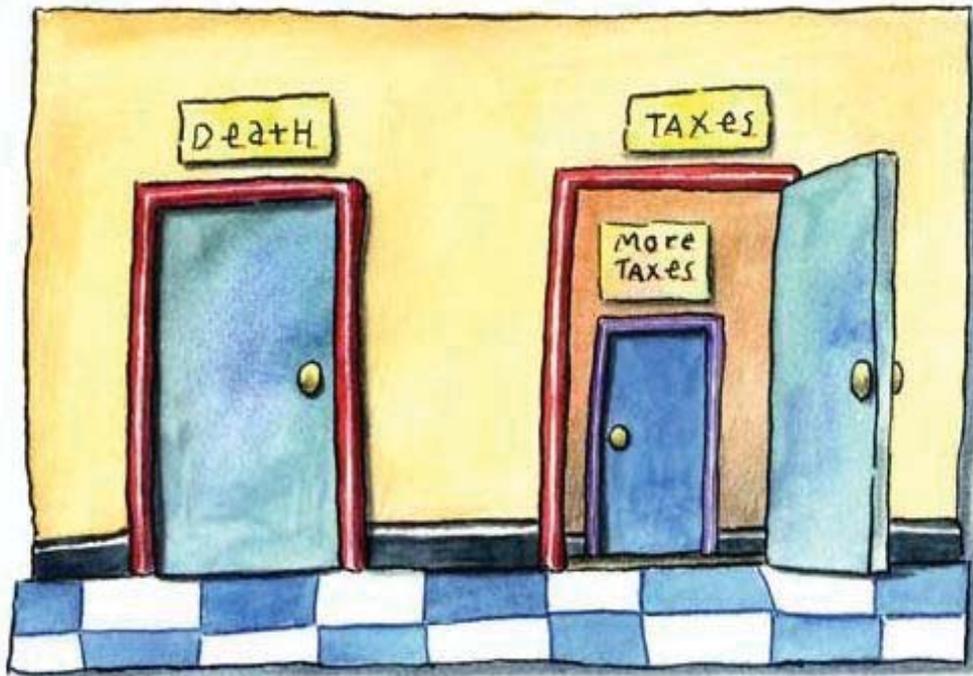
# Certitude Attitude: Uncertainties and Quality in Risk Estimates for Radiation- Induced Detriment

2016 EPRI IDEA Workshop  
Lawrence T. Dauer, PhD, DABHP  
Associate Attending Physicist  
Dept of Medical Physics / Dept of Radiology



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Death?





## Purpose Statements



- Risks of exposure to ionizing radiation are much better known than other agents.
- However, at lower doses (e.g. <math><100\text{ mGy}</math>) of low-LET radiation, the uncertainties associated with epidemiological studies become increasingly large and tend to mask any possible effect.
- Estimation of risk requires judgments against a backdrop of uncertainty and ongoing scientific debate.



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## Purpose Statements

- Many epidemiological studies derive risk estimates with “credible intervals” that often only express impact of statistical fluctuations of the data in the frame of the risk model chosen (and ignore other sources).
- Therefore, an understanding of uncertainty and quality concepts needs to be addressed and communicated to improve decision-making.



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## Objectives

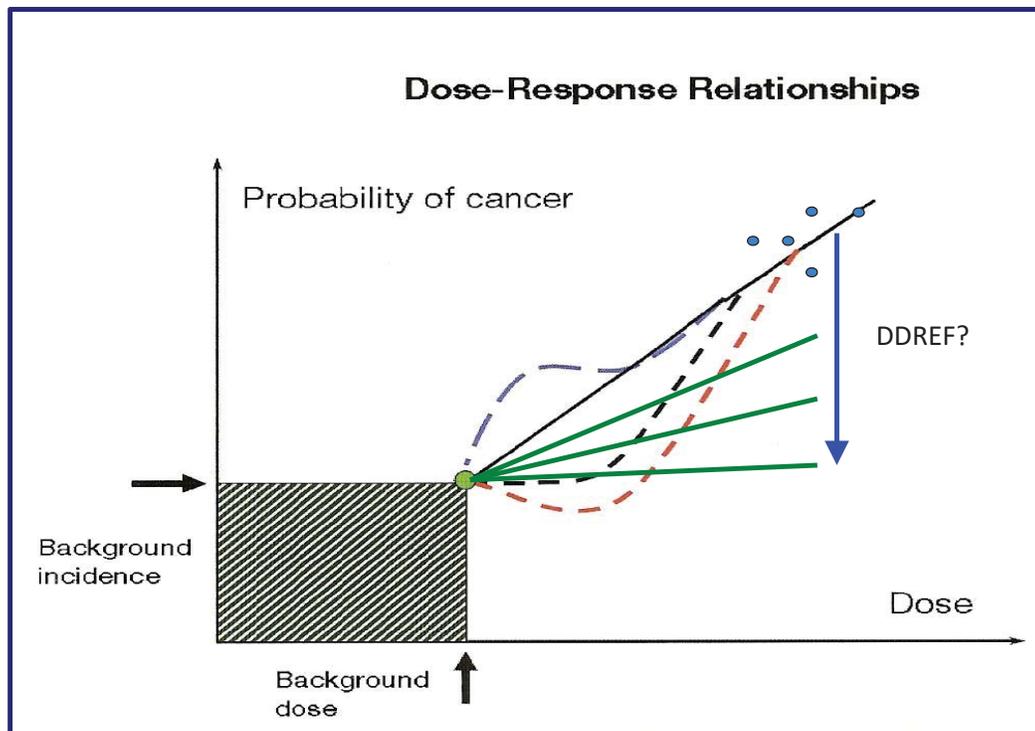
- ID fundamental concepts.
- Recognize sources of uncertainty.
- Explore impact of uncertainties.
- Discuss examples assessing quality.
- Challenge to contribute to research.
- Review Conclusions



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## Paracelsus Quandary





# ICRP Publication 103

## Nominal Risk Coefficients for Stochastic Effects after Exposure to Radiation at Low Dose or Low Dose Rate



Exposed Population	Cancer (%/Sv)	Heritable (%/Sv)	Total (%/Sv)
Whole	5.5	0.2	<b>5.7</b>
Adult	4.1	0.1	<b>4.2</b>

Uncertainties in such risk estimates have been suggested as being up to **a factor of 3 lower or 3 higher** than the value itself. (UNSCEAR, 2012).



## Uncertainty in Epidemiology

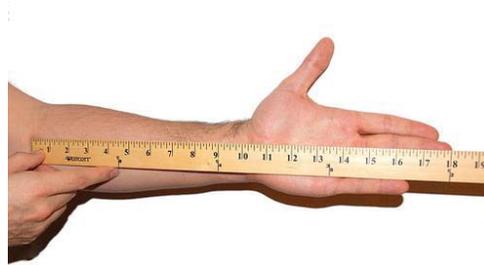
- **Error** = difference between estimate and the true (*but unknown*) value.
- **Uncertainty** = probability distribution of the possible errors composed of mixtures of systematic and random errors.





## Unshared Errors

- **Classical Error** – measurement error due to imprecise but unbiased measuring device. Bias dose response.
- **Berkson Error** – due to assignment to representative values (grouping into bins). Less bias typically.

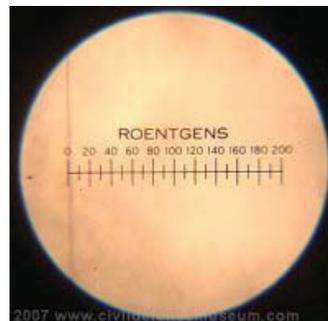


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## Shared Errors

- Shared measurements (e.g., improperly calibrated device) and/or shared assignments (wrong values for model input parameters).
- Inevitably lead to bias and failure to account for them can lead to overconfidence in risks estimates.

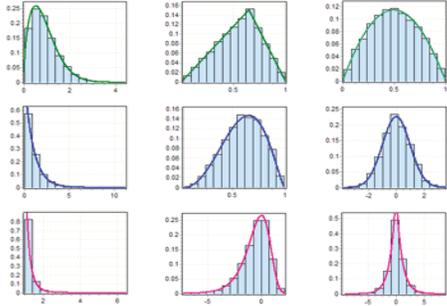


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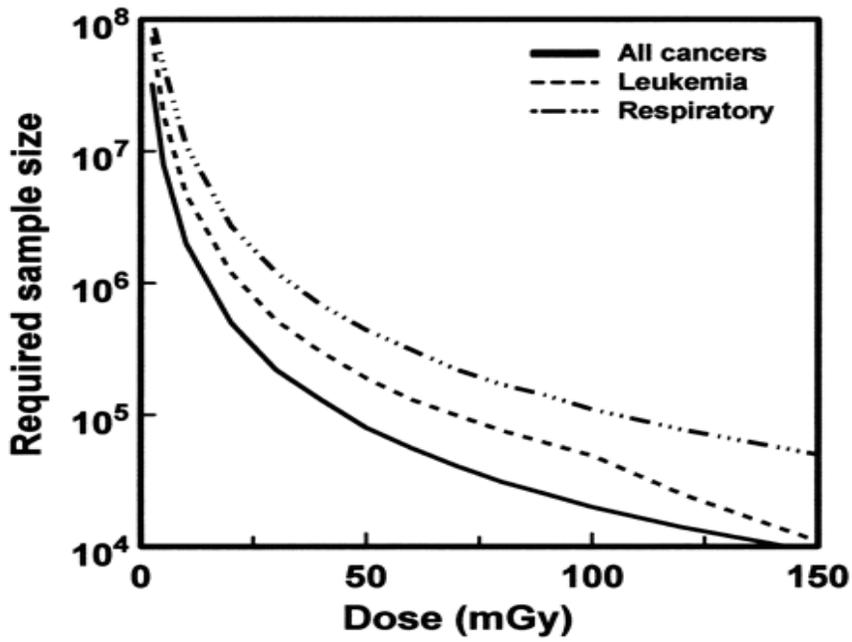


# Inference and Uncertainty Propagation

- **Statistical Inference** – based on data and models used to analyze it.
- **Propagation** – combined statement of overall uncertainty.
- **Sensitivity analyses** on model inputs can help ID largest influencers.
- **Probability Density Functions** (likelihood).
- Frequentist (A-Bomb).
- Bayesian – use prior to estimate posterior. Good for limited data or doses using Monte Carlo modeling.



# Statistical Power – Data Needed are Large at Low Doses



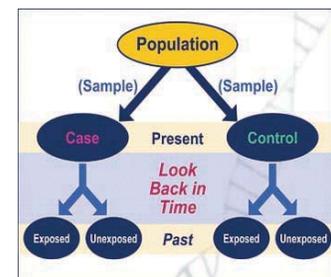
National Research Council (1995). Radiation Dose Reconstruction for Epidemiologic Uses.

## Epidemiologic Studies



- **Cohort Studies** – long-term follow-up of an exposed population having individually characterized exposures.
  - Can provide unbiased risk estimates.
  - Allow for modifying factors (sex, age at exp.)
  - Rates of disease computed directly.
  - Costly! Challenging!
  - Lack statistical power for rare outcomes.
  - Competing risk factors often tough to take into account.

## Epidemiologic Studies



- **Case-Control Studies** – ID cases for an outcome of interest in a population together with a control sample of disease free individuals.
  - Matched on sex, vital status, etc.
  - Retrospective.
  - Smaller population groups.
  - Cost less.
  - Risk estimates likely have more bias.



## Cause – Effect Relationship?

- Studies may suggest associations.
- Single investigations do not establish unequivocally, often due to confounding factors.
- **Look for consistency of results with plausible biological reasoning.**

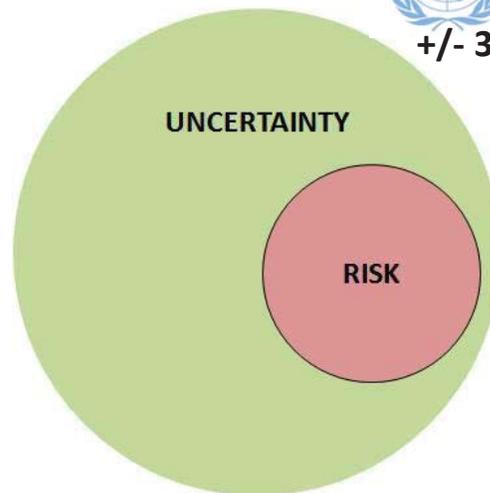


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## Sources of Uncertainty in Radioepidemiological Studies

- Dosimetry issues.
- Epidemiology issues.
- Methodology issues.
- Low power.
- Low precision.
- Risk data modeling.
- Generalization.
- Observational rather than Experimental.
- Tissue effect latency.



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## Uncertainties in Health Effect Info

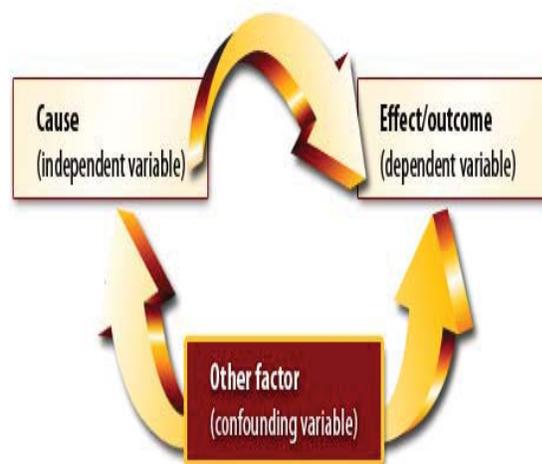
- **Selection Bias** – study population not representative of population of interest.
- **Information Bias** – erroneous or incomplete information about disease and/or exposure.
  - **Recall Bias** – e.g., cases recall exposure history differently than non-cases.
  - **Follow-up Bias** – e.g., subjects leaving the geographical study area, or simply 'lost'.



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## Uncertainties in Health Effect Info

- Failure to adjust for **confounding factors**:
  - Can distort risk est.
  - Sometimes very difficult to deal with (e.g., Smoking).
- Other **unknown factors** – genetic predisposition, pre-existing illnesses, repair capacity, varied immunology.



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## Uncertainties in Exposure and Dose Assessment

- Fuzzy measurements, lab procedures, record keeping, data input, programming, or computation.
- Serious impacts on significance, slopes, and confidence.
- Especially important because they input directly to models for organ absorbed dose



- Typical issues:
  - Energy response.
  - Geometry.
  - Biokinetic models.
  - Dosimetric models (absorbed fractions).
  - Type of data available.
  - Reference phantoms.
  - Missing dose.
  - Others...



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## Impact of Exposure Uncertainty

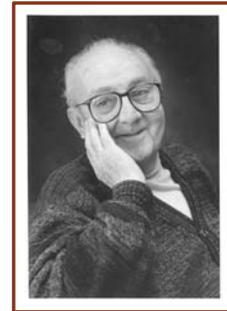
- Errors may vary in complex fashion according to the level of dose.
- Shared errors rarely considered. Bias.
- Differential measurement errors can have serious consequence (e.g., more effort for those with disease).
- General statement about average relative uncertainty in dose estimates (e.g. 30%) is not sufficient.
- Monte Carlo dose systems with multiple realizations of individual dose (max likelihood calcs) are better.



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“Essentially,  
all models are wrong,  
but some are useful.”

George E.P. Box, 1987



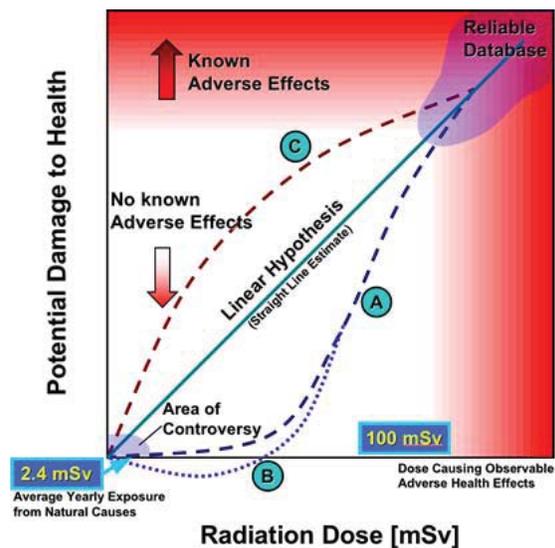
Box G and Draper N. 1987. In: Empirical Model Building and Response Surfaces, p. 424, John Wiley & Sons, NY.



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## Impact of Model Uncertainty

- Models are *simplified* descriptions.
- Often less impact at upper dose categories and for the central regions of co-variables (birth y, age at exp, age at Dx or death, smoking).
- Very large impact at low doses and borders of the ranges.



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## Transferring Risk Quantities to other Conditions or Populations

- Another population or time period.
- Relationships may vary by organ site and population
  - >Breast Ca in US
  - >Gastric Ca in Japan
- Radiation risks tend to reduce exponentially with age attained.
- DDREF ?



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## Impact of Uncertainties In Health Effect Information

- Systematic errors in the estimates or risk or the precision.
- Low statistical power studies (small size or small dose) usually yield indeterminate results.
- Combined or meta-analyses may help (if quality studies are compatible)



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## Systematic Literature Review

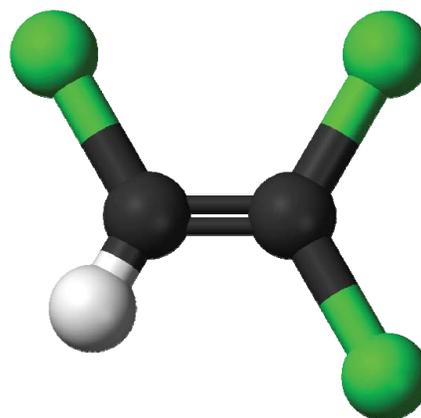


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## Quality Assessment – Commonly Used for Exposure Outcomes

- U.S. EPA evaluations
- Wartenberg et al 2000 as an example.



---

### Trichloroethylene and Cancer: Epidemiologic Evidence

Daniel Wartenberg,<sup>1</sup> Daniel Reyner,<sup>1</sup> and Cheryl Siegel Scott<sup>2</sup>

<sup>1</sup>Environmental and Occupational Health Sciences Institute, UMDNJ—Robert Wood Johnson Medical School, Piscataway, New Jersey USA;

<sup>2</sup>U.S. Environmental Protection Agency, Washington, DC USA

Environmental Health Perspectives • Vol 108, Supplement 2 • May 2000



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## Quality Scoring of Literature

- Assess for methodological strengths and weaknesses/limitations.
- Transparent Criteria
  - o = expected design
  - +1 = strength
  - 1 = shortcoming
- Sum Score
- Classify Studies by Quality Tiers

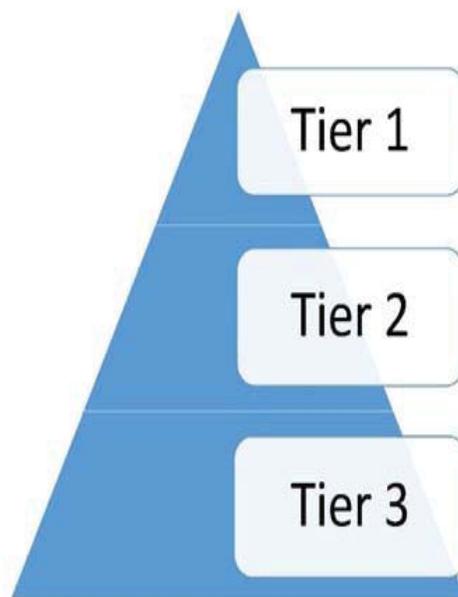


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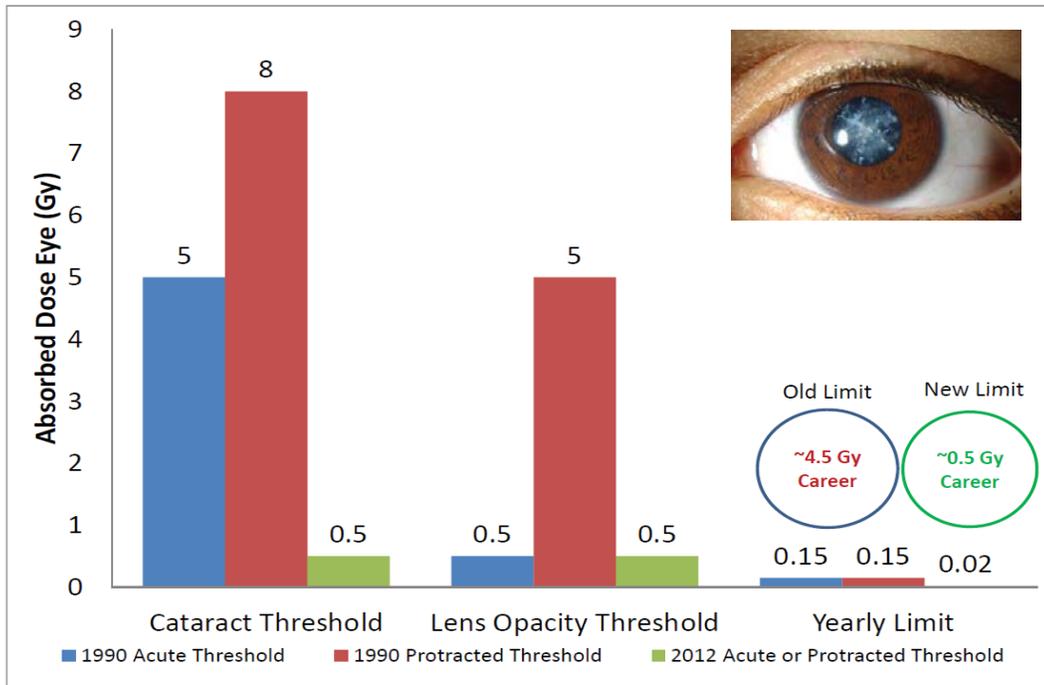
## Classify into Three Tiers

- Tier I (Total >1)  
considered most informative.
- Tier II (Total 0-1)  
considered less useful due to shortcomings.
- Tier III (Total <0)  
considered unreliable for meta-analysis.  
Mentioned for completeness and general trends.



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## Cataract Risks – ICRP-118



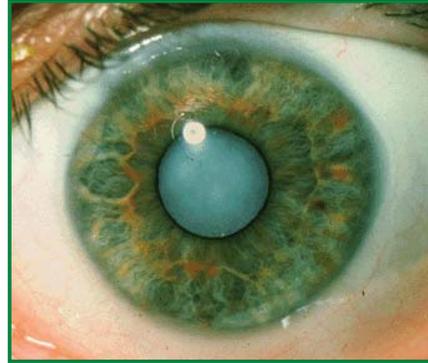
## EPRI – Cataract Risk Epi Evaluation

	Quality Score Criteria
1	Study Design: Cohort or Case/Control=0, Prevalence only=-1
2	Dosimetry: Individual Meas=+1, Reconstructed=0, No doses=-1
3	Age adjustment: yes=0, no=-1
4	Confounding: unlikely/addressed=+1, possible/not evident=0, not address=-1
5	Numerical risk assessment: yes (HR,RR,OR)=0, no = -1
6	Exposure response analysis: yes=+1, no=0
7	Account for Latency: >=5y = 0, <5y = -1
8	Reporting Bias: unlikely/adjusted=+1, possible/not evident=0, likely=-1
9	Selection Bias: unlikely/addressed=+1, possible/not evident=0, likely=-1
10	Outcome Pathology Method: slit-lamp physician=0, photos?=+1, other=-1
11	Blinded Pathology or Scoring: blinded=0, not blinded=-1
12	Cataract Scoring Method: defined/characterized=0, 'opacities' or not def=-1



## Cataract Epidemiology Study Evaluation

- 59 Studies Evaluated.
  - 9 – Tier 1
  - 17 – Tier 2
  - 33 – Tier 3
- Only 4 Tier 1 or 2 studies provided risk ratios for a given dose.
  - A-Bomb
  - US Radiology Techs
  - Infant Clinical Study
  - Chernobyl Cleanup Workers

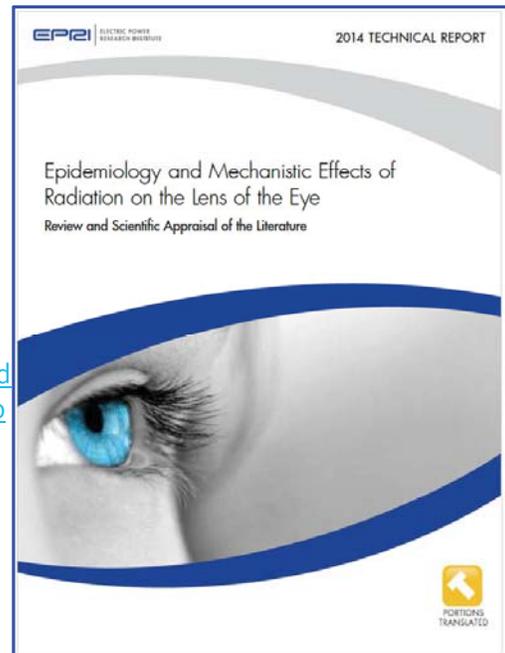


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## EPRI Cataracts Review 2014 – REF.

- Epidemiology and Mechanistic Effects of Radiation on the Lens of the Eye: Review and Scientific Appraisal of the Literature. 25-Nov-2014.
- <http://www.epri.com/abstracts/Pages/ProductAbstract.aspx?productId=000000003002003162>



# EPRI – CVD Risk Epi Evaluation

## DRAFT – Work in Progress

Quality Score Criteria	
1	Study Design: Cohort or Case/Control=0, Prevalence only=-1
2	Dosimetry: Individual Meas=+1, Reconstructed=0, No doses=-1
3	Outcome definition: defined/sub-categories=+1, defined=0, not defined=-1
4	Sample size: allows for sub-category analysis=+1, adequate=0, inadequate=-1
5	Numerical risk assessment: yes (HR,RR,OR)=0, no = -1
6	Age consideration: analysis by age=+1, considered=0, not included=-1
7	Lifestyle factors: directly addressed=+1, generally addressed=0, not=-1
4	Confounding: unlikely/addressed=+1, possible/not evident=0, not address=-1
6	Exposure response analysis: yes=+1, no=0
7	Account for Latency: evaluated=0, not evaluated=-1
8	Reporting Bias: unlikely/adjusted=+1, possible/not evident=0, likely=-1
9	Selection Bias: unlikely/addressed=+1, possible/not evident=0, likely=-1

## Important to Address Uncertainties



- We should.
- Workers do.
- Patients do.
- Public does.
- Public \$pending certainly does!





## **IOMP, AAPM, UNSCEAR, ICRP, HPS...**

- If  $\sim <100$  mSv of ionizing radiation during medical imaging procedures.
- Estimates should include a statement that highly speculative due to uncertainty.
- Epidemiological methods do not have the power to directly reveal Ca risks  $\leq 100$  mSv.
- Do not multiply very low doses by large #'s of individuals to estimate effects at or lower than natural background.
- Effective dose not for individual risks.
- Problems if heterogeneous dose.
- Benefit should be noted as well.



## **Research Needs – A Challenge**

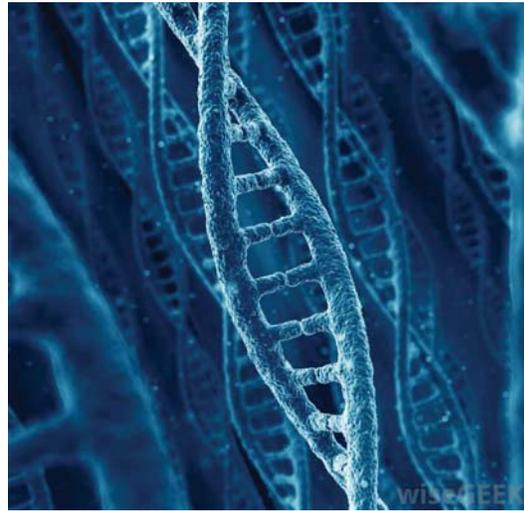
- ID sources of measurement error and how to account.
- Tools for efficiently using Monte Carlo uncertainty propagation for multiple realizations of cohort dose sets.
- Methods to address model uncertainty and multi-model use.





## Research Needs – A Challenge

- Still must quantify risks at low-dose and low-dose-rate exposure to low-LET radiation and modifying factors and uncertainties.
- Well designed CT studies.
- Million Person Study.
- 2<sup>nd</sup> Cancer studies.
- Non-cancer studies (CVD).
- How to incorporate radiobiologics?
  - Markers of low dose?



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## A Few Conclusions...



- Estimates of risk from exposure to ionizing radiation derived from epidemiology studies are uncertain especially because:
  - Typically low statistical power,
  - Intrinsic stochastic variability of cases,
  - Imprecise characterization of risk factors and dose, and
  - Impacts of confounding factors.
- Results often distorted.



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## A Few Conclusions...



- Reports of estimates of risk from radiation exposure should always include a clear and thorough discussion of limitations of the data and realistic assessment of how these might impact results.
- Failure to account for dose uncertainty can lead to biased risk estimates and overly optimistic statements about confidence.
- Neglecting model uncertainty may underestimate risks. Multi-models?



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## A Few Conclusions...



- Sources of uncertainty in transferring risk estimates from one population or exposure situation to another need to be considered and addressed.
- Care must be especially taken when using estimates of excess relative risk (ERR).
- Estimates are NEVER to individuals.
- Need communication tools.
- Stakeholder involvement paramount.



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## A Few Conclusions...



- Uncertainty analysis is a powerful tool that could be used to help prioritize research on issues of importance to risk assessment.
- Bottom lines:
  1. We are **certain of uncertainty** in risk estimates for radiation-induced cancer and other diseases or detriments.
  2. Continue practicing fundamental radiation safety principles:  
**Justification / Optimization / Limitation**
  3. Read articles very carefully.



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## Additional Information on Uncertainties in Radiation Risks

- UNSCEAR-2012; UNSCEAR-2013.
- NCRP-158, NCRP-163, NCRP-164, NCRP-171
- ICRP-99, ICRP-103, ICRP-118.
- Dauer et al, *Rad Prot Dosimetry*, 2010.
- Dauer, *Health Physics*, 2011.
- Hendee, *Radiology*, 2013.
- Preston et al, *JRP*, 2013.
- Walsh, Shore, Auvinen, Jung, Wakeford, *CT Epidemiology, JRP*, 2014.
- EPRI – Cataracts, 2014.
- Bouville et al, 2015, *Health Physics*.
- Simon et al, Monte Carlo, *Rad Res*, 2015.
- Land et al, Thyroid Risks, *Rad Res*, 2015.
- Brenner et al, *PNAS*, 2003.
- Zanzonico & Stabin, Benefit-Risk, *Semin Nucl Med*, 2014.



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# **Certitude Attitude: Uncertainties in Risk Estimates for Radiation-Induced Detriment**

2016 EPRI IDEA Workshop  
Lawrence T. Dauer, PhD, DABHP



[dauerl@mskcc.org](mailto:dauerl@mskcc.org)

# **10**

## **THE ONE MILLION U.S. PERSONS STUDY OF LOW-DOSE RADIATION EFFECTS (MPS): DOSIMETRY ASPECTS**

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EPRI IDEA Workshop  
Charlotte, North Carolina  
9 November 2016

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# The One Million U.S. Persons Study of Low-Dose Radiation Effects (MPS)

## DOSIMETRY ASPECTS

André Bouville (on behalf of John Boice)

U.S. National Cancer Institute (retired)



## OUTLINE

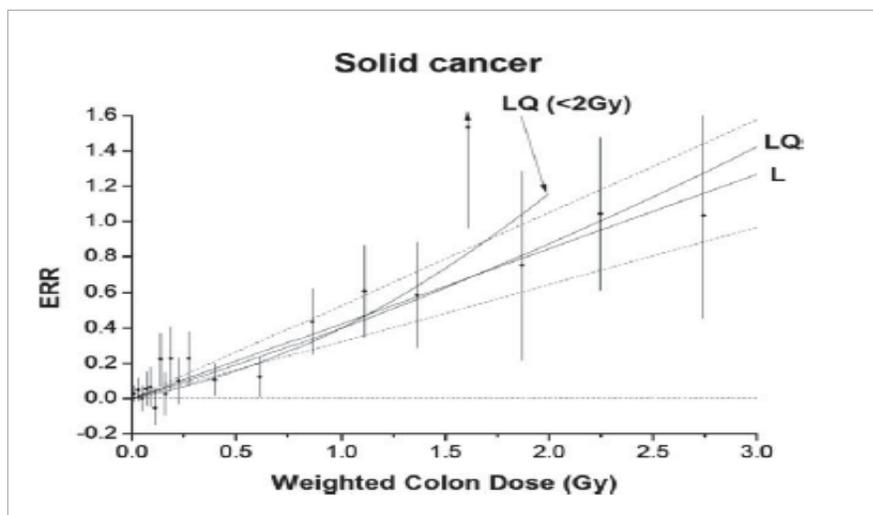
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- **Purpose and goals of the MPS**
- **Available data and results:**
  - all components of the MPS study,
  - focus on the nuclear power plant workers
  - Validation and uncertainties
- **Coordination and publications**

# PURPOSE AND GOALS OF THE MPS

## Why Study One Million U.S. Radiation Workers?

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- Low level risk is highly uncertain (A-bomb studies)
- Better if risk assessment is based on healthy Americans

# Why study workers?

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- Because they form a relatively homogeneous group of relatively healthy adults.
- Because most of them have dose records and other dose-related information.
- Because they have been monitored for many years and can accumulate relatively high doses

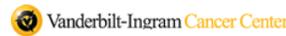
5

## Sub-cohorts of the MPS

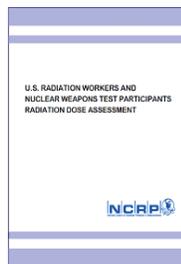
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<b>Sub-Cohort</b>	<b>Number of Subjects</b>	<b>Status of analysis</b>
DOE - Manhattan Project	360,000	Partially completed
DOD - Atomic Veterans	115,000	Completed?
Industrial Radiographers	126,000	Dose records collected
Medical & Related	255,000	Dose records collected
Nuclear Utility Workers	145,000	Dose records collected
<b>TOTAL</b>	<b>1,001,000</b>	

# Sponsors – A National Effort



## SC 6-9: Deriving organ doses and their uncertainty for epidemiologic studies



**A Bouville**  
Chairman



**R Toohey**  
Co-Chairman



**H Beck**



**T Brock**



**L Dauer**



**K Eckerman**



**D Hagemeyer**



**R Leggett**



**B Napier**



**K Pryor**



**M Rosenstein**



**J Thompson**



**D Schauer**



**S Sherbini**



**D Miller**



**D Stram**



**J Till**



**C Yoder**



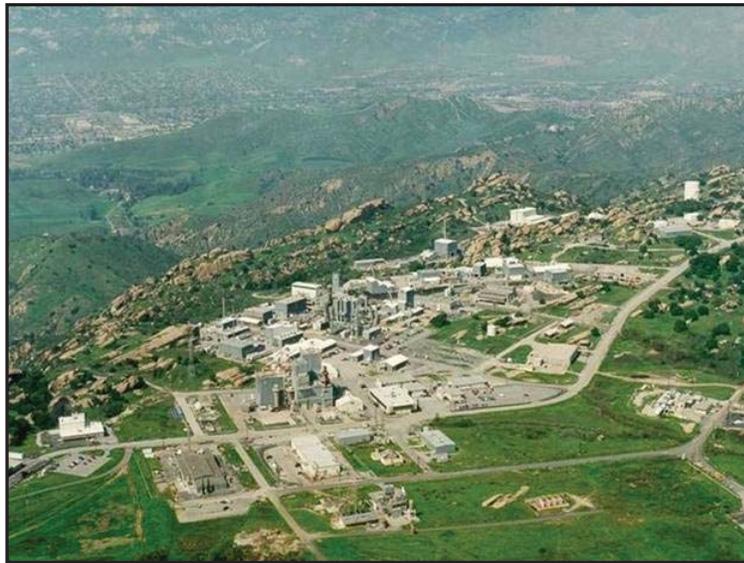
**C Zeitlin**

## Role of NCRP SC 6-9

- To provide guidelines to the various groups of dosimetrists to ensure **consistency** in the treatment of the various sub-cohorts considered in the MPS study:
  - Calculation of **annual** absorbed doses (**unbiased**) in the organs of interest
  - Separation of Low-LET and High-LET components. Estimation of **radiation-weighted** doses when necessary
  - Evaluation of **uncertainties**
  - Quality assurance and quality control

**Available data and results:  
DoE (ROCKETDYNE and MOUND)**

## Rocketdyne/Atomics International Santa Susana Field Laboratory



Leggett et al. J Radiol Prot 2005  
Boice et al. Health Physics 2006

Boice et al. Radiat Res 2006  
Boice et al. Radiat Res 2011

11

## Rocketdyne: data used for dose assessment

- 1948-1999: 5,801 workers monitored for radiation:
  - 3,569 external only
  - 58 internal only
  - 2,174 both external and internal
- Monitoring for internal irradiation (U, Pu, Th, Cs, Ru, T):  
over 100,000 urine measurements + some fecal data
- 1,477 workers not monitored for radiation at Rocketdyne  
were found to have worn dosimeters at other nuclear  
facilities.

12

## Radiation-weighted career lung doses (mGy) of the Rocketdyne workers

Cumulative radiation-weighted lung dose (mGy)	Number of workers	Percentage of workers
<5	3,728	64.0
5 - <10	609	10.6
10 - <25	673	11.7
25 - <50	366	6.4
50 - <100	203	3.5
100 - <250	147	2.6
250 - <500	51	0.89
500 - <1,000	18	0.31
1,000+	6	0.10
All	5,801	100

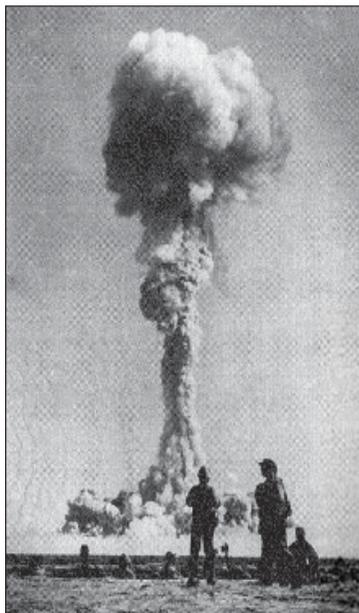
### Mound Laboratory: data used for assessment of internal doses

- bioassays for polonium-210: 2,800 workers
- bioassays for tritium: >1000 workers
- bioassays for plutonium (>800 workers), mainly Pu-238 (used to make heat sources) but also for Pu-239
- Some Ac-227, Pa-231, Ra-228, Ra-226, and Th and U present but no dose reconstruction was attempted; site history and sparsity of bioassay suggested limited potential for exposure

## Radiation-weighted career lung doses (mGy) of the Mound workers

Cumulative radiation-weighted lung dose (mGy)	Number of workers	Percentage of workers
<5	2,162	48.0
5 - <10	351	7.8
10 - <25	463	10.3
25 - <50	425	9.4
50 - <100	394	8.7
<b>100 - &lt;250</b>	<b>371</b>	<b>8.2</b>
<b>250 - &lt;500</b>	<b>172</b>	<b>3.8</b>
<b>500 - &lt;1,000</b>	<b>112</b>	<b>2.5</b>
<b>1,000+</b>	<b>59</b>	<b>1.3</b>
All	4,509	100

## Available data and results: ATOMIC VETERANS



# Atomic Veterans

Whole-body dose (mGy)	Number	%
<5	63,193	55.6
5 - <10	19,969	17.6
10 - <25	18,791	16.6
25 - <50	9,658	8.5
50 - <100	1,700	1.5
100 - <250	227	0.2
250 - <500	40	0.04
500 - <1,000	2	<0.01
All	113,580	100

20-25% wore film badges, accounting for > 80% of exposure.

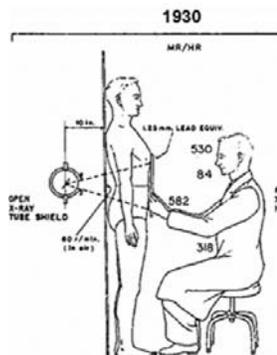
## Available data and results: INDUSTRIAL RADIOGRAPHERS



# Industrial Radiographers: H<sub>p</sub>(10) Dose Distribution

Career dose mSv	N	%
< 5	85,011	66.5
5 - <10	9,443	7.4
10 - <25	11,866	9.3
25 - <50	8,437	6.6
50 - <100	6,804	5.3
<b>100 - &lt;250</b>	<b>5,172</b>	<b>4.0</b>
<b>250 - &lt;500</b>	<b>1,106</b>	<b>0.8</b>
<b>500 - &lt;1,000</b>	<b>141</b>	<b>0.1</b>
<b>1,000+</b>	<b>20</b>	<b>&lt;0.01</b>
All	127,910	100

## Available data and results: MEDICAL WORKERS



## Medical Workers - Landauer Data Hp(10) Cumulative Dose Distribution (mSv)

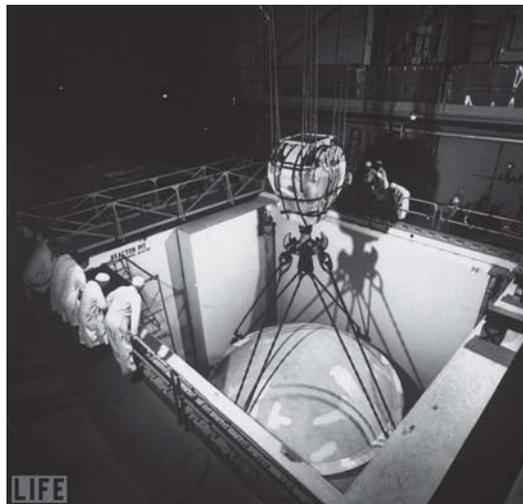
Recorded dose (mSv)	Number of workers	% of workers
10 - <25	122,324	50.3
25 - <50	60,470	24.8
50 - <100	36,403	15.0
100 - <250	19,230	7.9
250 - <500	3,811	1.6
500 - <1,000	910	0.4
!,000+	300	0.1
All	243,448	100

• Japanese atomic bomb survivors > 1000 mSv = 2,389 (Preston Rad Res 2004)

Japanese atomic bomb survivors > 100 mSv = 18,444 compared with 23,807 above

21

## Available data and results: NUCLEAR UTILITY WORKERS

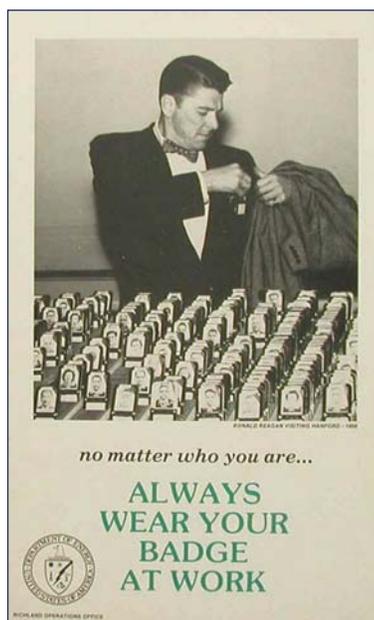


# Exposure Conditions

- **Mostly external photon**
- **Neutron (low)**
- **Internal (low)**
- **Engineering controls & PPE used frequently**
  - HEPA
  - Respiratory Protection
  - Gloves/boots
  - Coveralls
  - Eye shields
- **Most dose during outages**

Work Function	% Collective Dose (1975-1985)
Reactor Operations and Surveillance	9-13%
Routine Maintenance	<b>27-53%</b>
Inservice Inspection	3-9%
Special Maintenance	<b>19-47%</b>
Waste Processing	3-7%
Refueling	4-8%

# Dosimetry Monitoring Records



## Early NPP Worker Study: Data Sources

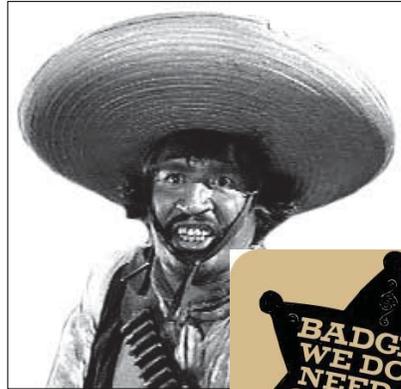
- **NRC REIRS Database**
  - Began in 1969, initially voluntary
  - Annual distribution of dose per licensee
  - Terminal records of individual exposure
  - Mandatory as of 1994
  - Backfilled data provided GL94-04
- **Landauer Database**
  - Began in 1977
  - Up to ~25% NPP workers
- **Other sources (NPPs?)**
  - Type of Licensee (NRC)
  - Dates of monitoring
  - External Dose
    - Deep Dose
    - Shallow Dose (skin)
    - Shallow Dose Max Extrem
  - Internal Dose
    - Old % MPBB or dose to organ
    - Since 1994, CEDE, CDE, intake  $\mu\text{Ci}$ , radionuclide
  - Name, SSN, DOB

### **$H_p(10)$ Dose Distribution Early NPP Study Group (1957-1985)**

Recorded Dose (mSv)	N	%
<5	26,330	18.1
5 - < 10	3,620	2.5
10 - <25	44,269	30.5
25 - <50	29,635	20.4
50 - <100	21,734	15.0
100 - <250	15,947	11.0
250 - <500	3,379	2.33
500 - <1000	306	0.21
>1000	7	<0.01
<b>All</b>	<b>145,227</b>	<b>100</b>

## Issues with $H_p(10)$ Doses: Unmonitored / Missed Doses

- Threshold reporting (<XX mSv)
- Rounded reporting
- Not recorded
- Not legibly recorded
- Not worn



## Issues with $H_p(10)$ Doses: Transient Worker Dose & Non-NPP Dose

- 1979 NRC
  - 1,500 quarterly transient with avg. 4.7 mSv
  - 3,200 yearly transients with avg. 10.5 mSv
- Cross-link population rosters with dose records
- EPRI study (1991)
  - 14% received doses at DOD/DOE/Shipyards, 23% of previous exposure
- Occupational Medical exposures (e.g. Operators)



## Issues with $H_p(10)$ Doses: Measurement Uncertainty

- Dosimeter sensitivity, energy response, angular dependence, calibration, processing, fading
- Temporal variations, environmental conditions, human factors
- Procedures, practices, policies for dosimetry
- Note NVLAP *after* 1984

## Dose Reconstruction: Getting from $H_p(10)$ to $D_T$

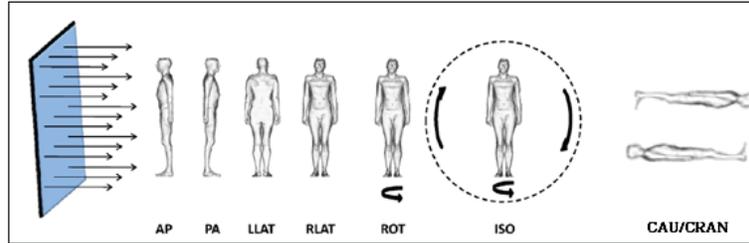
NCRP REPORT No. 163

RADIATION DOSE  
RECONSTRUCTION:  
PRINCIPLES AND  
PRACTICES

**#163**



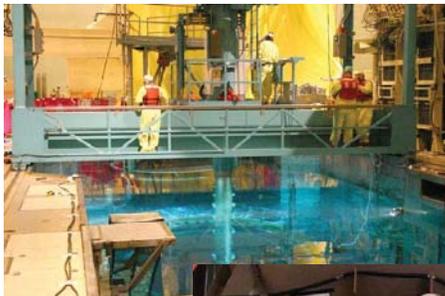
# Model Uncertainty



- Radiation field: types and energies
- Exposure conditions
- Geometry
- Badge placement
- Conversion coefficient from  $H_p(10)$  to absorbed dose

## Field Geometry & High Dose Gradients

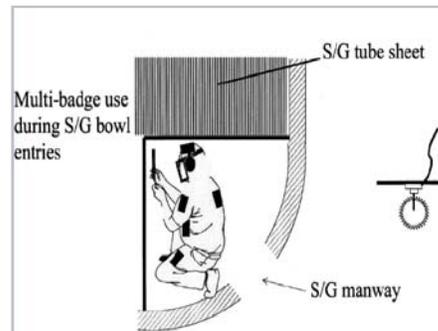
From Below \ From Above



ORNL Study  
for Cranial  
or Caudal  
Geometries

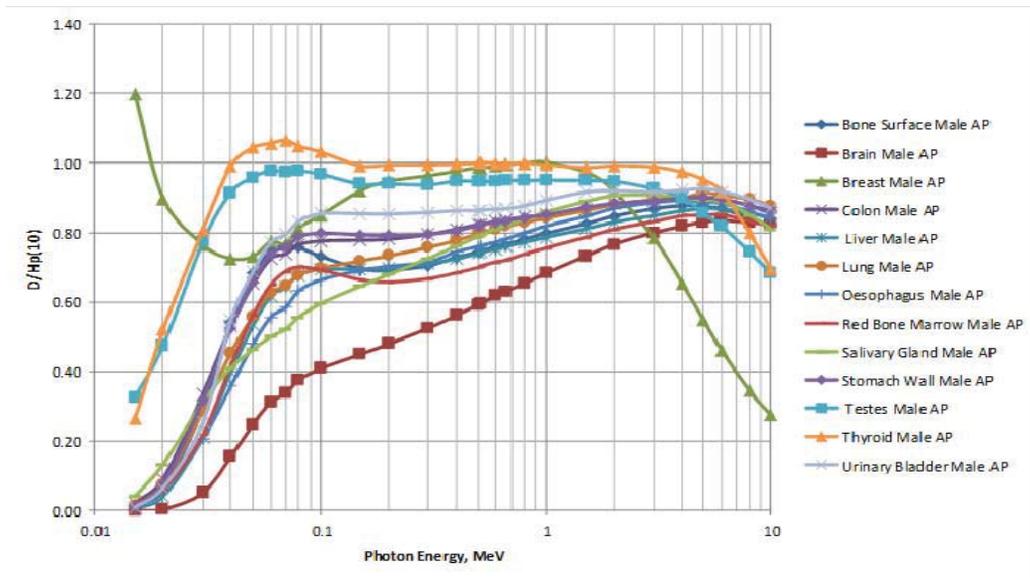


Multiple Dosimetry...

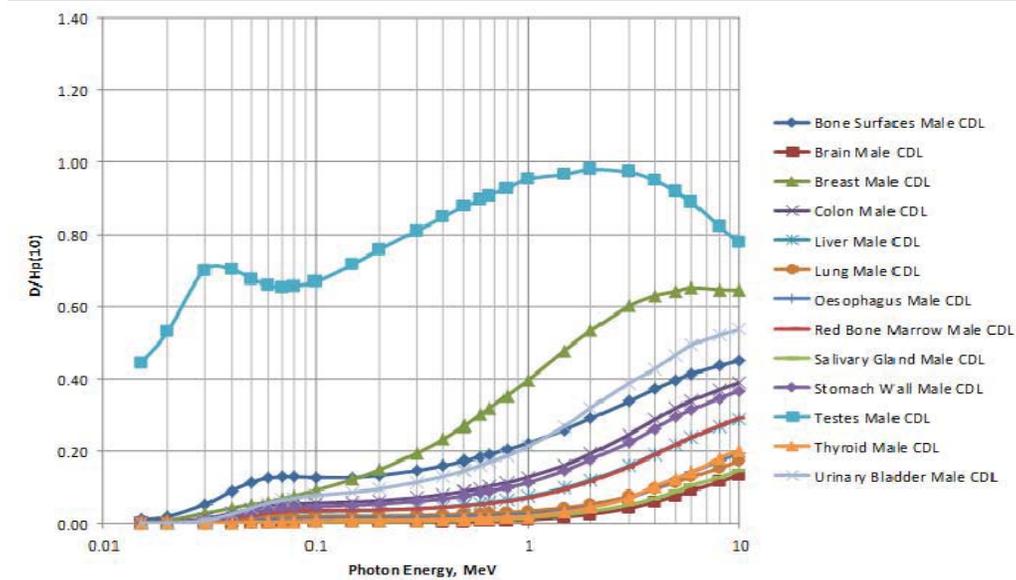


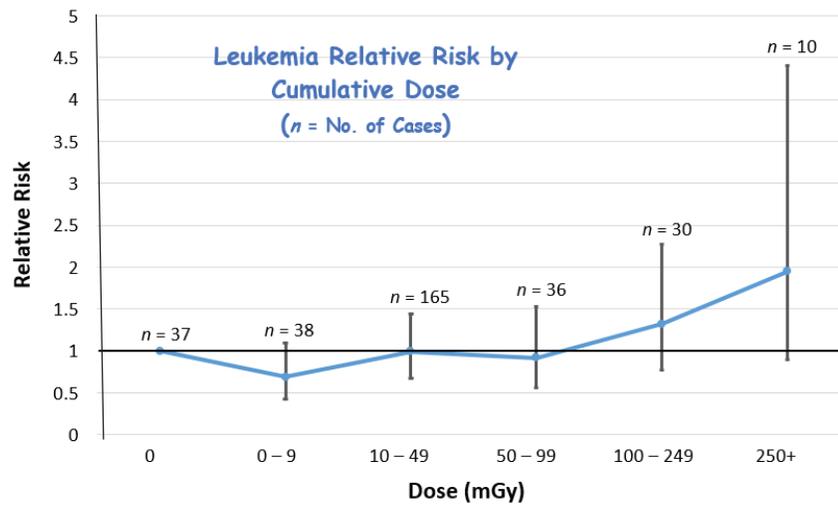
Then: Highest Reading = DDE  
Now: ANSI/HPS N13.41  
EPRI Task Reports, Xu HPJ  
2006.  
NRC Reg Guide 8.40 (EDEX)

## D/H<sub>p</sub>(10): AP geometry, male workers



## D/H<sub>p</sub>(10): Caudal-cranial geometry, male workers





316 Leukemias; 40 >100 mGy.

A-Bomb 312 total; 129 >100 mGy.

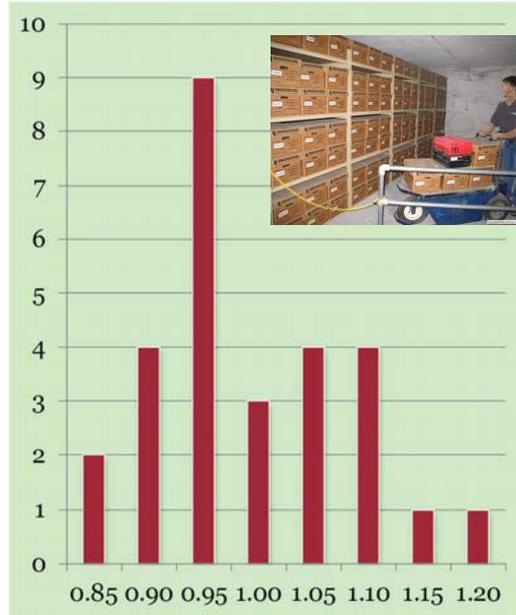
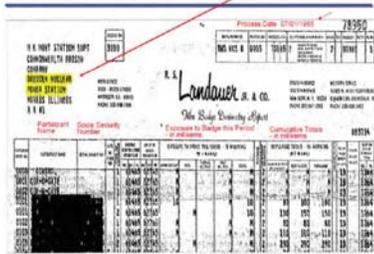
**STAY TUNED – MUCH MORE TO COME**

**Available data and results:  
VALIDATION and  
UNCERTAINTIES**

# Validation of Film Badge Doses: Salt Mine Pilot

- Compare
  - 1977 Recorded Dose
  - 2013 Re-read/evaluated
- 28 Badges
- 7.9-1300 mSv
- Ratio of  $1.02 \pm 0.09$

Microfilm Image - Dresden NPP



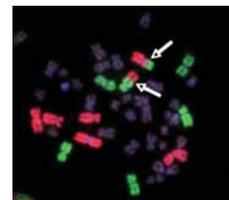
## Validation of Doses to Atomic Veterans (Comparison of three dosimetry methods)



Film badges

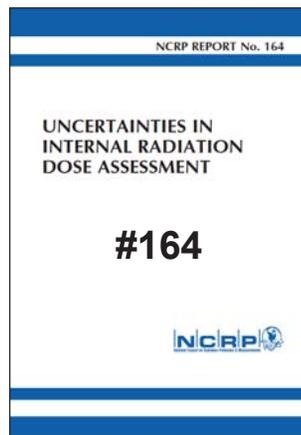
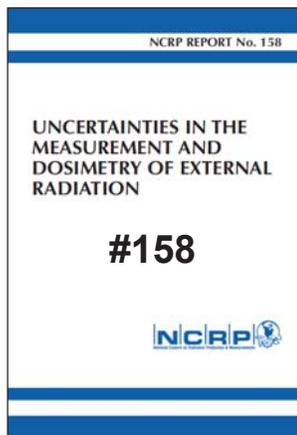


Environmental Measurements + Questionnaires



Biological dosimetry (FISH)

# Uncertainty Assessments



- Thierry-Chef 2007
- Schafer & Gilbert 2006
- Gilbert 1996, 1998, 2009
- Stram & Kopecky 2003
- NRC 1989
- Simon 2006, 2013
- NCRP SC 6.9



## Assessment of the dosimetric uncertainties for epi purposes

- Identify all sources of uncertainty and classify them according to shared or unshared
- If the shared uncertainties are small, use the estimate of unshared uncertainty in the epi analysis
- If the shared uncertainties are not small, develop a covariance matrix of shared versus unshared uncertainties. Statistical analysis will indicate if it is necessary to go to the following step.
- If the shared uncertainties are large, develop a complex two-dimensional Monte-Carlo analysis.
- **NOTE:** the shared component of the uncertainty in doses from external irradiation is usually small, so that a complex analysis is not warranted.

## Practical considerations

- Conditions of exposure (radiation field, badge location, etc.) are generally not known
- Finite resources in terms of personnel, time, and money, make it impossible to assess uncertainties for all individual subjects of large cohorts
- The recommended approach has only been implemented so far for the atomic veterans

**COORDINATION AND  
PUBLICATIONS**

## Coordination: role of NCRP SC 6-9

- The NCRP Committee SC 6-9 was created to provide guidelines to the various groups of dosimetrists to ensure consistency in the treatment of the various sub-cohorts considered in the MPS study:
  - Calculation of annual absorbed doses in the organs of interest.
  - Separation of low-LET and high-LET components.
  - Evaluation of uncertainties.
  - Quality assurance and quality control.
- The NCRP Committee, which met for the first time in April 2013 and then at regular 6-month intervals, has prepared a report that was distributed last week to all Council members for review.
- In addition to NCRP Council members, anybody is welcome to send comments. The draft report is available from [John.Boice@ncrponline.org](mailto:John.Boice@ncrponline.org), [Atwell@ncrponline.org](mailto:Atwell@ncrponline.org), or [abouville@aol.com](mailto:abouville@aol.com)

43

## List of publications (dosimetry)

**BOICE, J.D. JR., et al. (2006).** “A comprehensive dose reconstruction methodology for former Rocketdyne/Atomics International radiation workers,” *Health Phys.* 90(5), 409–430.

**BOICE, J.D., JR., et al.. (2014).** “Mortality among Mound workers exposed to polonium-210 and other sources of radiation, 1944–1979,” *Radiat. Res.* 181(2), 208–228.

**TILL, J.E. et al. (2014).** “Military participants at the U.S. atmospheric nuclear weapons testing—methodology for estimating dose and uncertainty,” *Radiat. Res.* 181(5), 471–484.

**BOUVILLE, A. et al. (2015).** “Dose reconstruction for the Million Worker Study: Status and guidelines,” *Health Phys.* 108(2), 206–220.

**STRAM, D.O. et al. (2015).** “Shared dosimetry error in epidemiological dose-response analyses,” *PLOS One* 10(3), e0119418.

## List of publications (epidemiology)

CALDWELL, G. G. et al. (2016). "Leukemia among military participants at the 1957 PLUMBBOB nuclear weapons test series and from leukemia among participants at the SMOKY test," J. Radiol. Prot. 36, 474-489.

BOICE, J.D., JR. et al. (2016). "Leukemia among early nuclear power plant workers employed between 1957 and 1984 in the United States," Radiat. Res. (submitted).

BOICE, J.D., JR. et al. (2016). "Male breast cancer among U.S. nuclear weapons test participants," (submitted).

**THANK YOU  
FOR YOUR ATTENTION**

# **11**

## **OVERVIEW OF THE UNITED STATES DEPARTMENT OF ENERGY RADIATION HEALTH STUDIES PROGRAMS**

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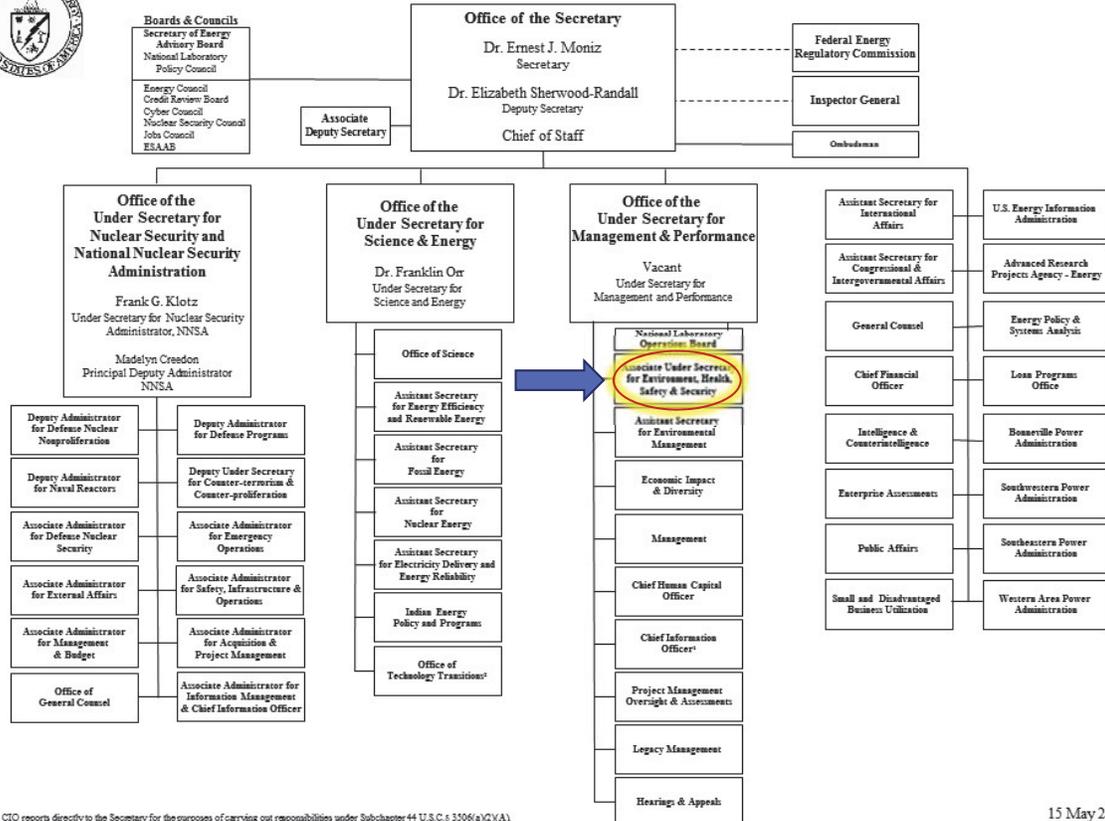
# Overview of the United States Department of Energy Radiation Health Studies Programs

International Dose Effect Alliance Workshop  
Charlotte, NC  
November 9, 2016

Isaf Al-Nabulsi, PhD  
Senior Technical Advisor  
Japan Program Manager  
Office of Health and Safety

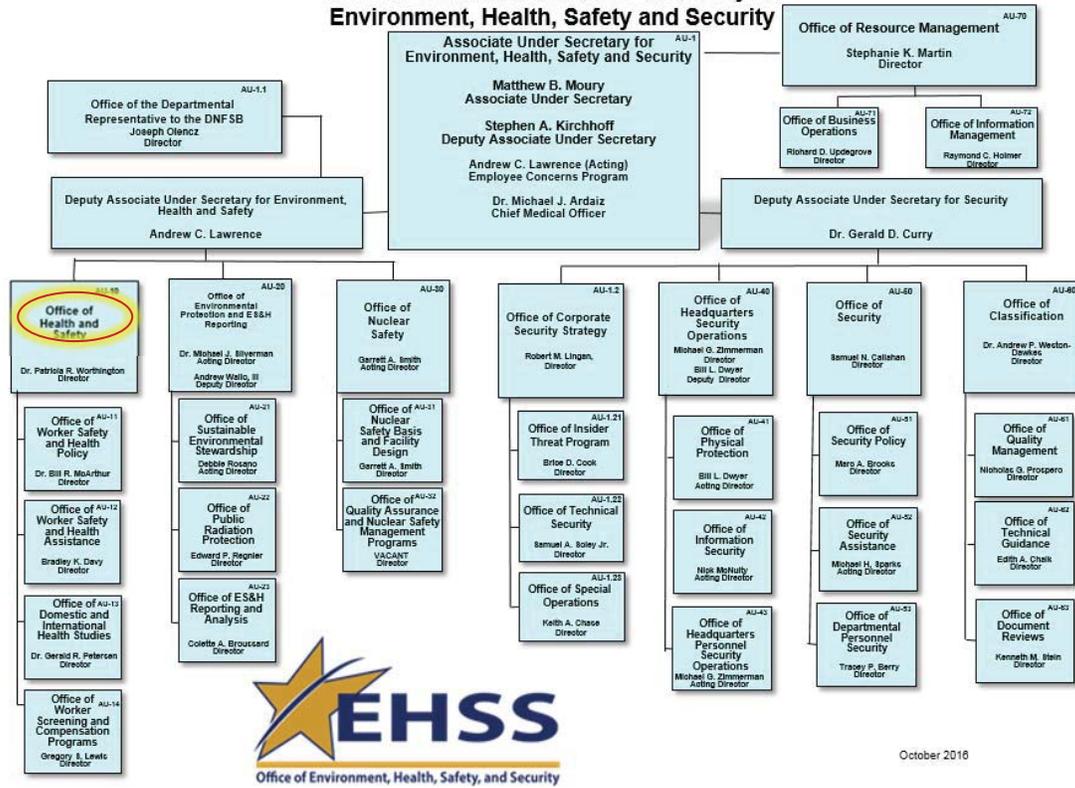


## DEPARTMENT OF ENERGY

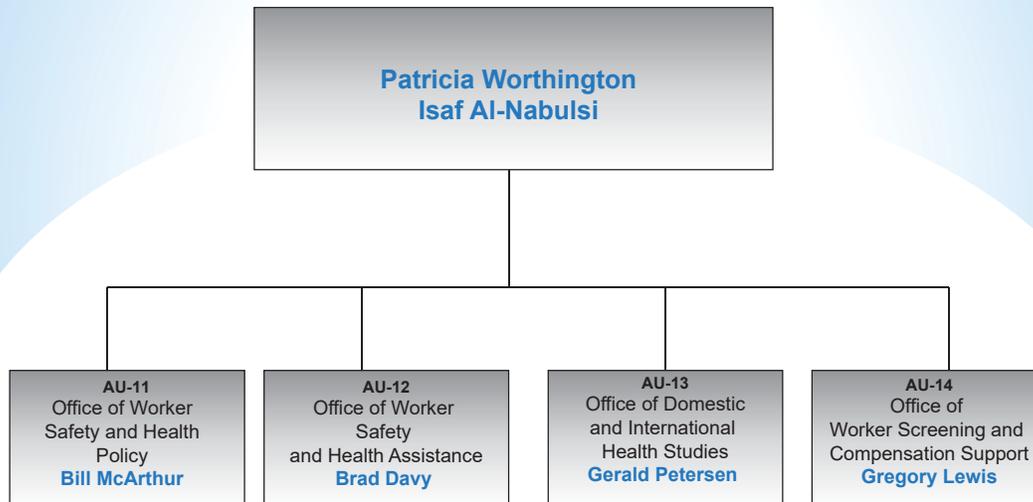


<sup>1</sup> The CIO reports directly to the Secretary for the purposes of carrying out responsibilities under Subchapter 44 U.S.C. § 3506(a)(2)(A).  
<sup>2</sup> The director of the Office of Technology Transitions also serves as DOE's Technology Transfer Coordinator who reports to the Secretary of Energy.

## Office of the Associate Under Secretary for Environment, Health, Safety and Security



## Office of Health and Safety (AU-10)



## Office of Health and Safety (AU-10) Mission

- Establishes worker safety and health requirements and expectations for the Department to ensure protection of workers from the hazards associated with Department operations.
- Conducts health studies to determine worker and public health effects from exposure to hazardous materials associated with Department operations and supports international health studies and programs.
- Implements medical surveillance and screening programs for current and former workers and supports the Department of Labor in the implementation of the Energy Employees Occupational Illness Compensation Program Act (EEOICPA).
- Provides assistance to Headquarters and field elements in implementation of policy and resolving worker safety and health issue.



5

## AU-10 Programs

### Worker Health and Safety Policy

Develops and implements health policies and regulations to ensure the DOE workforce conducts work safely and productively.

### Office of Workers Safety and Health Assistance

Promotes safety and health excellence through cooperative efforts among labor, management, and government at the DOE contractor sites.

Voluntary Protection Program

Employee Assistance Program

Cross-Cutting Worker Safety and Health Issues

Occupational and Environmental Medicine

Differing Professional Opinion (DPO) Program



6

## AU-10 Programs (cont.)

### Office of Domestic and International Health Studies

- Manages a portfolio of domestic and international health studies that fulfills the requirements and directives of the Legislative and Executive branches.
  - The results from these programs are the primary basis for worldwide radiation protection standards.
- Represents DOE on Federal work groups planning and preparing for public health crisis.
- Supports the operation and maintenance of the CEDR, USTUR, REAC/TS, and the Beryllium Registry.



7

## AU-10 Programs (cont.)

### Office of Worker Screening and Compensation Support

- Supports the implementation of EEOICPA.
  - Implemented a secure electronic data-sharing portal for data exchange DOL and NIOSH in support of claims.
- Provides ongoing medical screening examinations, at no cost, to all former DOE Federal, contractor, and subcontractor workers who may be at risk for occupational diseases.
  - Uses independent occupational health experts.
  - Initiated the early lung cancer detection program using low-dose spiral CT scans.



8

## Mission of the Health Study Program at the Department of Energy

- Conduct research to reduce work-related illnesses and injuries
- Promote safe and health workplaces
- Enhance workplace safety and health
- Promote protection of all workers



9

## History of Health Studies at the Department of Energy

Atomic Energy Commission (AEC) established - 1946

1960's—studies to determine the feasibility of using personnel records to conduct epidemiologic mortality studies

1965—pilot studies initiated, T. Mancuso at University of Pittsburgh  
Hanford mortality study of 500,000 workers, 1964-76  
Association of cancer and low levels of radiation  
Controversies, Congressional Hearings, GAO report

1970—Worker Health and Mortality Study implemented - Hanford  
Environmental Health Foundation

1977—A. Stewart, Mancuso, G. Kneale study of Hanford workers



10

## History of Health Studies at the Department of Energy

AEC → Energy Research and Development Administration 1974 →  
DOE established in 1977

Creation of the Office of Environment, Safety and Health -1990

Worker and Public Health Activities Program established  
to study the health consequences of exposures to ionizing  
radiation and other hazardous materials used in DOE operations  
and the general public in surrounding communities

Until 1990s, studies were carried out by DOE contractors at Hanford, Oak  
Ridge and Los Alamos.

After 1990s, energy-related health studies relevant to DOE operation were  
carried out by the United States Department of Health and Human Services



11

## History of Health Studies at the Department of Energy

Examples:

***NIOSH - National Institutes of Safety and Health***

Conducts research on occupational exposures to workers,  
including epidemiologic studies. All analytic studies of workers  
transferred to NIOSH's Occupational Energy Research Branch

***NCEH - National Center for Environmental Health***

Historical dose-reconstruction studies of environmental exposures  
to estimate past levels of exposure to radiation in communities  
surrounding DOE sites

***ATSDR - Agency for Toxic Substances and Disease Registry***

Assesses environmental exposures and related health effects in  
communities surrounding DOE sites



12

## Health Study Population

~600,000 current and former DOE workers

Exposure of interest:

External and internal ionizing radiation exposure  
Asbestos, metals and solvents

Time intervals: 1940s to present

Type of studies:

Exposure assessments for past and current workers  
Feasibility analysis  
What are the joint effects of radiation and chemical exposures?

Health outcome of interest: primarily cancer



13

## Epidemiologic Studies of DOE Workers

$N \approx 60$

BEIR V (1990) included 4 DOE studies

Site specific mortality studies:

Hanford  
Fernald Feed materials Production Center  
Idaho National Engineering and Environmental Laboratory  
Los Alamos National Laboratory  
Mound Plant  
Oak Ridge National Laboratory  
Pantex Weapons Facility  
Paducah Gaseous Diffusion Plant  
Portsmouth Gaseous Diffusion Plant  
Portsmouth Naval Shipyard  
Rocketdyne  
Rocky Flats  
Savannah River Site  
Y-12 Plant (OR)



14

## Epidemiologic Studies of DOE Workers

DOE single-site mortality studies (Hanford, ORNL, LANL, Mound)

DOE multi-site mortality study (Hanford, ORNL, RF)

DOE multi-site leukemia study (Hanford, ORNL, LANL, SRS)

DOE multi-site multiple myeloma study (ORNL, Hanford)

DOE multi-site female nuclear workers mortality study (SRS, LANL)

DOE multi-site offspring leukemia study (INL, ORNL, Hanford)

Million worker study (Boice, et al)

DOE, DOD, Nuclear Plant workers

International studies

15 country study (IARC)

3 country study (US, UK, France)

Exposures considered:

plutonium

polonium

uranium

external ionizing radiation including beta, gamma and neutrons

internal alpha



## Key Findings

- Workers at Rocky Flats show plutonium related elevation in lung cancer risk
- At Hanford and ORNL, older workers may be at higher risk of radiation-induced cancer
- At Idaho national Lab, most cancers not associated with radiation (leukemia, NHL, brain tumors, breast cancer)
- No radiation related cancer risk at Portsmouth GDP
- No overall excess risk due to exposure to external radiation at multisite multiple myeloma



## Benefits to DOE

- Fulfill obligation to all employees to provide the best information about health effects.
- Establish worker safety and health requirements and expectations for the Department to ensure protection of workers from the hazards associated with Department operations.
- Contribute to the scientific knowledge regarding exposure to radiation that are relevant to radiation protection on nuclear workforce in the United States and the world.
- Improve methods for reconstructing past exposures that are important to the evaluation of workers and public health effects at DOE sites.
- Understanding of workplace risks.
- Improving the worker health and safety by establishing roles and policy.



17

## Comprehensive Epidemiologic Data Resource (CEDR)

*A public use data repository* to facilitate access to the data collected under DOE's epidemiologic research programs.

### Program Goals:

- To create a central repository of data related to epidemiologic and health concerns.
- To permit access to data from the DOE epidemiological studies program to researchers and other interested stakeholders.
- To provide opportunities for new scientific understanding.
- To identify and document data potentially useful for other health studies.



<https://www3.ornl.gov/CEDR/default.aspx>



18

## Comprehensive Epidemiologic Data Resource (CEDR)

- Most of CEDR's holdings are derived from epidemiologic studies of DOE workers at many large nuclear weapons plants, such as Hanford, Los Alamos, the Oak Ridge reservation, Savannah River Site, and Rocky Flats.
- These studies primarily use death certificate information to identify excess deaths and patterns of disease among workers to determine what factors contribute to the risk of developing cancer and other illnesses.
- In addition, many of these studies have radiation exposure measurements on individual workers.

### Contents

- Site descriptions, including location, early operations
- 60 data sets used in published studies
- 118 unedited data files
- Bibliographic collection of more than 1250 citations



<https://www3.ornl.gov/CEDR/default.aspx>



19

## Japan Health Studies Program Purpose and Goals

- "Conduct research and studies for peaceful purposes on medical effects of radiation and associated diseases in humans, with a view to contributing to maintenance of the health and welfare of the atomic bomb survivors and to enhancement of the health of all humankind."
- There are over 117 ongoing research protocols, and several fixed cohorts or sub-cohorts were established to provide epidemiological and clinical data on the health status and mortality of the survivors and their children in addition to laboratory-based research studies in the fields of radiobiology, immunology, genetics, and molecular epidemiology that contributed to the understanding of the mechanisms of disease and cancer induction.
- The results of RERF research become the world's most important guide for radiation-induced health effects, especially cancer, and are also used to develop standards for occupational exposures and to assess risks from medical exposure sources.



20

## Description of Cohorts

- The Life Span Study (including 120,000 individuals, 30 percent of whom are still alive) - investigates mortality and cancer incidence of the A-bomb survivors;
- The Adult Health Study (about 25,000 individuals) - provides biennial health exams, health counseling, and collects tissue samples from those who volunteer when they are tested through this study;
- In Utero Study (about 3,600 individuals) - examine the lifetime health status of those who were in the womb at the time of bombing;
- Genetics Studies of Children of Atomic-Bomb Survivors (F1) Study (including 77,000 individuals) - determines genetics effects that could be related to parental exposure, and mechanisms of radiation effects on developing diseases and cancers. They include studies on
  - Mortality and Cancer Incidence (77,000 individuals)
  - Cytogenetic Study (16,000 individuals)
  - Birth Defects (77,000 individuals)
  - Cancer Incidence (77,000 individuals)
  - Chromosome Aberrations (16,000 individuals)
  - Biochemical Genetics Study (24,000 individuals)
  - Molecular Genetics (DNA) (1,000 families, 1,500 individuals)
  - Clinical Examinations (12,000 individuals)



## Tissue Repository

- 652,000 tissue samples from 145,000 individuals
- 165,254 blood samples from 19,732 individuals
- Biodosimetry: 1,721 teeth from 920 individuals
- Physical dosimetry: 740 samples



## Major RERF results

- RERF Life Span Study is core study of 120,000 A-bomb survivors that relates radiation exposure to risk of mortality, cancer, and other diseases.
- Data show an early increase in leukemia and an increase in a variety of solid cancers, which is related linearly to radiation dose.
- Relative risk for solid cancer is largest among those exposed at young ages.
- No genetic effects have been observed in children of the survivors.



23

## Russian Health Studies Program Purpose and Goals

- To assess worker and public health risks from radiation exposure resulting from nuclear weapons production activities in the former Soviet Union.
- To better understand the relationship between health effects and chronic, low-to-medium dose rate radiation exposures.
- To estimate cancer risks from exposure to gamma, neutron, and alpha radiation.
- To provide information to the national and international organizations that determine radiation protection standards and practices.



24

## Description of Cohorts

- Mayak worker cohort (25,757 workers) is a unique resource for evaluating:
  - Risk of cancer from exposure to plutonium
  - Risk of cancer from extended external exposure
- Techa River cohort (29,719 individuals) is a unique resource for evaluating long-term environmental exposures, such as those in communities surrounding DOE nuclear facilities.



25

## Tissue Repository

- About 238,941 biological specimens from 7,946 individuals
- Includes samples from 6,622 Mayak workers and 1,324 Ozersk residents without occupational exposure to ionizing radiation



26

## DOE SC Low-Dose Program

Started in 1998 to provide critical scientific basis for setting radiation protection regulations by applying new techniques to measure biological changes at a very low-dose region.



27

## DOE SC Low Dose Program Results

- Biological systems can detect and respond to very low doses of radiation.
- Cells not directly exposed can show a biological response to the low-dose radiation exposure of neighboring cells.
- Cell-cell and cell-matrix communication are critical in the total response to radiation, resulting in whole tissue responses as compared to individual cell responses.
- Different molecular-level mechanisms of action result in responses to low doses of radiation vs. high doses of radiation.
- Many cellular responses demonstrate non-linear responses with respect to radiation dose.
- In addition to radiation-induced DNA damage, other processes are induced by radiation that participates in the prevention of the development of cancer as a function of radiation exposure parameters, including dose, dose-rate, and dose-distribution.



28

## Congressional Actions

- November 17, 2014 - The U.S. House of Representatives passed the Low-Dose Radiation Research Act of 2014, which is intended to increase understanding of low-dose radiation.
- January 2015 - The U.S. House of Representatives has restarted efforts to boost research into the health effects of low-dose radiation, both in the natural environment and in medical imaging procedures (H.R. 35: Low-Dose Radiation Research Act of 2015).
  - ✓ Introduced by the House Committee on Science, Space, and Technology on January 6, 2015; Passed January 7, 2016
  - ✓ Received in the Senate and Read twice and referred to the Committee on Energy and Natural Resources on January 8, 2016
  - ✓ Hearing held on June 9, 2016



29

## H.R. 35: Low-Dose Radiation Research Act of 2015

- HR 35 directs the U.S. Department of Energy's Office of Science to enter into an agreement with the National Academies to study the current status and development of low-dose radiation research. The effort would also identify scientific challenges to studying the effects of ionizing radiation in the long term, as well as recommend an agenda to address these challenges.
- The legislation authorizes no money; instead, it directs the agencies involved to use funds appropriated in other spending measures.
- Requires such study to:
  - ✓ identify current scientific challenges for understanding the long-term effects of ionizing radiation,
  - ✓ assess the status of current low dose radiation research,
  - ✓ formulate overall scientific goals for the future of low-dose radiation research,
  - ✓ recommend a long-term strategic and prioritized research agenda to address scientific research goals for overcoming the identified scientific challenges in coordination with other research efforts,
  - ✓ define the essential components of a research program that would address this research agenda within the universities and the National Laboratories, and
  - ✓ assess the effectiveness of such a program.
- Directs the Secretary of Energy to deliver to Congress a five-year research plan that responds to the study's findings and recommendations and identifies and prioritizes research needs.



30

## S.2012 - North American Energy Security and Infrastructure Act of 2016

09/09/2015 Introduced in Senate

09/09/2015 Committee on Energy and Natural Resources.

04/20/2016 Passed/agreed to in Senate: Passed Senate with an amendment

05/25/2016 Passed/agreed to in House

05/25/2016 To conference: On motion that the House insist upon its amendment, and request a conference

09/08/2016 Conference committee actions: Conference held



31

## S.2012 - North American Energy Security and Infrastructure Act of 2016

### *SEC. 505. BIOLOGICAL AND ENVIRONMENTAL RESEARCH*

#### *(e) LOW DOSE RADIATION RESEARCH PROGRAM.—*

*(1) IN GENERAL.—The Director of the Department of Energy Office of Science shall carry out a research program on low dose radiation. The purpose of the program is to enhance the scientific understanding of and reduce uncertainties associated with the effects of exposure to low dose radiation in order to inform improved risk management methods.*



32

## S.2012 - North American Energy Security and Infrastructure Act of 2016

*(2) STUDY.—Not later than 60 days after the date of enactment of this Act, the Director shall enter into an agreement with the National Academies to conduct a study assessing the current status and development of a long-term strategy for low dose radiation research. Such study shall be completed not later than 18 months after the date of enactment of this Act. The study shall be conducted in coordination with Federal agencies that perform ionizing radiation effects research and shall leverage the most current studies in this field. Such study shall—*

*(A) identify current scientific challenges for understanding the long-term effects of ionizing radiation;*

*(B) assess the status of current low dose radiation research in the United States and internationally;*

*(C) formulate overall scientific goals for the future of low-dose radiation research in the United States;*

*(D) recommend a long-term strategic and prioritized research agenda to address scientific research goals for overcoming the identified scientific challenges in coordination with other research efforts;*

*(E) define the essential components of a research program that would address this research agenda within the universities and the National Laboratories; and*

*(F) assess the cost-benefit effectiveness of such a program.*



33

## S.2012 - North American Energy Security and Infrastructure Act of 2016

*(3) RESEARCH PLAN.—Not later than 90 days after the completion of the study performed under paragraph (2) the Secretary of Energy shall deliver to the Committee on Science, Space, and Technology of the House of Representatives and the Committee on Energy and Natural Resources of the Senate a 5-year research plan that responds to the study's findings and recommendations and identifies and prioritizes research needs.*

*(4) DEFINITION.—In this subsection, the term "low dose radiation" means a radiation dose of less than 100 millisieverts.*

*(5) RULE OF CONSTRUCTION.—Nothing in this subsection shall be construed to subject any research carried out by the Director under the research program under this subsection to any limitations described in section 977(e) of the Energy Policy Act of 2005 ([42 U.S.C. 16317\(e\)](#)).*



34

This will be the subject  
of a future post, so stay  
tuned!



[Isaf.AI-Nabulsi@hq.doe.gov](mailto:Isaf.AI-Nabulsi@hq.doe.gov)





# **12**

## **APPROACHES TO STUDYING THE BIOLOGICAL BASIS OF DOSE-RESPONSE**

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# Approaches to studying the biological basis of dose-response

Rory Conolly

US EPA

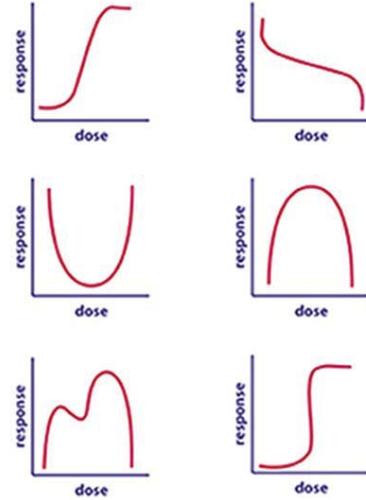
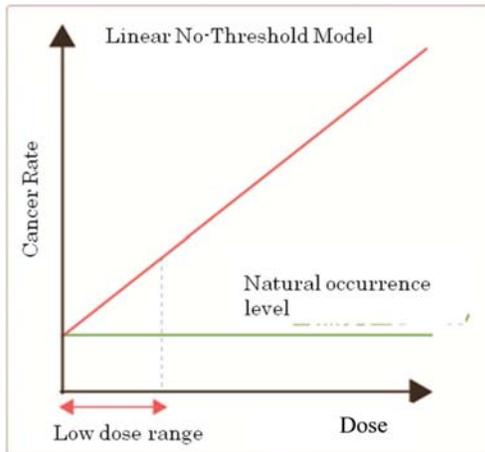
November 10, 2016

International Dose Effect Alliance Workshop 2016  
EPRI Charlotte

## Disclaimer

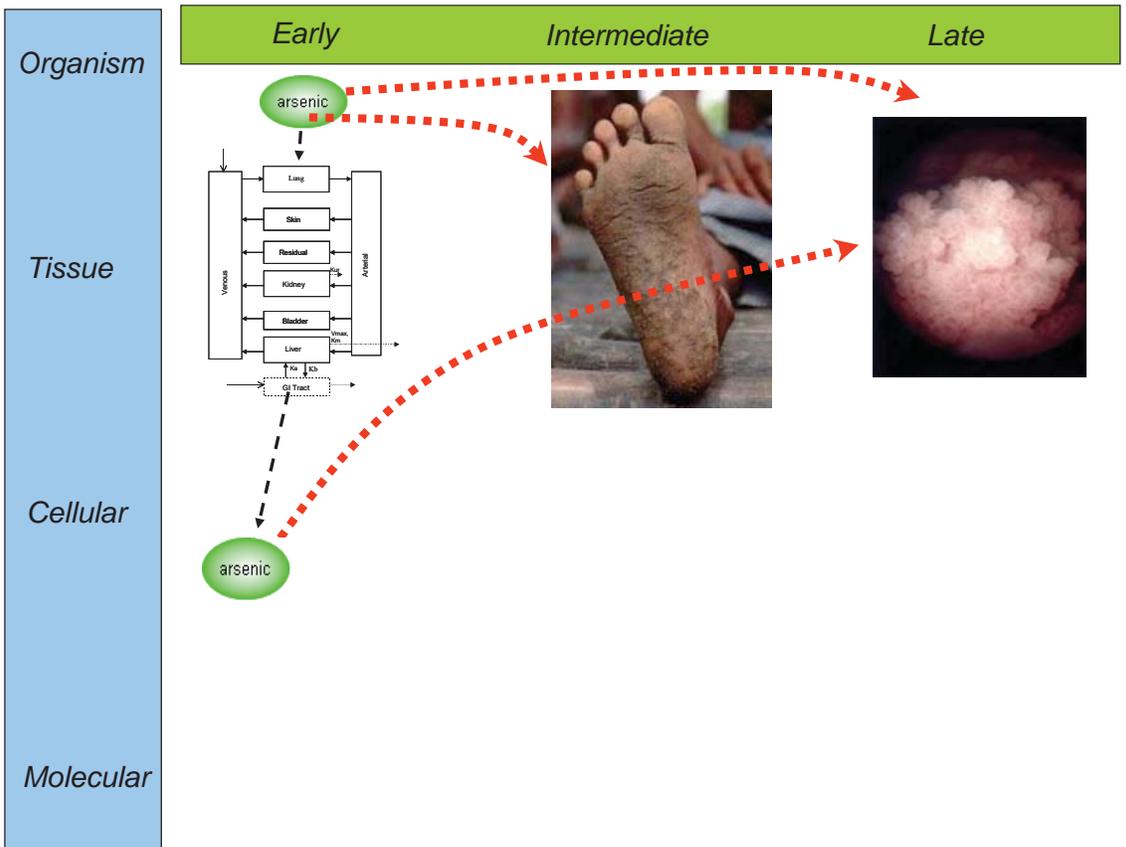
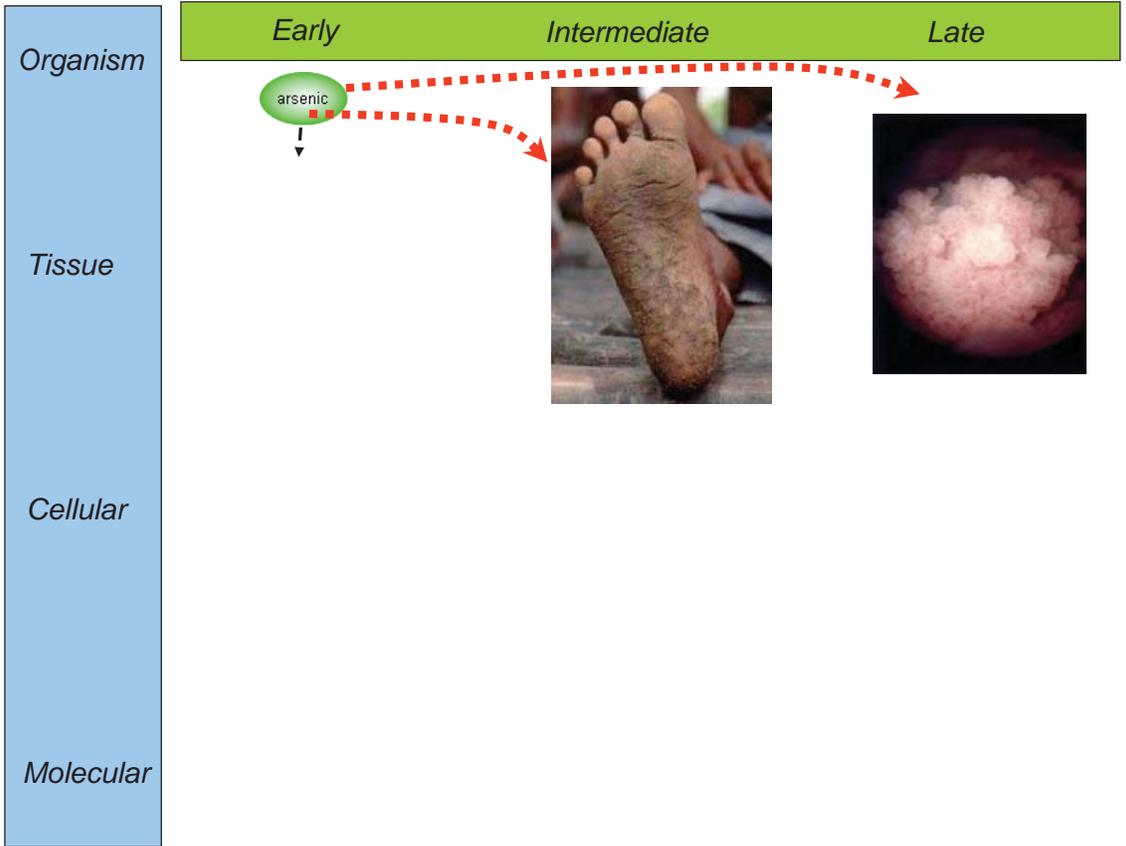
This is a presentation of the opinions of  
Rory Conolly, not of official policies of  
the US EPA.

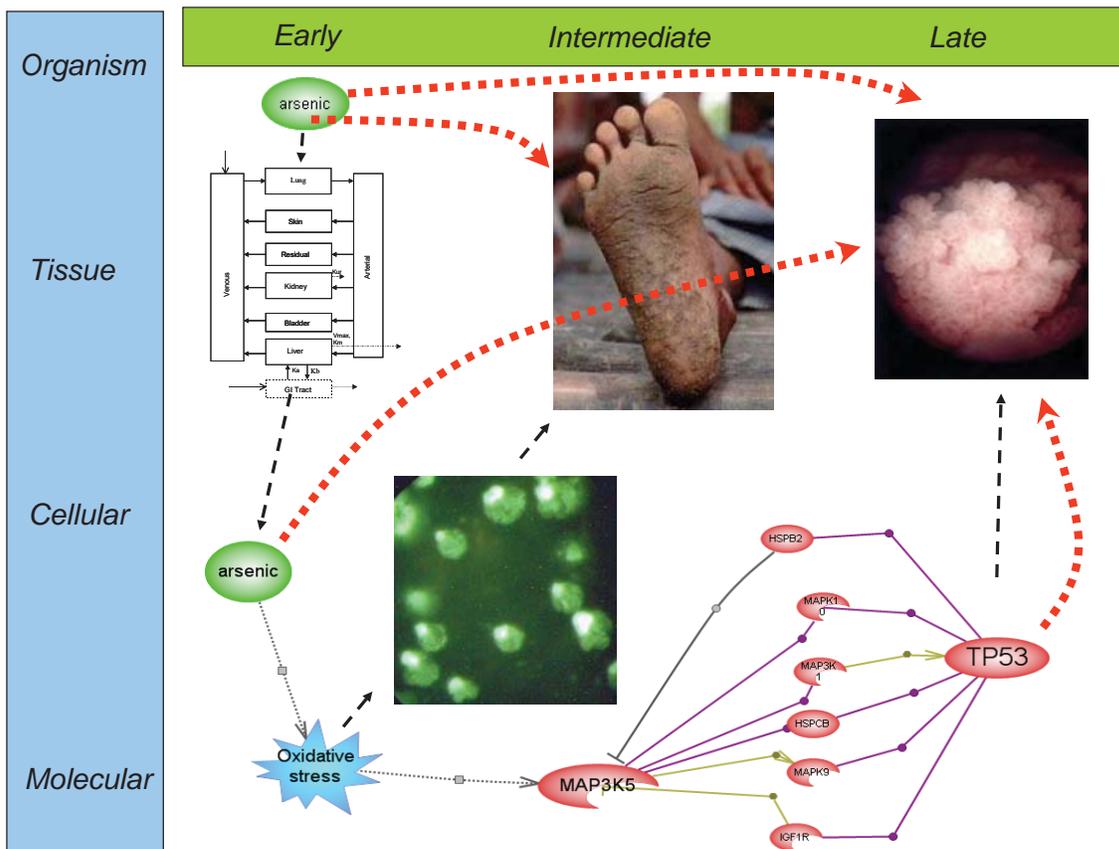
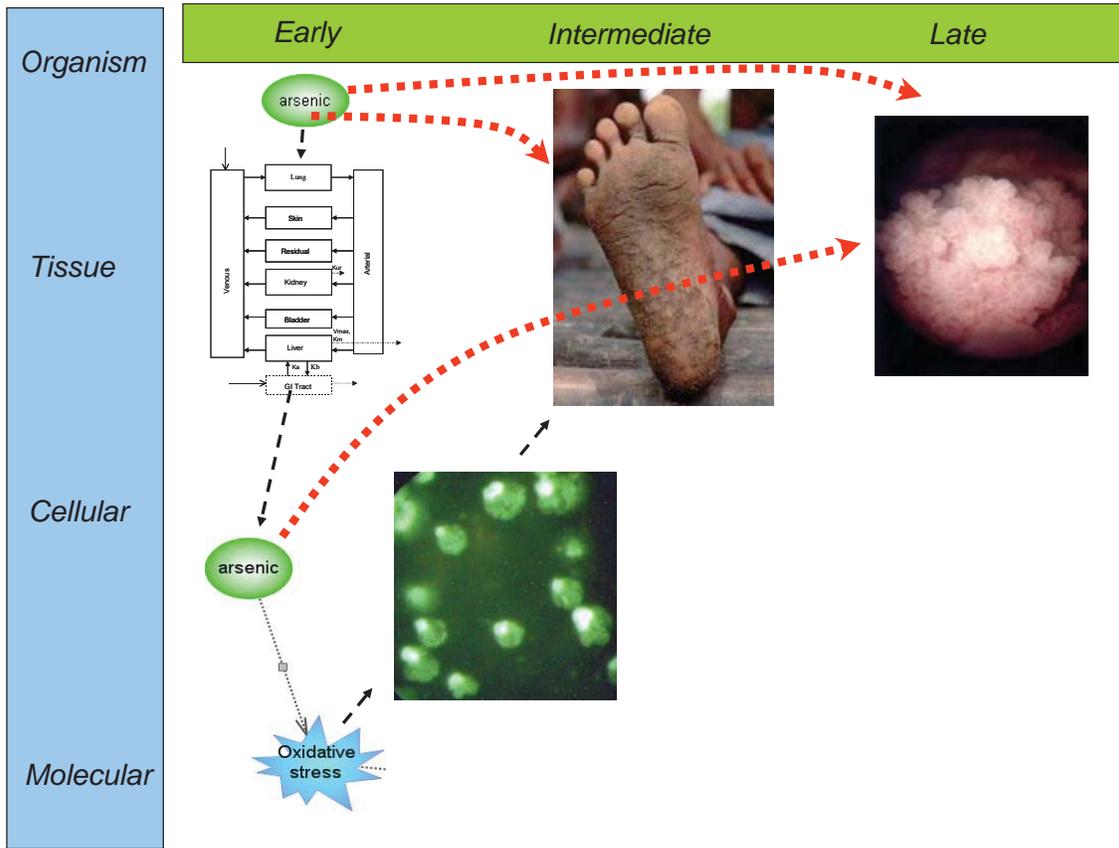
# How do we get from here to there?



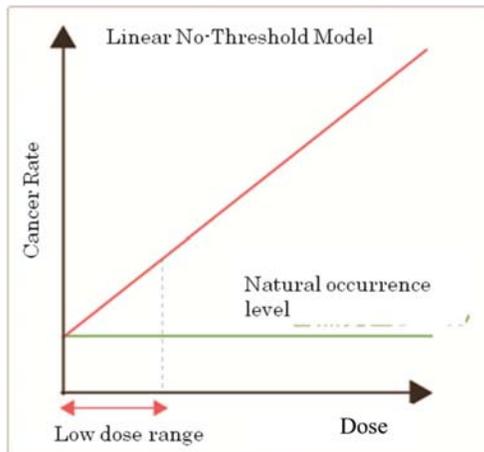
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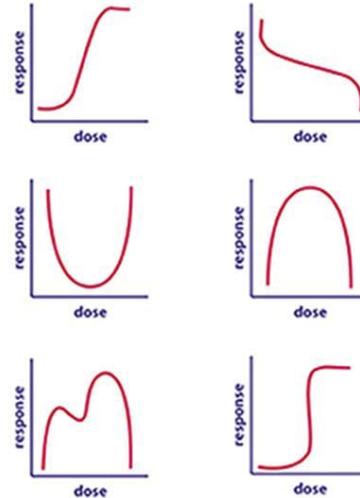




# It's the biology...



Biology



8

# Evolution of language

1. Mechanism of action
2. Mode of action
  1. MOA
3. Biologically based dose-response
  1. BBDR
4. Adverse outcome pathway
  1. AOP

9

# Mode of action (MOA)

## US EPA 2005 Cancer Guidelines

- It should be noted that **mode** of action is deliberately chosen in these new guidelines in lieu of mechanism to indicate using knowledge that is sufficient to draw a reasonable working conclusion without having to know the processes in detail at the molecular level, as the term mechanism might imply.

Wiltse and Dellarco (1998)

# Mode of Action (MOA) and Key Events

- MOA: A chemical's influence on the molecular, cellular and physiological functions in producing tumors
- Key Event: An **empirically observable**, precursor step that is a necessary element of the MOA, or is a marker for such an element.

*Hazard/Risk Assessment*

ADVERSE OUTCOME PATHWAYS: A CONCEPTUAL FRAMEWORK TO SUPPORT ECOTOXICOLOGY RESEARCH AND RISK ASSESSMENT

GERALD T. ANKLEY,\* RICHARD S. BENNETT, RUSSELL J. ERICKSON, DALE J. HOFF, MICHAEL W. HORNING, RODNEY D. JOHNSON, DAVID R. MOUNT, JOHN W. NICHOLS, CHRISTINE L. RUSSOM, PATRICIA K. SCHMIEDER, JOSE A. SERRRANO, JOSEPH E. TIETGE, and DANIEL L. VILLENEUVE

U.S. Environmental Protection Agency, Office of Research and Development, National Health and Environmental Effects Research Laboratory, Mid-Continent Ecology Division, 6201 Condon Boulevard, Duluth, Minnesota 55804

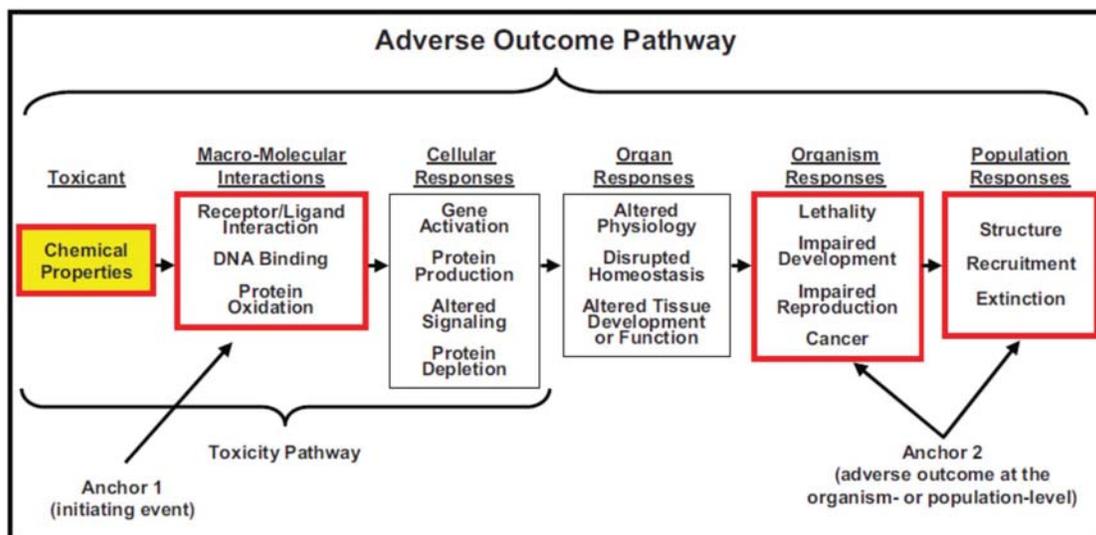


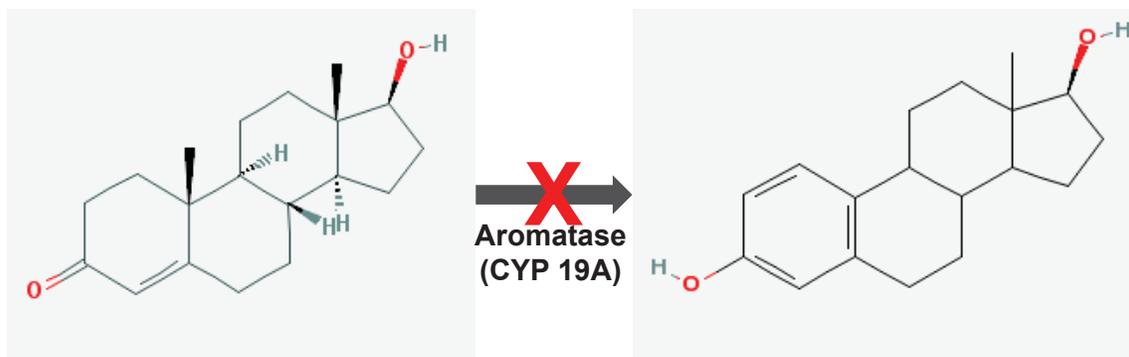
Fig. 1. Conceptual diagram of key features of an adverse outcome pathway (AOP). Each AOP begins with a molecular initiating event in which a chemical interacts with a biological target (anchor 1) leading to a sequential series of higher order effects to produce an adverse target outcome with direct relevance to a given risk assessment context (e.g., survival, development, reproduction, etc.; anchor 2). The first three boxes are the parameters that define a toxicity pathway, as described by the National Research Council [3].

## Example: *Aromatase inhibition AOP*

Aromatase inhibition leading to reproductive dysfunction in fish

14

Molecular initiating event:  
Aromatase inhibition

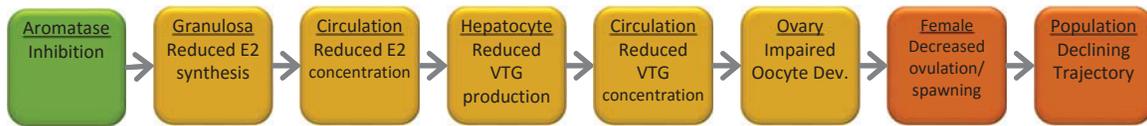


Testosterone

17β-estradiol (E2)

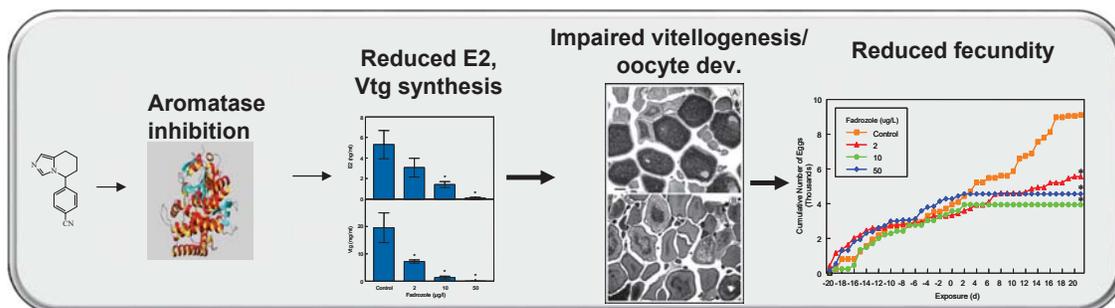
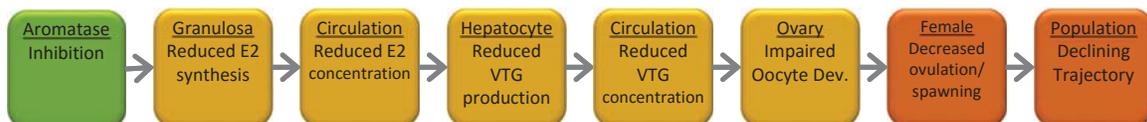
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# Structure of the AOP



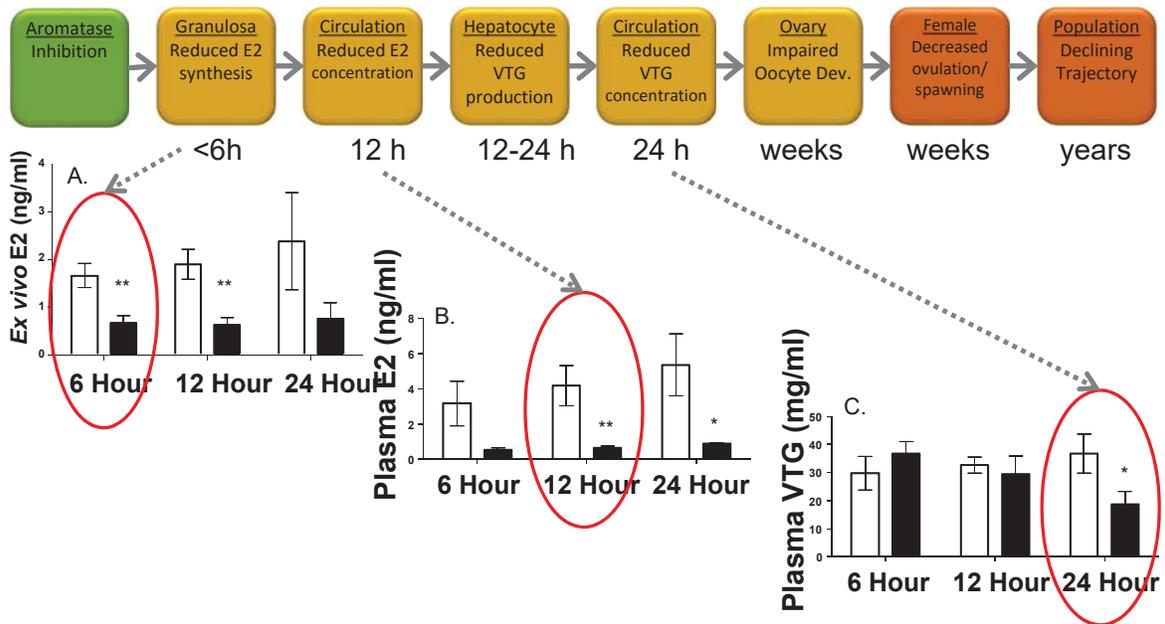
16

# Data supporting the AOP



Fadrozole, fathead minnow: *Toxicol. Sci.* 2002. 67:121-130  
 Prochloraz, fathead minnow: *Toxicol. Sci.* 2005. 86: 300-308  
 Propiconazole, fathead minnow: *Toxicol. Sci.* 2013. 132: 284-297.  
 Letrozole, Japanes medaka: *Compar. Biochem. Physiol. Pt. C*, 2007, 145: 533-541

## Temporal concordance of key events



2011 *Aquatic Toxicol.* 103:170-178

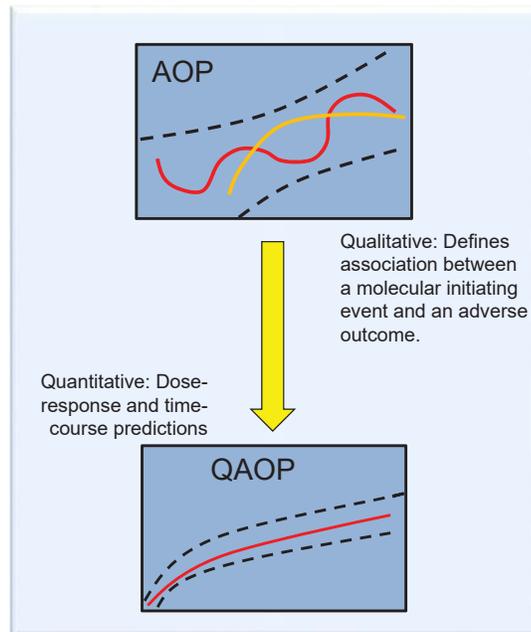
18

## Quantitative implementation of the AOP

- ❖ How do we integrate laboratory data on dosimetry and AOPs to obtain a quantitative, predictive model of dose-response and time-course behaviors?

19

# AOP → QAOP



20

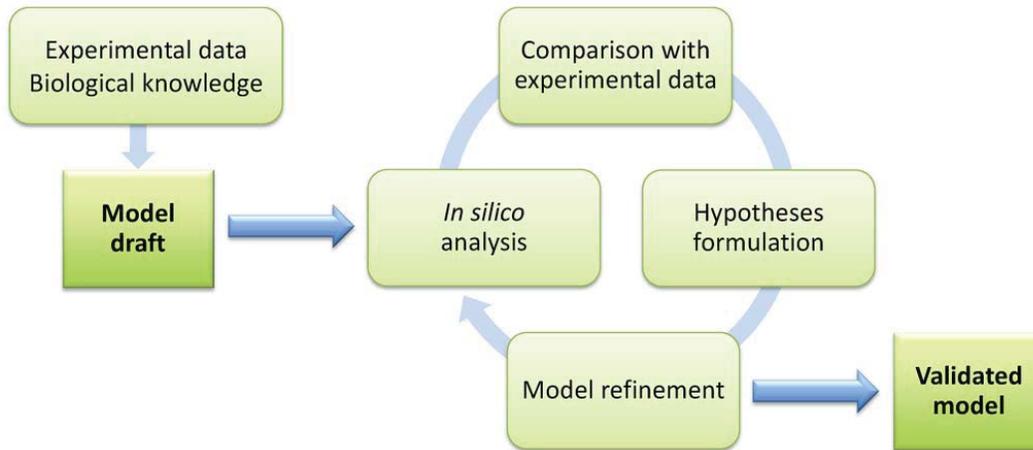
## Computational Biology

**“If I were a senior or first-year graduate student interested in biology, I would migrate as fast as I could into the field of computational biology.”**

**- Francis Collins, Director, NIH**

21

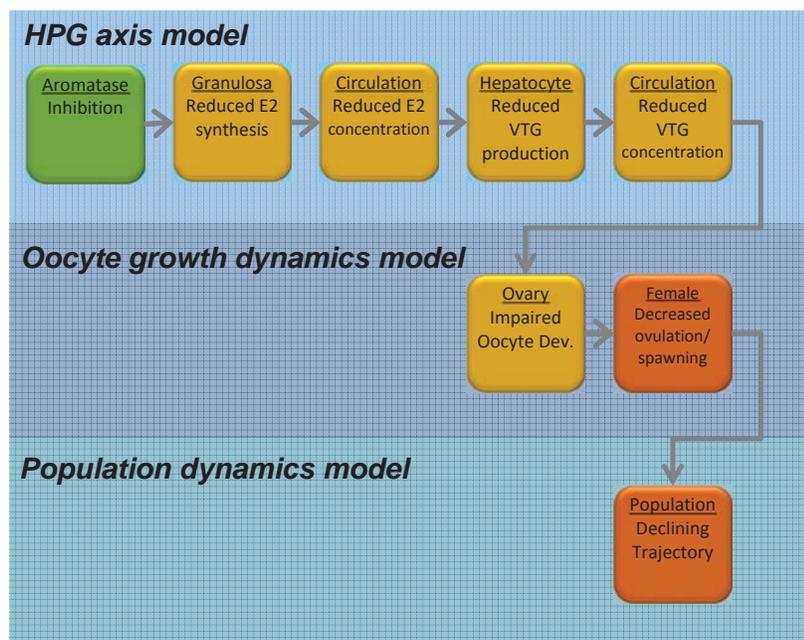
# The computational model reflects current understanding



<http://www.mdpi.com/2218-1989/4/4/1034/htm>

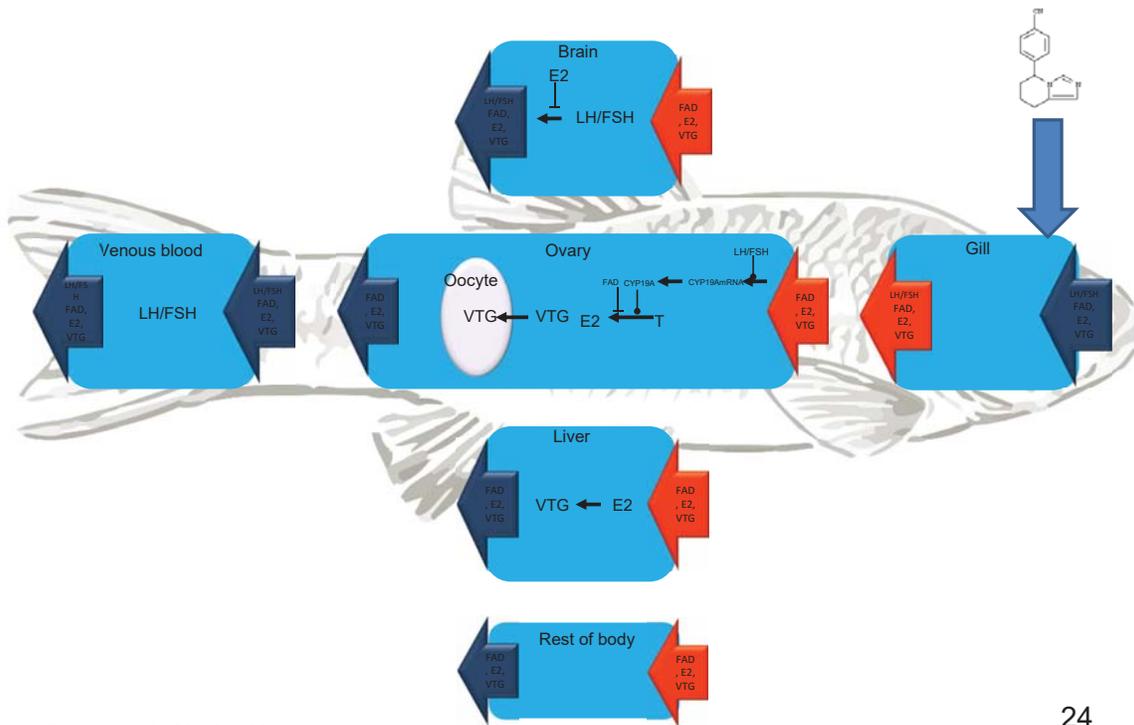
22

## The qAOP: A combination of linked quantitative models



23

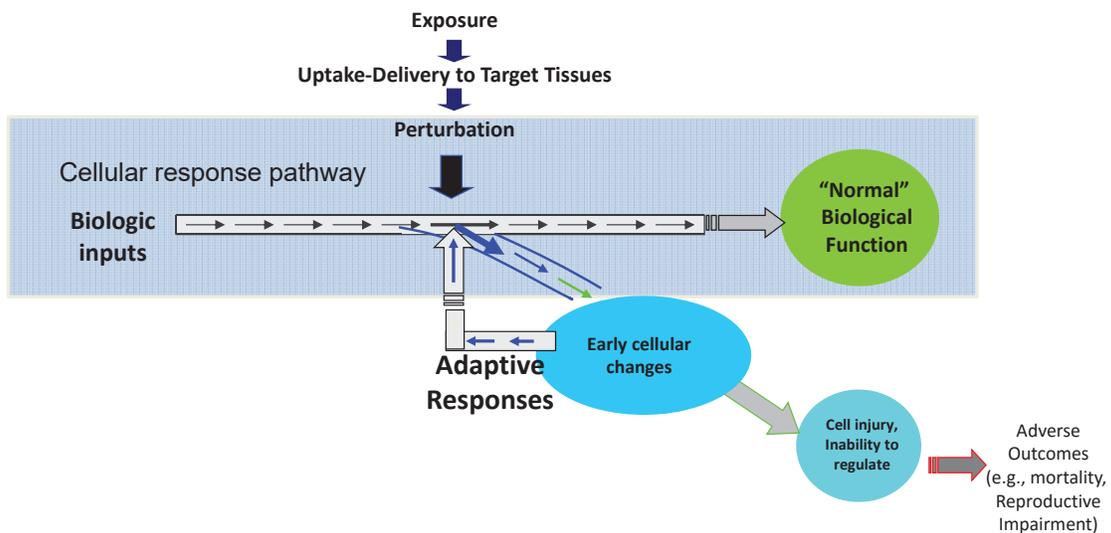
# Fathead minnow HPG axis model



Tox Sci 133(2), 234–247 2013

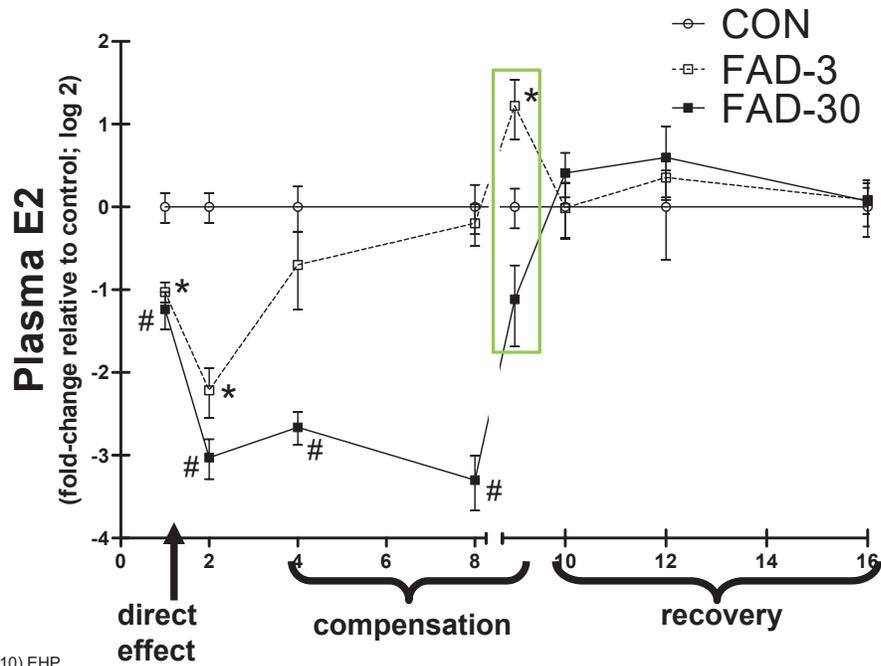
24

# Homeostasis: Adaptation/Compensation



25

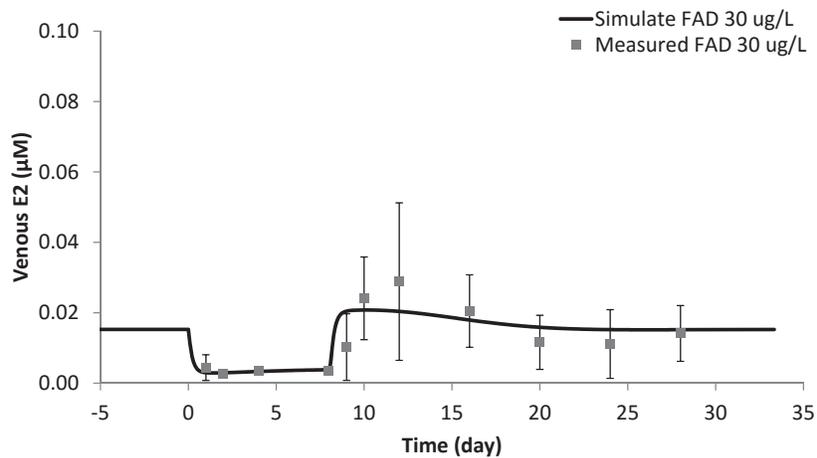
## Adaptation: Plasma estradiol in fathead minnows exposed to fadrazole



Villeneuve et al. (2010) EHP

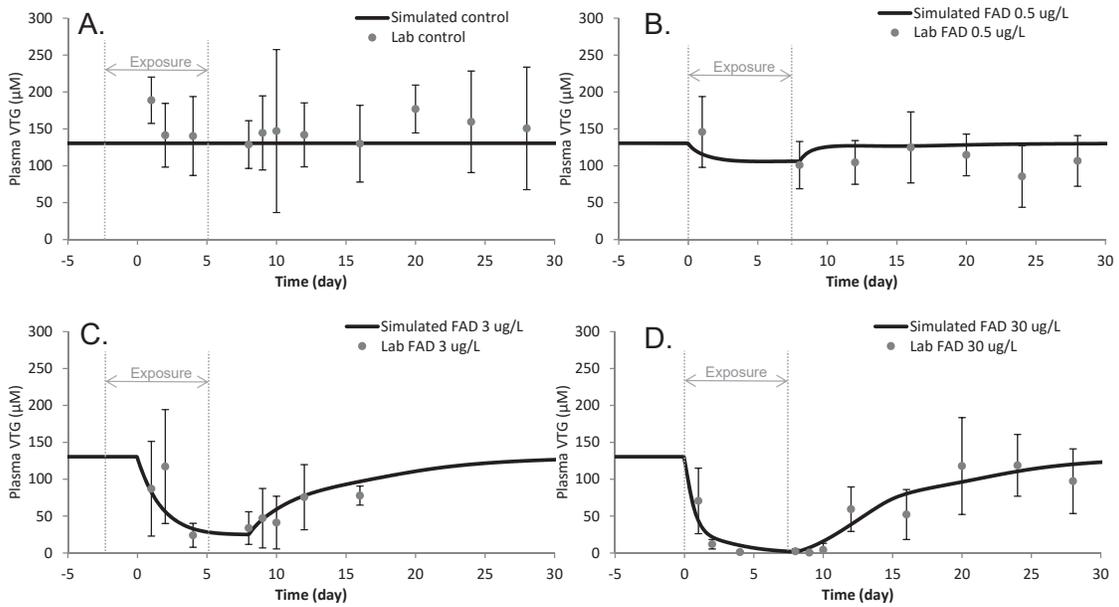
26

## HPG axis model: Effect of aromatase inhibition on venous estradiol



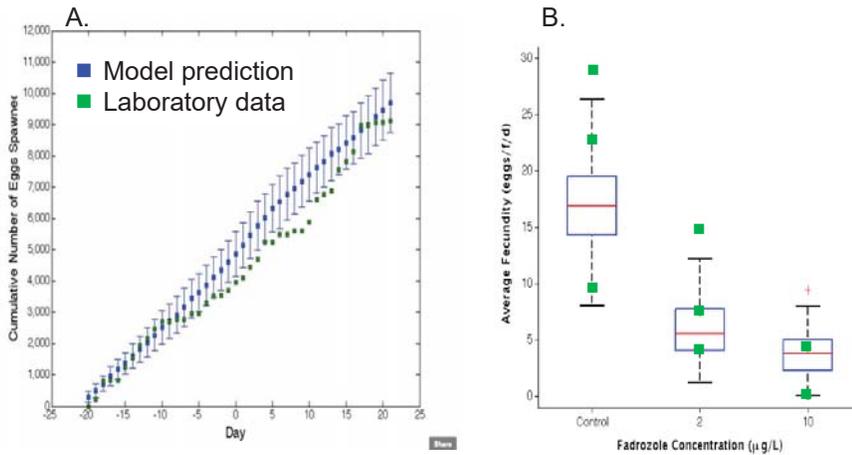
27

# HPG axis model: Effect of aromatase inhibition on venous VTG



28

# Oocyte growth dynamics model: Predicts fecundity based on VTG levels

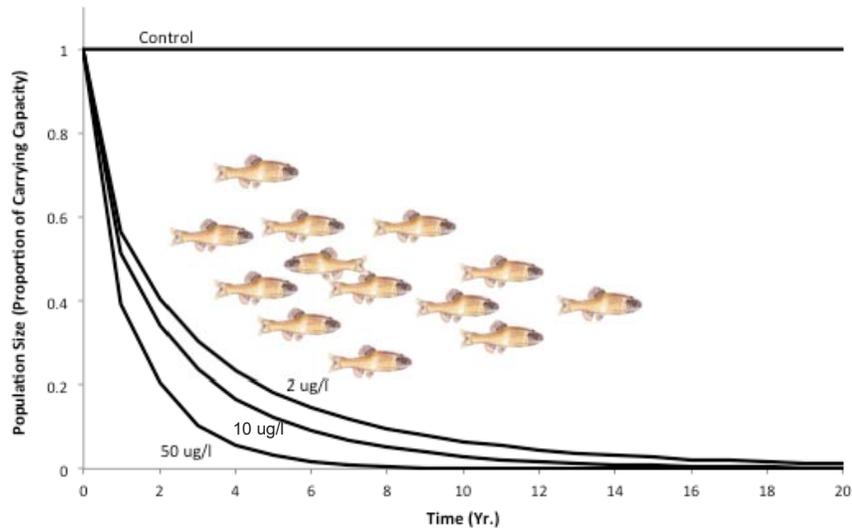


Prediction of normal fecundity vs Lab (mean) results at 21-days

Effects of fadrozole on predicted fecundity vs lab results

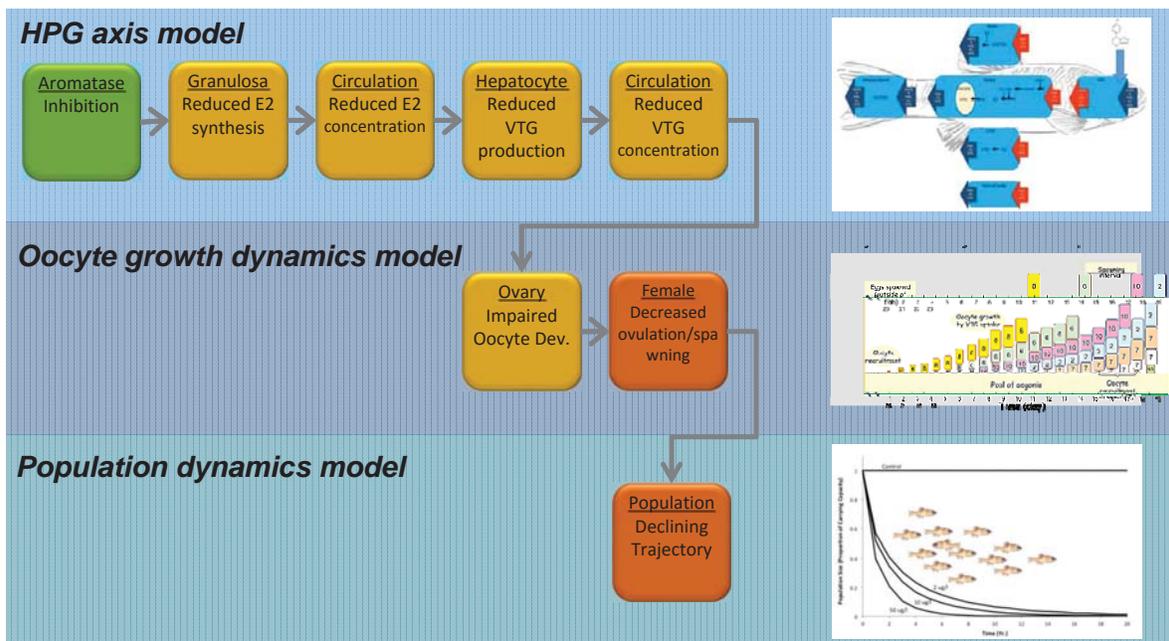
29

# Population dynamics model: Prediction of population dynamics



30

## The aromatase inhibition QAOP



31

## Does the new AOP terminology help?

- AOP specifies information needed to support regulatory decision making
  - Molecular initiating event
  - Key events
  - AO for individuals
  - AO for the population
- Richer language facilitates communication

32

## Experimental design

- ❖ BBDR and qAOP models can simulate behavior of the biological system over time.
- ❖ So best supported by experimental designs that include both time-course and dose-response.

33

## Return on the investment

- A fully developed QAOP is a powerful predictive tool.
  - Input exposure scenario of interest
  - Output prediction of change in adverse outcome
- But data needs are large
  - Expensive and time consuming

34

## Perfection

- ❖ Wanting perfection is a trap.
- ❖ The model should reduce uncertainty relative to where you stand without the model.
  - ❖ Model is only required to be useful.
- ❖ Sophisticated evaluation requires sufficient expertise in relevant biology, modeling technology, and an ability to “step back” and visualize the big picture.

35

[https://aopwiki.org/wiki/index.php/Main\\_Page](https://aopwiki.org/wiki/index.php/Main_Page)



- Navigation
  - Main page
  - AOP List
  - AOP Table
  - EAGMST Approved AOPs
  - Help
  - FAQ
  - Recent changes
  - Release notes
- Actions

Page Discussion

## Main Page

Main Page

### Contents [hide]

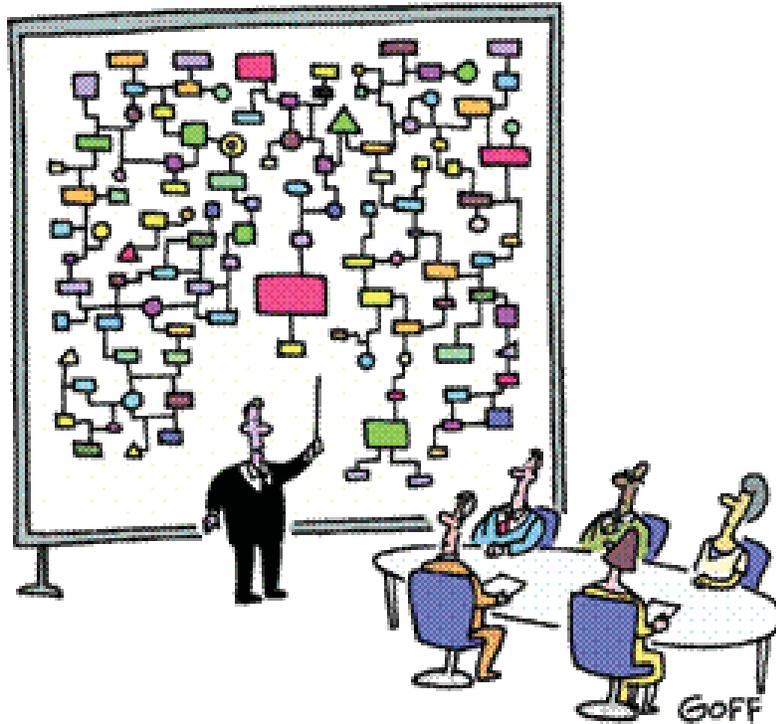
- 1 Announcements
- 2 Welcome to the Collaborative Adverse Outcome Pathway Wiki (AOP-Wiki)
  - 2.1 Disclaimer
- 3 How to add a new AOP
  - 3.1 Before You Start
  - 3.2 OECD User Handbook
  - 3.3 Commenting on AOPs
  - 3.4 To create a new AOP
  - 3.5 To edit AOP wiki pages
  - 3.6 To edit other wiki pages (key events, MIE's, etc.)

36

<http://www.oecd.org/chemicalsafety/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm>

The screenshot shows the OECD website interface. At the top, there is a navigation bar with links for "Data", "Publications", "More Sites", "News", and "Job Vacancies". Below this is the OECD logo and a search bar. A blue navigation bar contains "OECD Home", "About", "Countries", "Topics", and "Français". The main content area features a breadcrumb trail: "OECD Home > Chemical safety and biosafety > Adverse Outcome Pathways, Molecular Screening and Toxicogenomics". A sidebar on the left lists categories like "Testing of chemicals", "Assessment of chemicals", and "Risk management of chemicals". The main heading is "Adverse Outcome Pathways, Molecular Screening and Toxicogenomics". Under "WHAT'S NEW", a date "20/09/2016" is followed by the text: "OECD launched a new Series on Adverse Outcome Pathways on i-Library". The body text states: "OECD launched its knowledge base on Adverse Outcome Pathways (AOPs) in collaboration with the U.S Environmental Protection Agency and the European Commission Joint Research Centre in 2014. Two years later, the first five endorsed AOPs have been published in a new OECD Series on Adverse Outcome Pathways, available free of charge on the OECD public website. These publications are the result of joint efforts between AOP developers and AOP reviewers through an established OECD AOP development and review process. The first publication in the Series proposes a user guide for developing AOPs."

37



**"And that's why we need a computer."**

If you don't know where you're going, you might not get there.





### Small Fish Computational Toxicology Group

➤ **Academia**

K. Watanabe, Oregon Health and Science University

➤ **USACE – Vicksburg, MS**

M. Mayo, E. Perkins, N. Garcia-Reyero

➤ **USEPA (NHEERL)– Duluth, MN, and Grosse Ile, MI**

G. Ankley, E. Durhan, M. Kahl, K. Jensen, E. Makynen, D. Martinovic, D. Miller, A. Schroeder, D. Villeneuve

➤ **USEPA-RTP, NC**

R. Conolly, W. Cheng (ISTD)

40

End



# Extrapolation

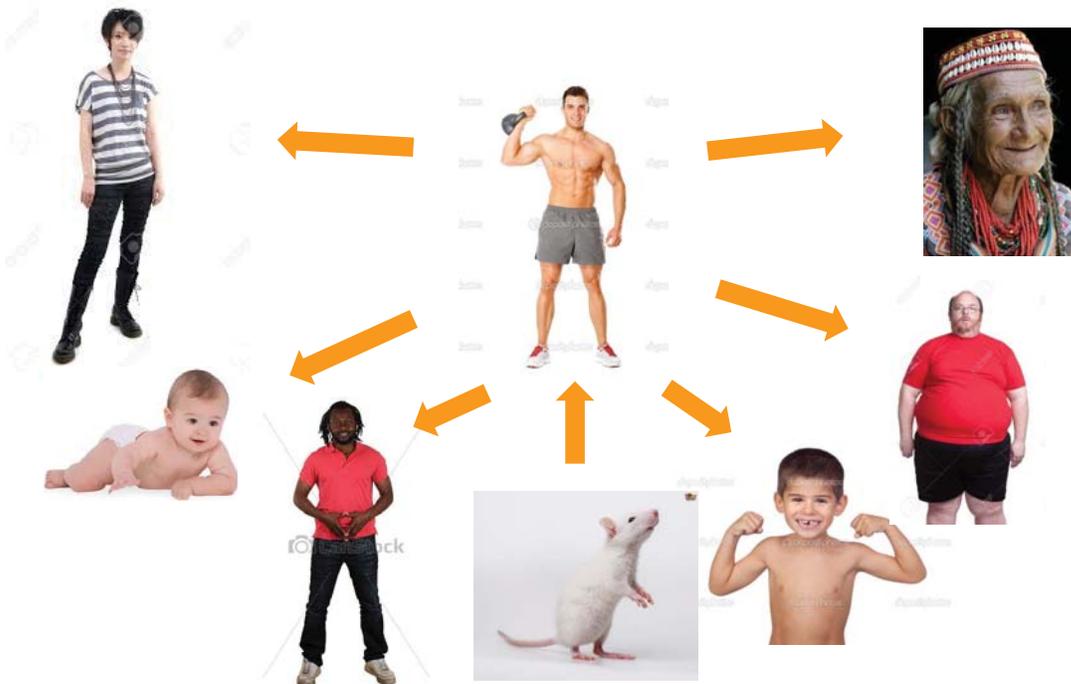


# Extrapolation



44

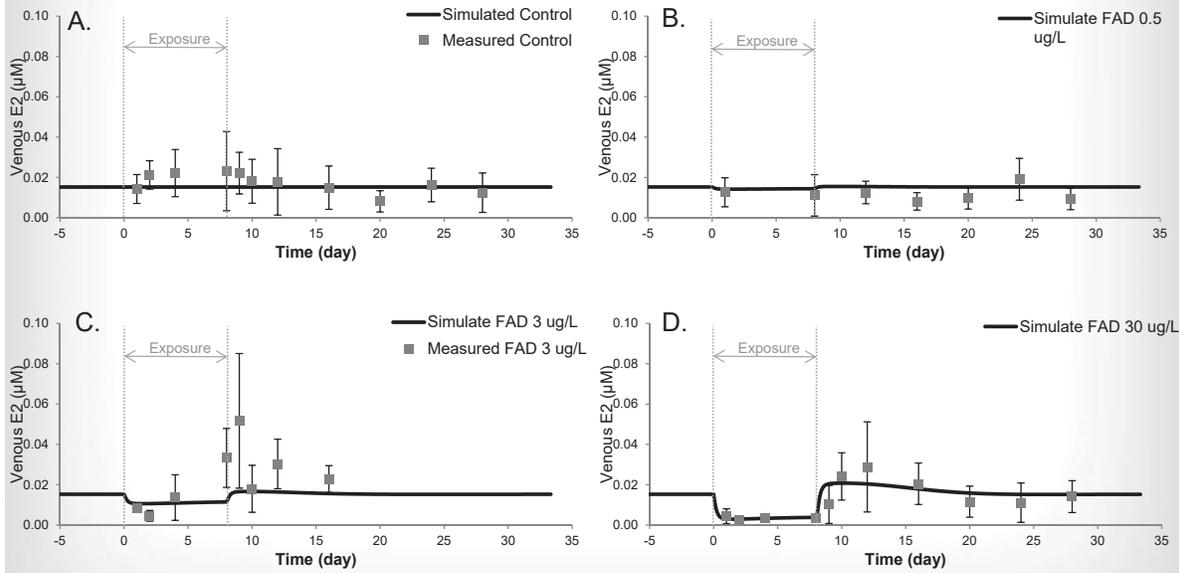
# Extrapolation



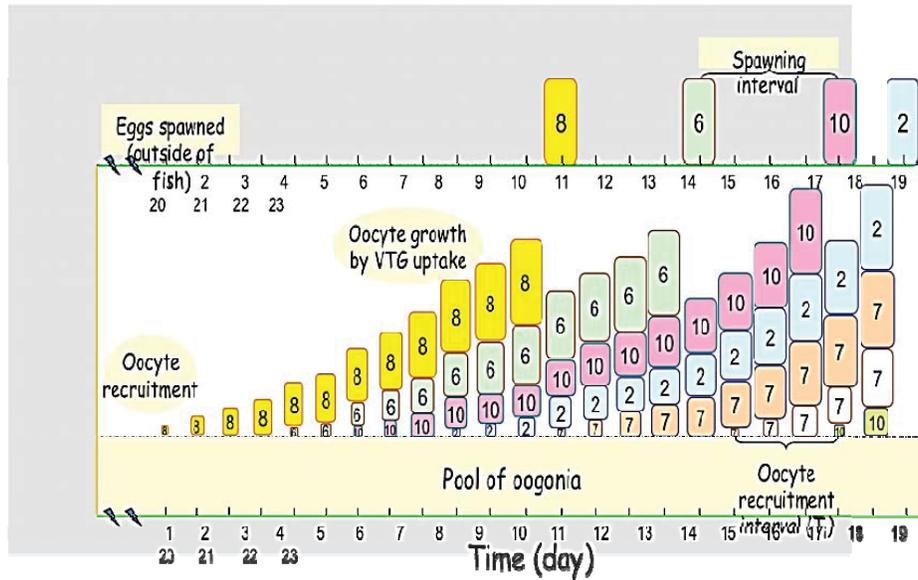
45

# HPGA axis model:

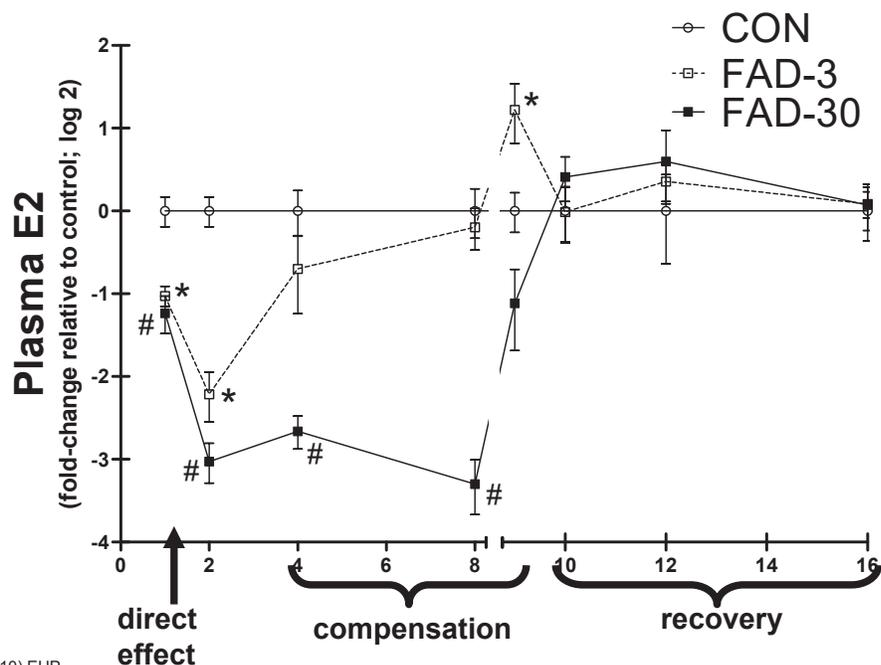
## Effect of aromatase inhibition on venous estradiol



## Oocyte growth dynamics model (Egg development in the fathead minnow ovary)



## Adaptation: Plasma estradiol in fathead minnows exposed to fadrazole



Villeneuve et al. (2010) EHP

48

## Plenty of published guidance on good modeling practice

TOXICOLOGICAL SCIENCES **126**(1), 5–15 (2012)  
doi:10.1093/toxsci/kfr295  
Advance Access publication November 1, 2011

### Physiologically Based Pharmacokinetic Model Use in Risk Assessment—Why Being Published Is Not Enough

Eva D. McLanahan,<sup>\*,1</sup> Hisham A. El-Masri,<sup>†</sup> Lisa M. Sweeney,<sup>‡</sup> Leonid Y. Kopylev,<sup>||</sup> Harvey J. Clewell,<sup>§</sup> John F. Wambaugh,<sup>¶</sup> and P. M. Schlosser<sup>||</sup>

<sup>\*</sup>National Center for Environmental Assessment and <sup>†</sup>National Health and Environmental Effects Research Lab, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711; <sup>‡</sup>Science Applications International Corporation, Wright-Patterson Air Force Base, Dayton, Ohio 45433; <sup>§</sup>Center for Human Health Assessment, The Hamner Institutes for Health Sciences, Research Triangle Park, North Carolina 27709; <sup>¶</sup>National Center for Computational Toxicology, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711; and <sup>||</sup>National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC 20460

<sup>1</sup>To whom correspondence should be addressed at, USEPA/ORD/NCEA, MD-B243-01, RTP, NC 27711.  
Fax: (919) 541-0245, E-mail: mclanahan.eva@epa.gov.

Received July 19, 2011; accepted October 19, 2011

49

## Confidence (uncertainty<sup>-1</sup>)

- ❖ Concern: The model increases uncertainty relative to not having the model.
  - ❖ Complicated structure relative to defaults
  - ❖ Errors in the model
  - ❖ Uncertainty about mechanism depicted in the model

50

## Complicated structure...

- ❖ Delineation of sources of uncertainty does not mean uncertainty is increased.
- ❖ As long as good modeling practice is observed then model development coordinated with laboratory experiments is informative about roles of PK and key events.
- ❖ Uncovers hidden assumptions

51

## Errors in model

- ❖ Coding errors definitely possible.
- ❖ But observation of good modeling practice, including rigorous code checking, addresses this concern.

52

## Uncertainty about mechanism

- ❖ This can be a valid concern but it applies to any work involving mechanisms, not just development of computational models.
- ❖ Addressed by peer review, scientific rigor
- ❖ Bradford Hill criteria

53

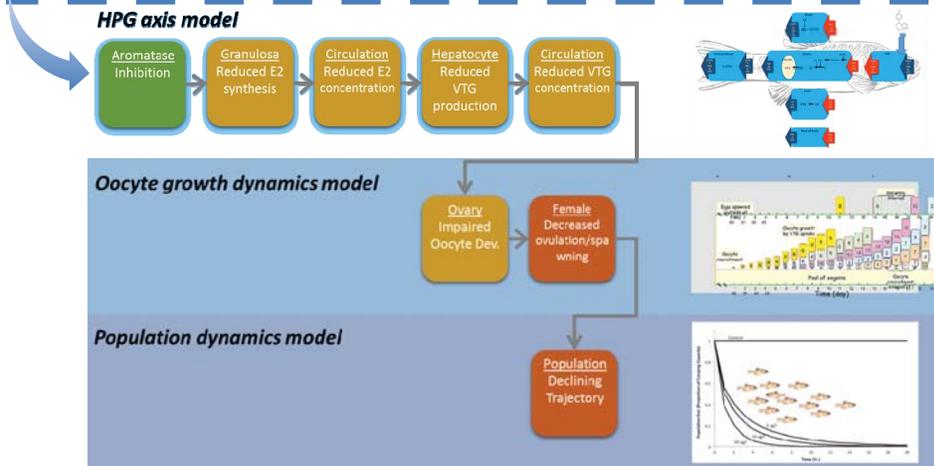
# Return on the investment

Mature QAOP could serve as an “*in silico*” description of *in vivo* biology to aid in design of *in vitro* tests and interpretation of *in vitro* data

HTS assays for MIE activation



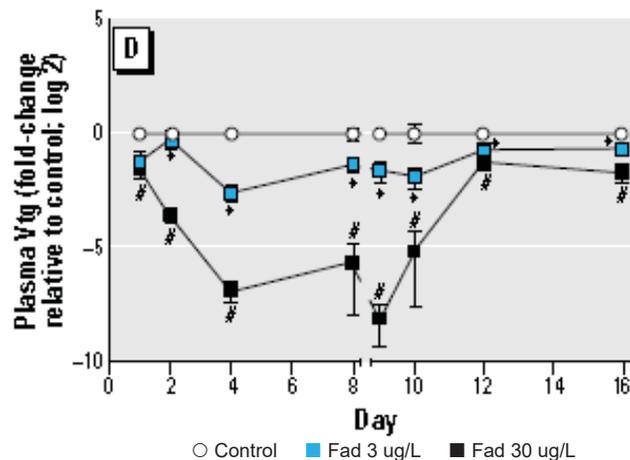
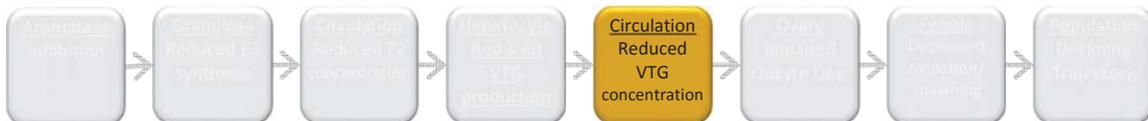
*in vitro*  
*in vivo*



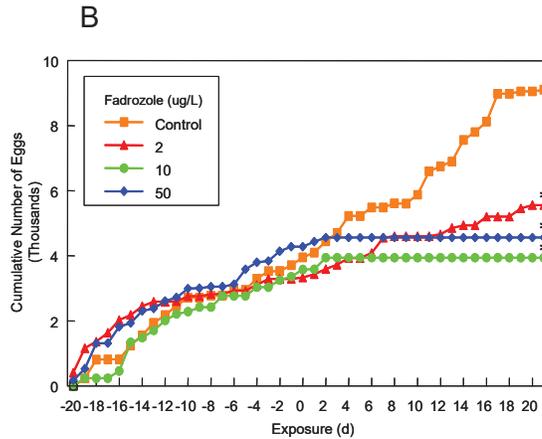
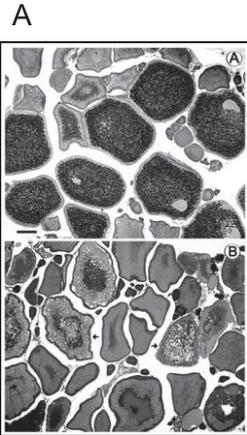
54

Key events:

Reduced VTG in circulation



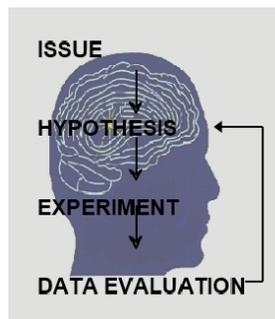
## Key events: Impaired oocyte development & spawning



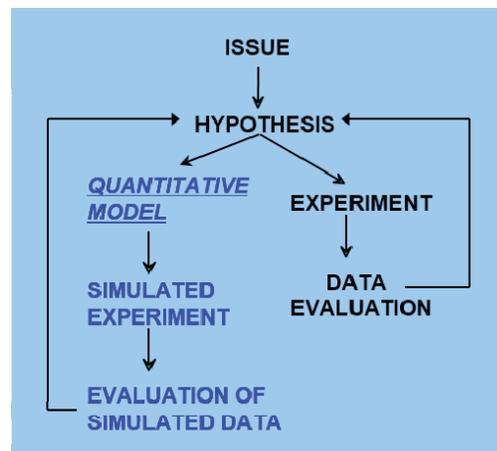
Toxi Sci 2002 67:121-130

56

## Computers are essential



*(Intuitive modeling)*



*(Formal + intuitive modeling)*

57

# 13

## LOW DOSE RESEARCH AT CHALK RIVER LABORATORY

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## Low Dose Research at Chalk River Laboratory

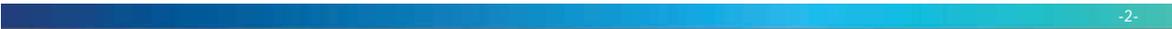
EPRI IDEA Workshop

November 9, 2016



Canadian Nuclear Laboratories | Laboratoires Nucléaires Canadiens

UNRESTRICTED / ILLIMITÉ -1-



-2-

**ch2m**

**FLUOR.**

**ENERGYSOLUTIONS**

**SNC • LAVALIN**



**CNEA**  
Canadian  
National  
Energy  
Alliance



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UNRESTRICTED / ILLIMITÉ -2-

# Canada is a Tier One Nuclear Nation

Canada is one of a small number of countries with a comprehensive nuclear sector

- Nuclear energy commitment
- Federal regulation
- Domestic supply chain
- Education and research
- Canadian Nuclear Laboratories



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UNRESTRICTED / ILLIMITÉ -3-



## CRL History

- Birthplace of Canada's nuclear industry
- First sustained nuclear criticality outside USA
- Supplied Cobalt-60 for first cancer treatment in Canada
- AECL established as a Crown Corporation in 1952
- Developed CANDU power reactor technology



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UNRESTRICTED / ILLIMITÉ -4-

# Missions

A broad mandate, serving both government and private sector



Decommissioning  
& Waste  
Management



Science and  
Technology for  
Government



Science and  
Technology for  
Industry



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UNRESTRICTED / ILLIMITÉ -5-



Canadian Nuclear Laboratories | Laboratoires Nucléaires Canadiens

The largest science & technology lab in Canada

- 9,000 acres in size, 200 acres lab complex
- 17 nuclear facilities, 70 major buildings
- 3,100 employees (500 PhDs and Masters)
- 1,600 engineering, scientific and technical staff
- >300 skilled trades people



# Over 50 Unique S&T Facilities

Analytical Chemistry Laboratories  
Biofouling and Biocorrosion Facilities  
**Biological Research Facility**  
CAN-DECON Test Loops #2 and #3  
Chemical and Corrosion Autoclave and Loop Test  
**Co-60 Gamma Irradiation Facility**  
Containment Chemistry Laboratory  
Core Disassembly Facility  
Deformation Technology Calandria Tube Burst Test and Creep Rupture Testing Laboratory  
Delayed Hydride Cracking Facility  
Digital Radiography and Computer Tomography  
Environmental Technologies Branch  
Fission Products Behaviour Laboratory  
Fluid Sealing Technology Metrology Facility  
Fuel Development Branch  
**Gammacell 220 Cobalt-60 Irradiator Facility**  
GEANT4 Dynamic Simulation Facility  
**Health Physics Neutron Generator**  
High Bay and Laboratories  
High Pressure Water Test Loop Facilities  
High Temperature and Pressure Test Loop Facilities  
High Temperature Fuel Channel Laboratory

Impact Fretting-Wear Facility  
Large Scale Containment Facility  
Large-Scale Vented Combustion Test Facility  
Laser Dimensioning  
Laser Welding Facility  
Mechanical Testing Laboratories  
Metallographic Services Laboratory  
Model Development Laboratory  
Molten Fuel Moderator Interaction Facility  
Nuclear Instrumentation Development Laboratory  
RD-14M Experimental Facility  
Recycle Fuel Fabrication Laboratories  
Single-Specimen Uniaxial-Stress Thermal Creep  
Small Scale Burst Test Facility  
Strainer Test Facilities  
Surface Science Laboratories  
Thermalhydraulics Laboratory  
Transmission Electron Microscopy Laboratory  
Tritium Facility  
Van de Graaff Accelerator Facility  
X-Ray Diffraction Laboratory  
ZED-2 Research Reactor

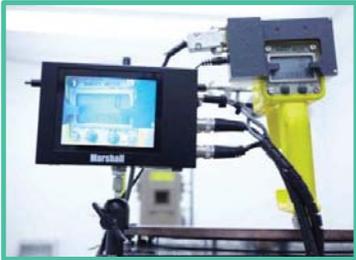


## Overview of Radiobiology Facilities and Capabilities



# Health

## Radiological Services



- Understand the effects of radiation on living things
- Research and develop medical applications for nuclear science
- Bioassay services, dosimetry experiments, alpha isotope expertise & licensing



# Radiobiology and Health Staff and Research Themes

## Understanding the Health Effects of Irradiation



- Address public concerns about the safety of radiation
- Understand how radiation, as a stressor, interacts with the disease process
- Inform the onward development of radiological protection
- Emphasis on low-dose radiation (i.e.  $< 100$  mSv)



# Biological Research Facility

1,600 m<sup>2</sup> building

22,500 mouse capacity



- Controlled environment (HEPA-filtered air supply/exhaust; computer-controlled temperature, humidity and lighting)
- Specific pathogen free (SPF) status
- Separate animal rooms and laboratories for radionuclide and chemical carcinogen toxicity studies
- Attached laboratories for cell culture and molecular biology, histology and tissue processing, etc.

Certified by the Canadian Council of Animal Care



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UNRESTRICTED / ILLIMITÉ -11-

# Biological Research Facility

Unique Opportunities For Radiological Hazard Research



- Low-dose external gamma radiation
- Internal radionuclide toxicity and decorporation studies (tritium: HTO, OBT, tritiated oil; strontium, alpha emitters: uranium)
- Irradiated fuels toxicity studies
- CNL Animal Care Committee Approval of all protocols



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UNRESTRICTED / ILLIMITÉ -12-

# Gamma Beam Irradiation Facility

Two gamma irradiation devices in a 30 m long irradiation hall

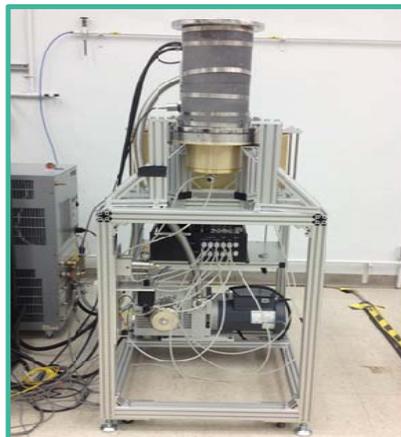


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UNRESTRICTED / ILLIMITÉ -13-

# HPNG Facility

Used for calibration and R&D applications; instrument / dosimeter development and calibration; radiation-physics studies; irradiation of biological samples



## DD-109 Neutron Generator

- Neutrons are produced when a deuteron beam strikes the titanium hydride target containing deuterium
- Neutron flux of  $10^9$  n/cm<sup>2</sup>/s at an energy of 2.5 MeV
- Possible addition of a DT unit (target containing tritium that will produce neutrons at energies of up to 14 MeV)



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UNRESTRICTED / ILLIMITÉ -14-

# Radiobiology Projects



## Low Dose Radiation Effects

- Effects of low dose radiation on genes and cancer
- Life-span study comparing the toxicity of gamma and tritium beta radiations
- Effects of low dose internal and external radiation on the development of cancer
- Effects of low dose radiation on the development of cardiovascular disease



## Medical Applications

- Improving radiation therapeutics
- High dose effects on bone marrow



## Dosimetry

- Effects of radiation dose and radiation quality on stem and other cells
- Effects of irradiation on the biosolubility of fuels and contaminated reactor components
- Space radiation, dosimetry, shielding and neutron metrology
- Development and implementation of GenmodPC



# Historically strong position of AECL/CNL in LDR research

Initiated in ~ 1978, lead by Dr. Ron Mitchel (retired in 2007)

- LDR induced a **radioadaptive response** in **yeast cells**; subsequently delineated the mechanism to be through better repair of DNA lesions
- LDR induced a **radioadaptive response** in cultured **mammalian cells *in vitro***;
- LDR lowered the rate of spontaneous neotransformation in cultured **mammalian cells *in vitro***;
- LDR induced a **radioadaptive response** in **mice *in vivo*** by suppressing tumor formation;
- LDR prolonged life span of **mice *in vivo***;
- LDR protected from atherosclerosis in predisposed **mice *in vivo***



## Project: Effects of Low Dose Radiation on Genes and Processes that could lead to Cancer and other Diseases

**Objective:** to characterize early molecular and cellular responses to low dose gamma radiation that contribute to aging-associated pathologies, such as cancer

**Methods:** Gene expression changes, DNA damage and repair, epigenetic modifications are measured in mammalian cells of different types *in vitro* and/or in mice *in vivo*. Exposed to 10-100 mGy of gamma-radiation

**Current results:**

- Improved repair of damaged DNA bases, but not double-strand breaks, in mice *in vivo*
- Delayed aging of human fibroblasts *in vitro*
- Improved immune status of aged mice
- No accelerated aging of mouse kidney *in vivo*



## Project: Life-span study comparing the toxicity of gamma and tritium beta radiations

**Objective:** examine relative effectiveness of internal beta-irradiation from <sup>3</sup>H and external gamma in causing cancer and aging of mice

**Methods:** CBA/Ca mice exposed to a range of doses (66 mGy to 1.3 Gy) from either external gamma-beam or internal beta-radiation from ingested water over 2 week period. Spontaneous tumor formation and life span monitored over the life of the mice.

**Current results:**

- >half of the animals (2555 out of 3300) have died and post-mortem analyses ongoing
- Lowest doses tend to not affect mean life span, but the control group is not complete yet



# Project: Effects of low dose internal and external radiation on the development of cancer

**Objective:** test the hypothesis that LDR increases cancer rates proportional to dose

**Methods:** three mouse cancer models:

- 1) Intestinal (APCmin mice)
- 2) Breast (MMTV-Neu mice)
- 3) Lung (A/J mice)

exposed to chronic 10 and 100 mGy of either gamma or internal HTO over 2 months and:

- Rates and frequency of cancer
- Life-span
- Cancer driving mechanisms monitored and measured

**Current results:**

- Pilot task to APCmin mice complete: assays and breeding optimized
- Pilot task MMTV-Neu is ongoing



## Thank you Questions?

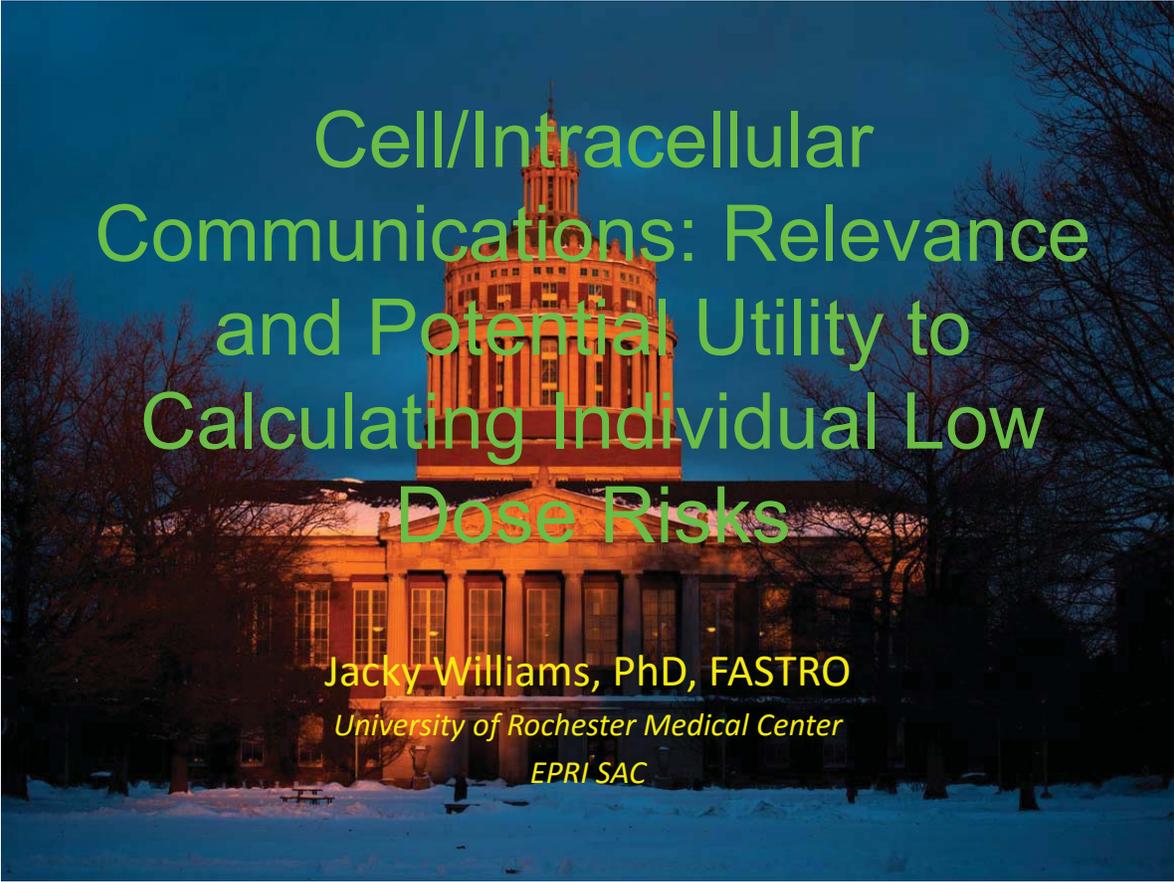




# **14**

## **CELL/INTRACELLULAR COMMUNICATIONS: RELEVANCE AND POTENTIAL UTILITY TO CALCULATING INDIVIDUAL LOW DOSE RISKS**

---



# Cell/Intracellular Communications: Relevance and Potential Utility to Calculating Individual Low Dose Risks

Jacky Williams, PhD, FASTRO

*University of Rochester Medical Center*

*EPRI SAC*

## **Disclaimer/Conflicts**

- External Advisory Committee (NSBRI)
- Chair, Scientific Advisory Committee, Center for Space Radiation Research (NSBRI)
- National Council of Radiation Measurement and Protection (NCRP)
- Scientific Advisory Board [Radiation], EPA
- Scientific Advisory Committee [Low Dose Radiation], EPRI

Opinions expressed in this talk are those of the presenter alone and do not represent a position taken by any of the above organizations

## Dose Effect/Radiation Risk Estimates

- Need for low dose/dose rate effect data:
  - Risk estimates (workers and public)
  - Safety measures
  - Pre- and post-exposure individual risk and/or countermeasures
- Available data: human (limited number of large cohorts; fewer with relevant exposures); animal models (relevance to human pathology/physiology; few studies using relevant doses and dose rates)

## Dose Effect/Radiation Risk Estimates

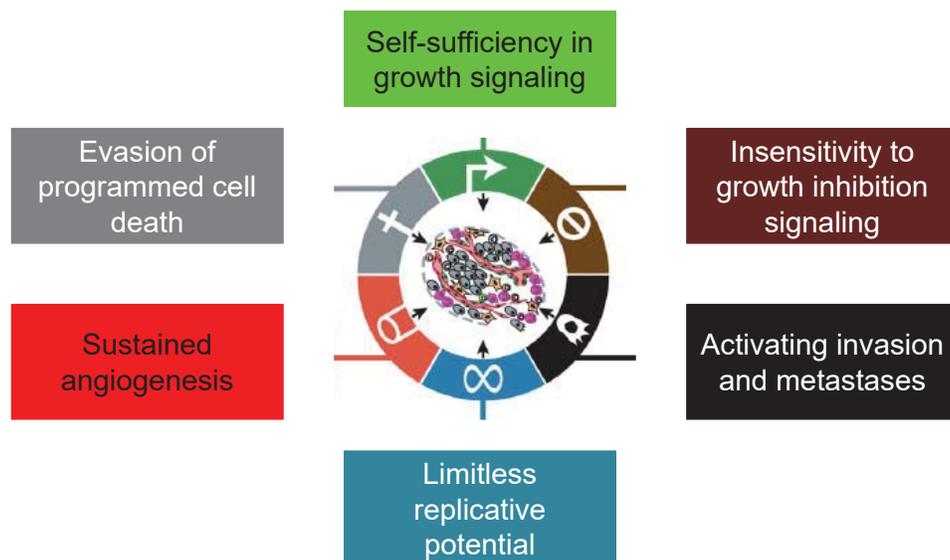
- Need for low dose/dose rate effect data:
  - Risk estimates
  - Safety measures } **General populations**
  - Pre- and post-exposure individual risk and/or countermeasures

Can we incorporate current understanding of low dose radiation biology to give alternative/supplemental means of identifying effects and calculating risk estimates for workforce, public populations and individuals?

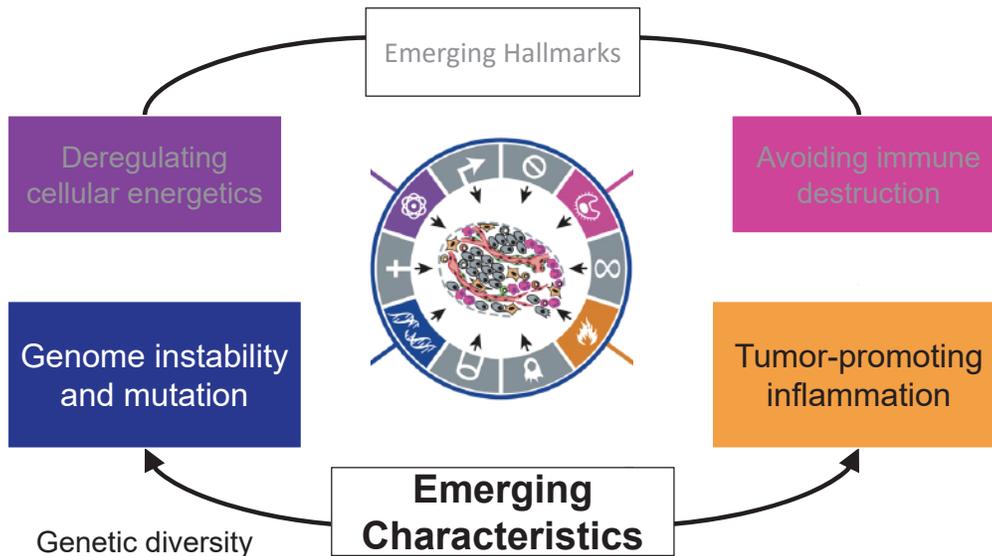
## Current Biological Understanding of Low Dose Radiation Response

- No longer predicated on “acute” response (e.g. cell death, mutation induction) alone
- Long-term degenerative effects have increased importance (e.g. cardiac events, immune dysfunction, cataract induction, etc.)
- Carcinogenesis remains greatest concern

## Conditions for Carcinogenesis

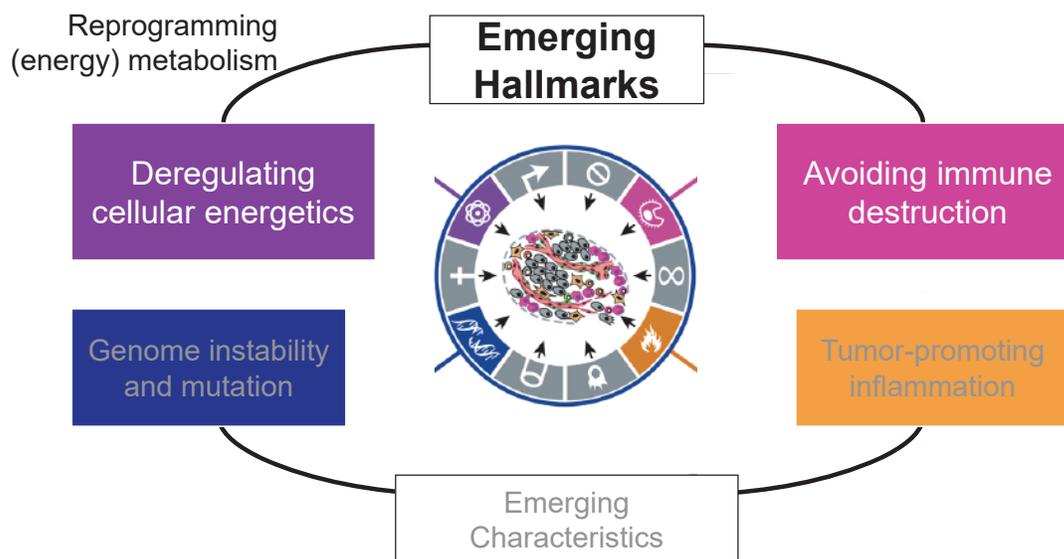


# Conditions for Carcinogenesis



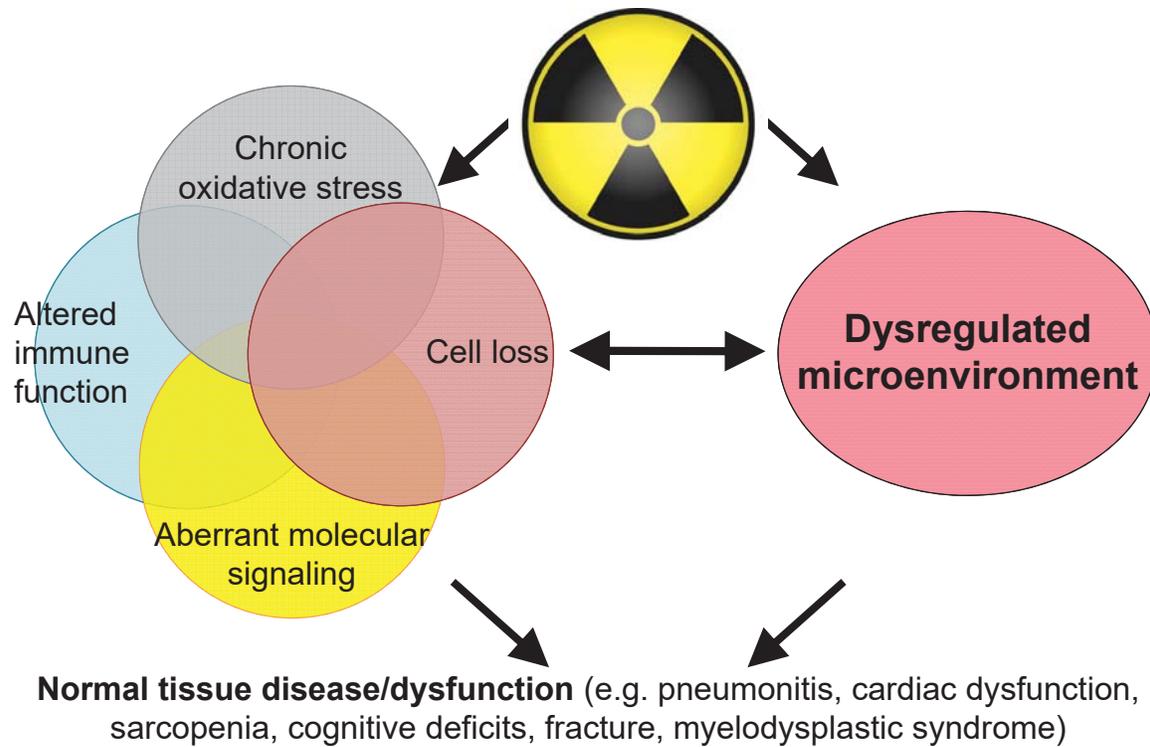
Hanahan & Weinberg, *Cell* 2011.

# Conditions for Carcinogenesis

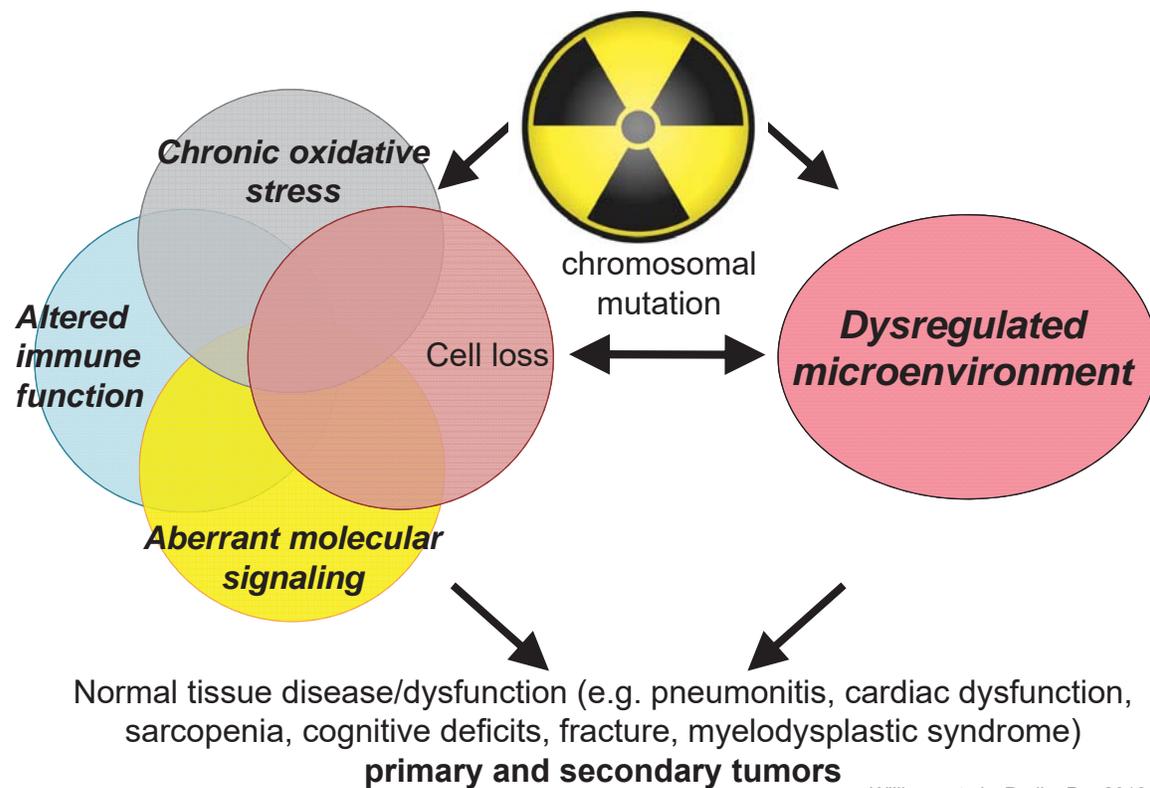


cancer versus normal cells → disrupted microenvironment

Hanahan & Weinberg, *Cell* 2011.



Williams et al., *Radiat Res* 2016.



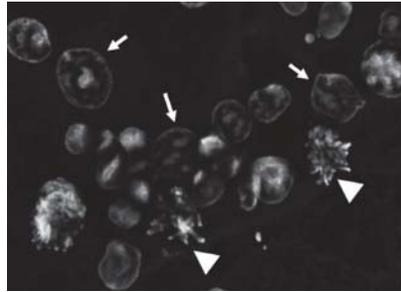
Williams et al., *Radiat Res* 2016.

# Cell Signals as Biomarkers of Microenvironmental Disruption

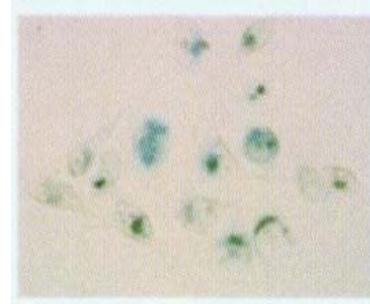
## 1. Cell loss/death



apoptosis



mitotic catastrophe



senescence



## Cell Signals of Cell Death/Loss

### 1. Cell loss/death

Alterations in cell gene/protein expression

- early response genes (e.g. AP1, EGR1), cell cycle arrest (e.g. GADD, cyclins, TP53), DNA repair (e.g. XRCC6, POLD family), cell death (e.g. NF $\kappa$ B, TP53), immune/inflammatory response (e.g. NFAT)

## Cell Signals of Radiation Response

### 1. Cell loss/death

Alterations in cell gene/protein expression

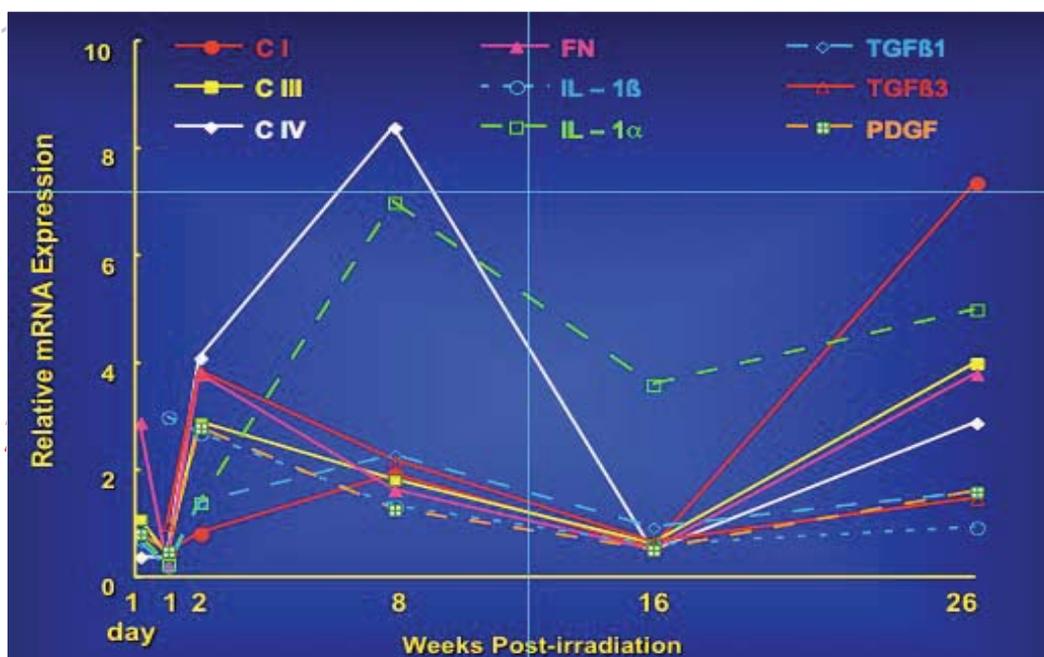
- early response genes (e.g. AP1, EGR1), cell cycle arrest (e.g. GADD, cyclins, TP53), DNA repair (e.g. XRCC6, POLD family), cell death (e.g. NF $\kappa$ B, TP53), immune/inflammatory response (e.g. NFAT)

### 2. Surviving (repaired/unrepaired) cells

Chronic alterations in intra- and extra-cell signaling (cytokines and growth factors)

- IL1, TNF $\alpha$ , IFN $\gamma$ , TGF $\alpha$ , PDGF, TGF $\beta$ , bFGF, IL6 – some found in circulation/urine/saliva

## Cell Signals of Radiation Response



IL6 – some found in circulation/urine/saliva

Modified from Rubinet *et al.*, *IJROBP* 1996.

# Cell Signals of Radiation Response

## 1. Cell loss/death

Alterations in cell gene/protein expression

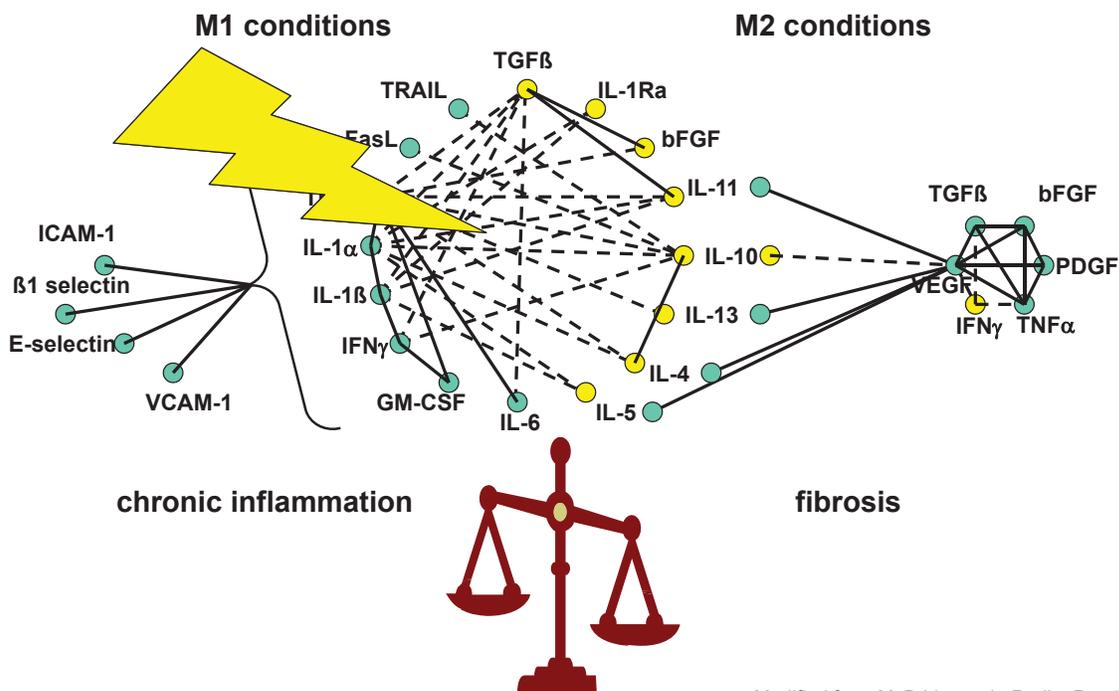
- early response genes (e.g. AP1), cell cycle arrest (e.g. GADD, cyclins, TP53), DNA repair (e.g. XRCC6, POLD family), cell death (e.g. NF $\kappa$ B, TP53), immune/inflammatory response (e.g. NFAT)

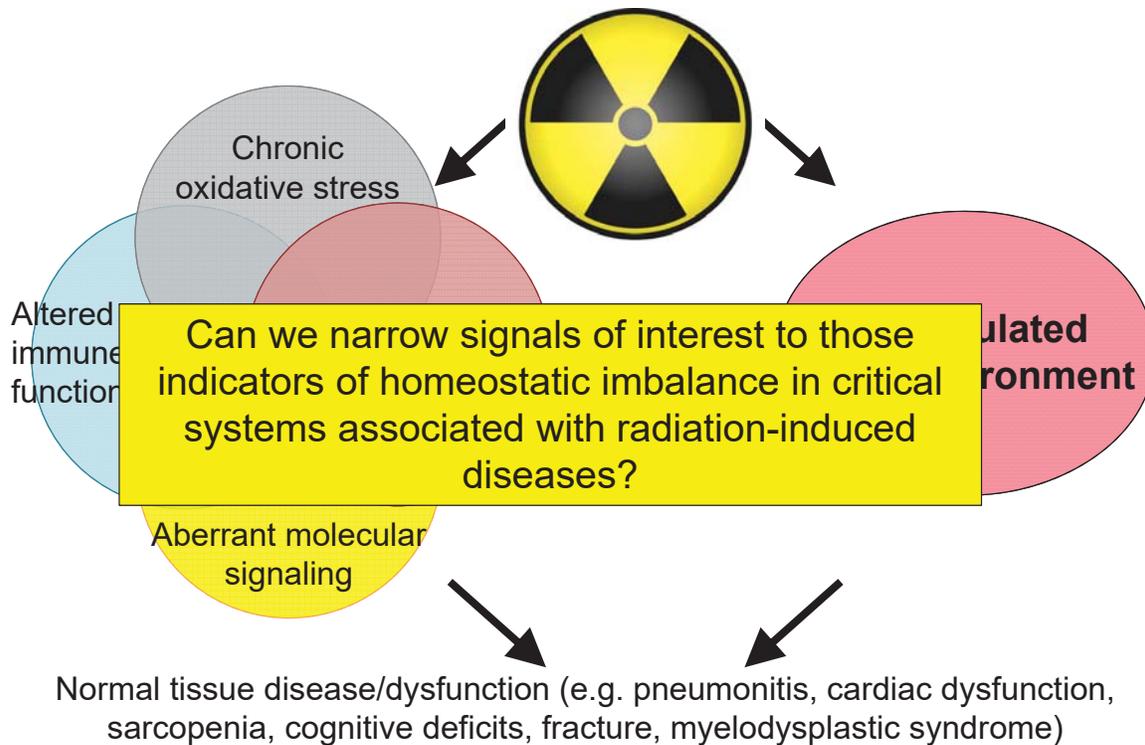
## 2. Surviving (repaired/unrepaired) cells

Chronic alterations in intra- and extra-cell signaling (cytokines and growth factors)

- Proinflammatory versus profibrotic environment

# Cell Signals of Radiation Response





Williams et al., *Radiat Res* 2016.

## Study Conclusions

- Animal models can verify gene/pathway involvement in radiation-induced disease
- Models should provide **dose** (persistence of signal) and **threshold** (loss of signal) information (strain/species specificity?)
- Models can eliminate "effect" pathways, e.g. senescence in radiation pulmonary fibrosis
- Need to prioritize endpoints of interest
- Need to choose models that mimic human disease characteristics
- Can use genetically modified models to identify *individual* inherent genetic risk/resistance

## Summary

- Genetic signatures provide measure of radiation exposure *and* cellular/tissue response
- Radiation-induced disruption of environmental homeostatic mechanisms is likely key factor in initiation and development of radiation-induced degenerative diseases and (possibly) cancer
- Identification of potential homeostatic bio-markers can be made through gene database interrogation, verified through animal modeling – **population & individual dose effect response**
- Final verification (human) through sample collection, e.g. IDEA



# 15

## LOW DOSE RISKS – ANIMAL EXPERIMENTS

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## Low dose risks – animal experiments

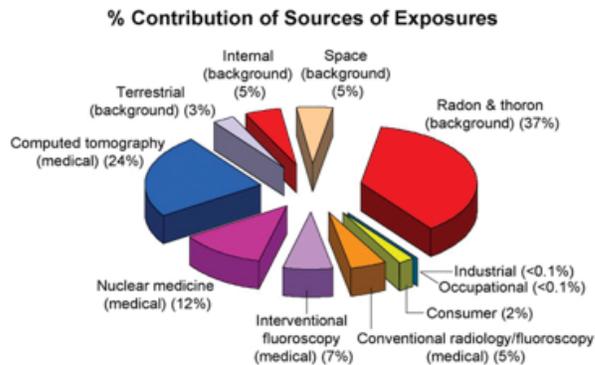
Gayle E Woloschak, PhD  
Radiation Oncology Dept.  
Feinberg School of Medicine  
Northwestern University

Introduction



# Sources of Ionizing Radiation

Annual risk (Americans, excluding radiation therapy)



**FIGURE 16.6** Percentage contribution of the various sources of exposure to the collective effective dose (1,870,000 person-Sv) and the average total effective dose per person in the US population (6.2 mSv) for 2006. Medical radiation and natural background radiation make almost equal contributions. (Data from National Council on Radiation Protection and Measurements. *Ionizing Radiation Exposure of the Population of the United States, Report 160*. Bethesda, MD: NCRP; 2009.)

Hall 2012 figure 16.6

- Radon, 'natural', but preventable, causes ~10% of all lung cancer, according to BEIR VI
- Medical imaging procedures contribute almost 50% of total exposure, which would contribute ~ 50K fatal cancers, however much of this is delivered to fatally ill patients.
- Occupational exposure only causes ~100 cancers per year, but this is concentrated in a small cohort -- consisting mostly of aviation and medical workers.

# Indirect Impact of Low Dose Research

- Health impact, use of radiation in medicine
- Energy production - nuclear power, global warming, carbon footprint
- Protection of the public from harmful doses of radiation
- Nuclear waste clean-up done in an acceptable manner
- National security, nuclear weapons, dirty bombs, nuclear terrorism

# Ionizing Radiation Dose Ranges (Sievert)



**Office of Science**  
U.S. DEPARTMENT OF ENERGY

Evidence for small increases in human cancer above 100 mSv acute exposure or 200 mSv chronic exposure

Typical mission doses on International Space Station (ISS)

Kerala coast, India high natural bkg/yr

Airport x-ray whole body scanner:  
0.00007 mSv/scan  
(Limit = 0.25 mSv/yr ≈ 4000 scans/yr)

Round-trip Los Angeles - New York (≈ 0.037 mSv)  
EPA dose limit public drinking water systems: 0.04 mSv/yr

**NOTE:** This chart was constructed with the intention of providing a simple, use-friendly, "order-of-magnitude" reference for radiation exposures of interest to scientists, managers, and the general public. In that spirit, most quantities are expressed as "dose equivalents" in the more commonly used radiation protection units, the rem and sievert. Medical diagnostics are expressed as estimated maximum organ dose, as they are not in "effective dose" they do not imply an estimation of risk (no tissue weighting). Dose limits are in effective dose, but for most radiation types and energies the difference is numerically not significant within this context. It is acknowledged that the decision to use these units is a simplification, and does not address everyone's needs. (NRC = Nuclear Regulatory Commission; EPA = Environmental Protection Agency; DHS = Department of Homeland Security) Disclaimer: Neither the United States Government nor any agency thereof, nor any of their employees, makes any warranty, express or implied, or

Whole body, acute: G-I destruction; lung damage; cognitive dysfunction (death certain in 5 to 12 days)\*

**Cancer Radiotherapy**  
total doses to **tumor**

acute exposure = all at once; chronic = hours, days, years

Whole body, acute: cerebral/vascular breakdown (death in 0-5 days)\*

Whole body, acute: marked G-I and bone marrow damage (death probable in 1-2 wks)\*

**\*Note:** Whole body acute prognoses assume no medical intervention (G-I = gastrointestinal)

Charged particle event (solar flare) dose on moon, no shielding

Estimated dose for 3-yr Mars mission (current shielding)

Total Body Irradiation (TBI) Therapy

Whole body, acute: circulating blood cell death; moderate G-I damage (death probable 2-3 wks)\*

**Acute Radiation Syndromes**

Human LD<sub>50</sub> range acute exposure with medical intervention

**Cancer Epidemiology**

**DOE Low Dose Program**

Medical Diagnostics (A-O) see chart >>

**Regulations & Guidelines**

**Medical Diagnostics mGy**  
(Estimated maximum organ dose)

**X-ray films**

A - Chest (PA & Lat)	0.14
B - Dental Panoramic	0.7
C - Lumbar-Sacral Spine	2 - 3
D - Mammogram	2 - 4

**Radiotracer Imaging**

E - Heart Stress (Tc-99m)	6 - 12
F - Bone (Tc-99m)	4 - 15
G - Dual Isotope Stress Test	40 - 45
H - PET: F-18 FDG (bladder)	55 - 80

**CT Scans (X-ray)**  
(multiple scan average dose)

I - Chest CT	20 - 30
J - Head CT	30 - 50
K - Abdominal CT	22 - 60
L - Full Body CT	50 - 100

**Fluoroscopy/Procedures**

M - Barium Contrast G.I.	10 - 22
N - Cardiac Catheterization	12 - 40
O - TIPS Procedure	400 - 1400

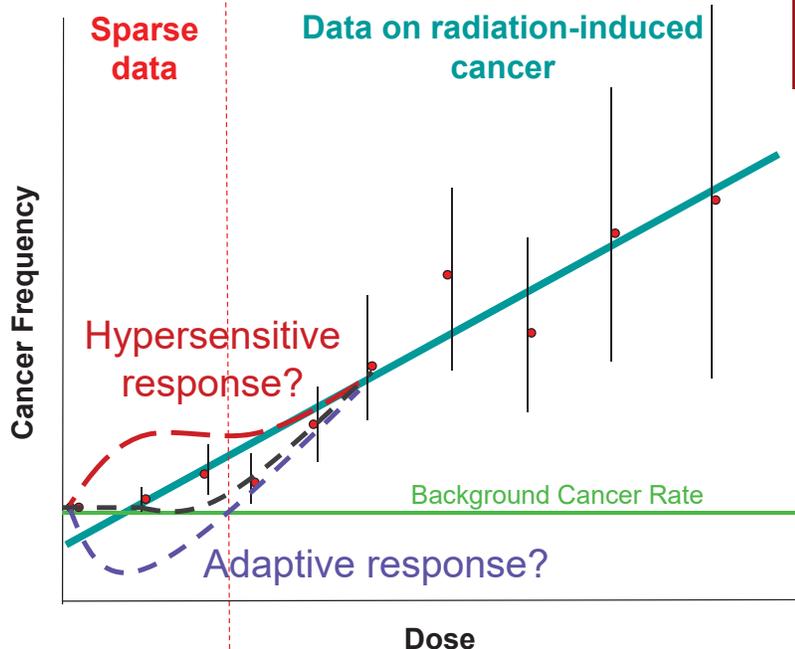
**LD<sub>50</sub> = Lethal Dose to 50%**  
(whole body dose that results in lethality to 50% of exposed individuals in 30-60 days)

**Dose Equivalent: 1 Sievert = 100 rem = (absorbed dose x radiation quality)**  
**Absorbed Dose: 1 Gray = 100 rad**  
**1 Sv ≈ 1 Gy for x- and gamma-rays**  
(\* ≈ stands for "approximately equal to")

Chart compiled by NF Metting, Office of Science, DOE/BER, "Orders of Magnitude" revised June 2010 <http://www.lowdose.energy.gov/>

Source: Office of Biological and Environmental Research (BER), Office of Science, U.S. Department of Energy

## Linear Non-Threshold Radiation Dose Response Model

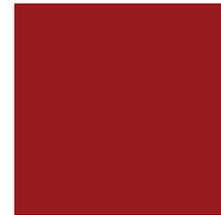


# Large-Scale Animal Studies



## Why Do Animal Studies?

- Human data can't answer everything....too many confounding factors especially for low dose rate studies.
- To determine risk: examine cell studies, examine animal effects, examine population effects that have occurred—and then look for consistency in the responses.
- Can expose animals to control conditions and doses that cannot be done with humans
- Using multiple species can often help in extrapolating to humans.



## Low dose radiation effects research world-wide: USA NURA: The Northwestern University Radiation Animal Archive



Northwestern University is creating a collection of data and tissue samples from materials made at different US National Laboratories during animal irradiation studies done between 1950's and 1990's .

Animal irradiation studies during that era were designed to test different

Qualities of radiation

Doses of radiation

Dose rates

Species comparisons

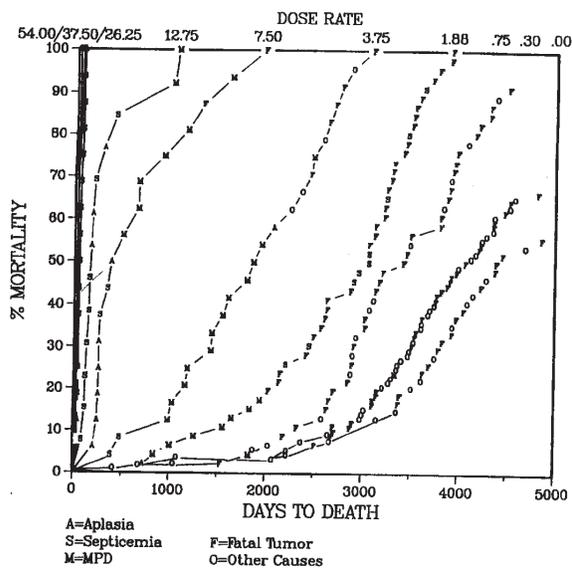
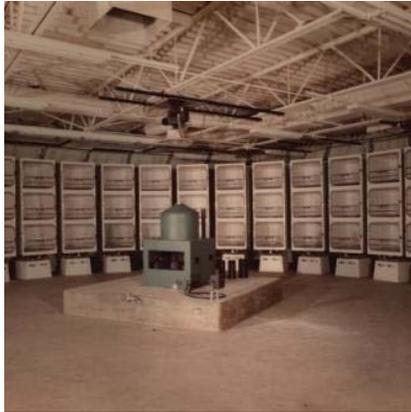
Different endpoints (e.g. lifetime studies, mutagenesis...)

## Dog Studies



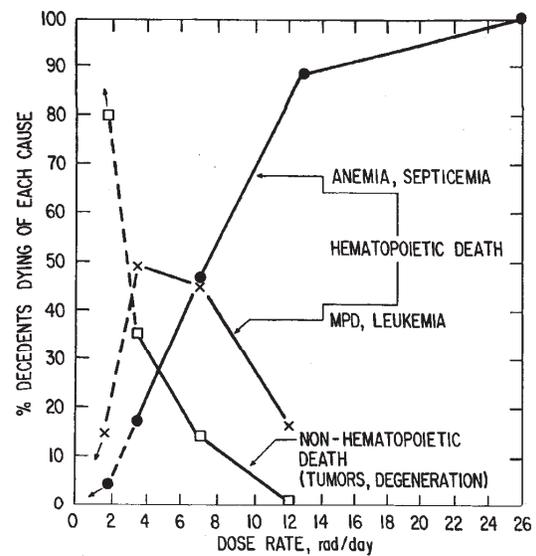
- ITRI—Lovelace—inhalation studies
- Univ. California Davis, Univ. Utah, PNNL—internal emitters
- Argonne National Laboratory—external beam studies
- 7,000+ dogs per site
- Life-time studies
- Early toxicities, cancer, life-shortening

# ANL: external beam studies



**Figure 2.** Relationship between dose rate, time to death and causes of death in adult beagles continuously irradiated ( $22 \text{ h day}^{-1}$ ) at several dose rates (rads  $\text{day}^{-1}$ ; average absorbed dose).

Fritz T. (2002) BJR Supplement 26, 103-111.

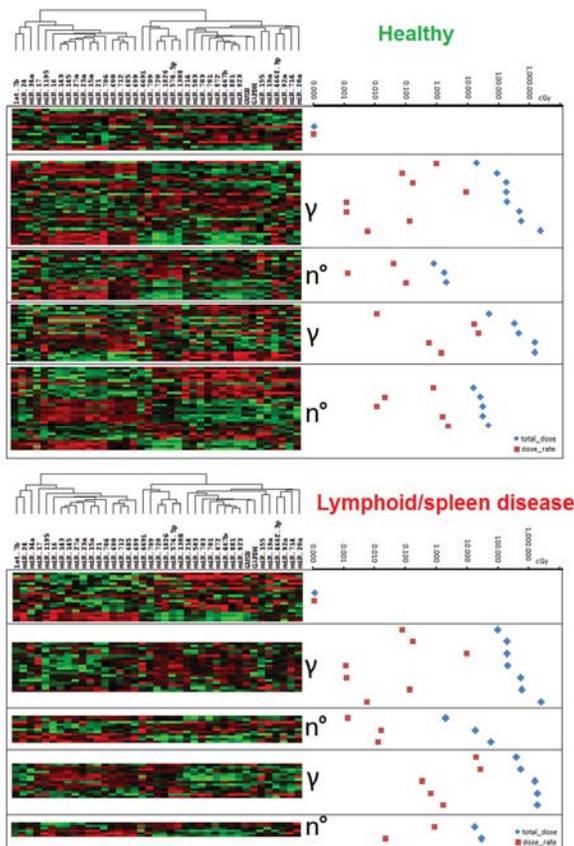


**Figure 1.** Relationship between causes of death and daily dose rate (average absorbed dose) in adult beagles exposed continuously ( $22 \text{ h day}^{-1}$ ) to  $^{60}\text{Co}$   $\gamma$ -irradiation.

Fritz T. (2002) BJR Supplement 26, 103-111.

# Mouse Studies

- Argonne National Laboratory---external beam studies (gamma and neutron)
- Oak Ridge National Laboratory---external beam studies (X-rays)
- Life-time studies
- Early toxicities, cancer, life-shortening
- Hundreds of thousands of animals!

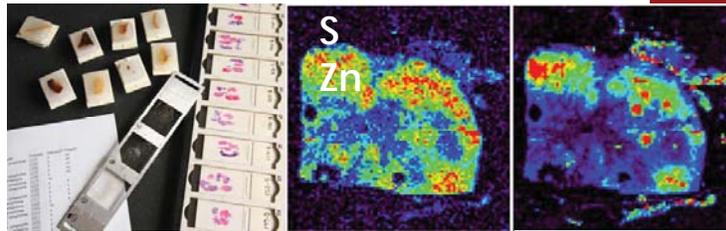


## miR analysis on 200 archival samples

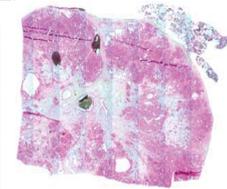
Archival tissues from healthy mouse spleens and spleens of mice with spleen cancer and/or lymphomas were sectioned and analyzed with custom miRNA array with 47 elements.

Heat map of miR expression pattern in spleen tissues of irradiated and control mice in animals that did or did not develop lymphoid or spleen diseases. Each row represents a single animal. Red fields in the heat map indicate high expression levels, green fields low expression. miR names are labeled above the heat map. Quality of radiation "radiation category" is indicated by signs γ = gamma rays and n° = neutrons for groups of samples encompassed by a rectangle. Variations between doses (blue diamonds) and dose rates (red rectangles) within a "radiation category" are indicated on the right.

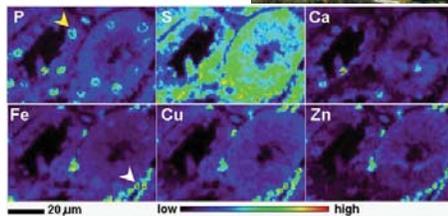
# Use of X-ray Fluorescence to Study Elementalomics of Archival Tissues



X-ray fluorescence Imaging at the APS synchrotron: Study of archival tissues from historic DOE and SUBI tissue archives



ANL: Prostate hyperplasia in beagle dog ID 2752 [Dose rate 3.8 cGy/day (22 hrs/7 days), from 412 days until total dose 15 Gy. Death at 14+ years (5245 days).



SUBI: Tritium in drinking water study. Mouse spleen showing normal overall and elemental morphology.

Paunesku T, Wanzer MB, Kirillova EN, Muksinova KN, Revina VS, Lyubchansky ER, Grosche B, Birschwilks M, Vogt S, Finney L, Woloschak GE. X-ray fluorescence microscopy for investigation of archival tissues. *PLoS One* 2013; 8(12): e82117.

# Use of Animal Archives – Evaluation of DDREF

# Risk

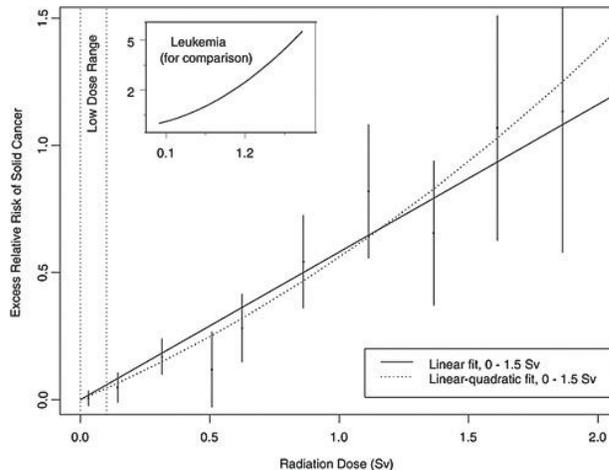


FIGURE 13-1 Excess relative risks of solid cancer for Japanese atomic bomb survivors. The insert shows the fit of a linear-quadratic model for leukemia, to illustrate the greater degree of curvature observed for that cancer.

BEIR VII 2006 pg 318

## Risk Estimates

- ICRP 5.7% detriment/Sv
- BEIR 3-12% fatal cancer/Sv
- NCRP estimates that in 2006 the U.S. population was exposed to ~1.9 million person-Sv

BEIR VII 2006 pg 280

Wrixon 2008

NCRP 160 2009

# Dose and Dose Rate Effectiveness Factor (DDREF)



## Definition

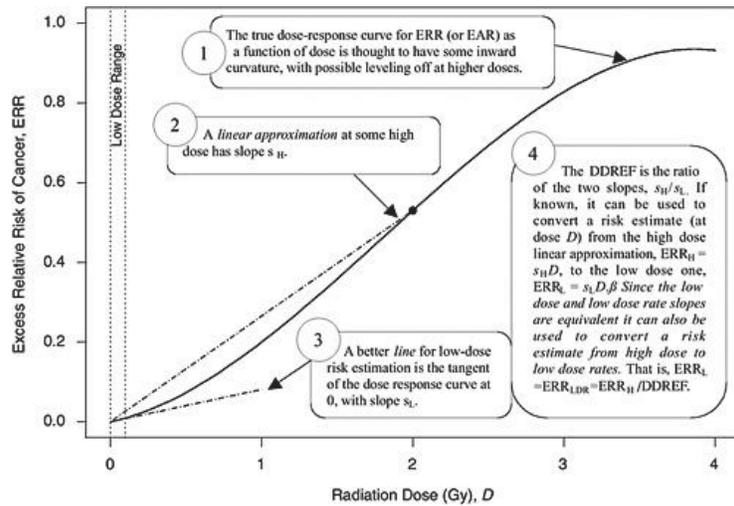
The risk observed from acute exposures is divided by DDREF in order to determine the risk of protracted exposure.

## Example

If a 1 Gy acute exposure increases cancer risk by 10% and DDREF is 2, then a 1 Gy exposure spread over a year will increase cancer risk by 5%.

- Sources of Information for DDREF Estimate
- LSS Cohort (A-bomb survivors data)
- Animal studies

# Dose and Dose Rate Effectiveness Factor (DDREF)



## ERR

- $\alpha * \text{Dose} + \beta * \text{Dose}^2$

## DDREF

- acute / protracted  $(\alpha * D + \beta * D^2) / (\alpha * D) = 1 + \beta / \alpha * \text{Dose}$

## LSS DDREF

(at 1 Gy)

- Estimated to be 1.5 (1.1 - 2.3) by the BEIR VII committee.

- FIGURE 10-1 A hypothetical dose-response curve with a linear approximation for low doses (*i.e.*, the tangent of the curve at dose zero) and a linear approximation based on risk at one particular high dose (*i.e.*, the line that passes through the origin and the true dose-response curve at the high dose), when the high dose is taken to be 2 Gy. The DDREF at this high dose is the larger slope divided by the smaller slope. Beir VII Phase II Figure 10-4

# LSS cohort



FIGURE 10.7 Illustrating the pattern of radiation-associated deaths in the life span study in the A-bomb survivors. Leukemia appeared first, reaching a peak by 5 to 7 years after irradiation, before falling off later. Solid cancers did not appear in excess for several years, but have continued to increase ever since. By about 1990, it was evident that there is also an excess of noncancer deaths, especially stroke and heart disease. (Courtesy of Dr. Mabuchi)

- The atomic bomb survivors of Hiroshima and Nagasaki have been closely tracked by the Life Span Study (LSS).

Dose, Gy	Subjects	Mean Dist, m	Cases	Excess
No in city	25,427	—	3,994	0
<0.005	35,545	3,969	5,603	3
0.005–	27,789	2,114	4,406	81
0.1–	5,527	1,608	968	75
0.2–	5,935	1,430	1,144	179
0.5–	3,173	1,260	688	206
1–	1,647	1,118	460	196
2–4	564	934	185	111
<b>Total</b>	<b>105,427</b>	<b>—</b>	<b>17,448</b>	<b>853</b>

Abbreviations: dist, distance; m, meter.

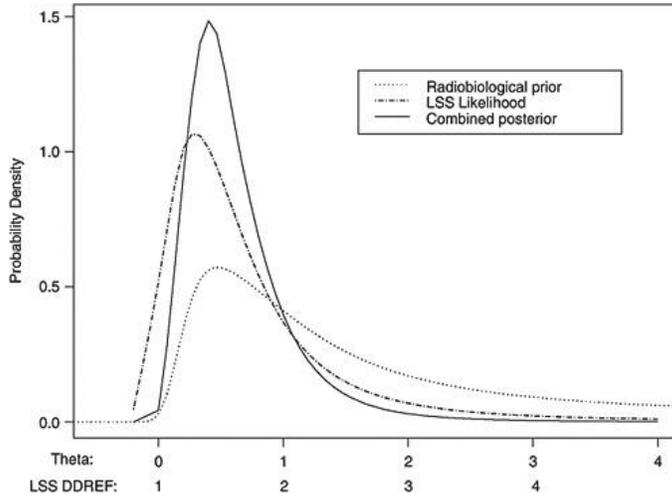
Source: Preston DL, Ron E, Tokuoka S, et al. Solid cancer incidence in atomic bomb survivors: 1958–1998. *Radiat Res.* 2007;168:1–164.

- LSS survivors suffered excess cases of leukemia, solid cancer, and heart disease.

- Most doses were small (<100 mSv), but high doses (>100 mSv) account for most of the negative health effects.

Hall 2012 figure 10.7 and table 10.1

# Current DDREF Estimate is Based on LSS and Animal Data



## Likelihood

- The relative likelihood of DDREF was estimated by fitting linear quadratic models of various curvatures to LSS and animal data.
- **Animal data suggests a higher DDREF than LSS data.**
- Results were combined by Bayesian update to form the final estimate.

## LSS DDREF

- $1 + \beta/\alpha = 1 + \theta$

**Radiobiological prior = ORNL Animal Data**

BEIR VII Part II, Figure 10-3 FIGURE 10-3 Results of a Bayesian statistical analysis of dose-response curvature and associated LSS DDREF values. The probability density labeled "radiobiological prior" expresses the belief about curvature deduced from animal data, as detailed in Annex 11B. Regions of high density correspond to more believable values of curvature. The LSS likelihood is the likelihood function of curvature  $\theta$  from the data displayed in Figure 10-2. The "combined" density is the Bayesian posterior obtained by updating the radiobiological density to account for information from the LSS data. The scale below the plot shows the implied values of LSS DDREFs corresponding to the  $\theta$  scale.

# Apparent Question: Consistency of Cancer Incidence in ORNL Data

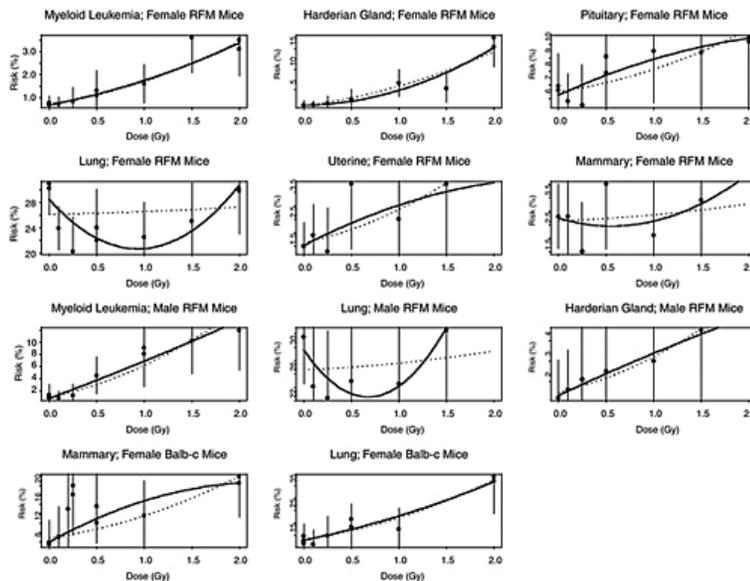


FIGURE 10B-2 Estimated risk of cancer versus radiation dose from various mouse experiments. SOURCE: Data from A.A. Edwards (1992) for cancer site, mouse strain, and sex combinations. Vertical bars extend two standard errors above and below each estimate. Solid curves are estimated LQ models based on each condition individually. Dotted curves are the best-fitting LQ models when curvature is constrained to be the same for all 11 conditions.

# ORNL Data Used for DDREF Estimate is Limited

TABLE I  
Experiment I—Radiation Doses, Sample Sizes, and Mean Ages at Death of RFM Mice Exposed to  $\gamma$  Rays at 45 rad/min

Strain and sex	Dose (rad)	No. of mice exposed	No. lost to follow-up*	Mean age at death (days $\pm$ SE)	Life shortening (days $\pm$ SE)
RFM $\varphi$ $\varphi$	0 <sup>b</sup>	4014	457	635.2 $\pm$ 2.88	—
	10	2827	43	631.8 $\pm$ 3.11	2.9 $\pm$ 4.24
	25	965	7	610.6 $\pm$ 5.29	24.1 $\pm$ 6.02
	50	1143	34	551.3 $\pm$ 5.21	83.4 $\pm$ 5.95
	75	246	1	535.2 $\pm$ 11.19	99.5 $\pm$ 11.55
	100	1100	16	536.6 $\pm$ 5.34	98.1 $\pm$ 6.07
	150	1043	15	485.4 $\pm$ 5.77	149.3 $\pm$ 6.45
	200	333	2	472.7 $\pm$ 9.58	162.0 $\pm$ 10.00
	300	4133	517	417.1 $\pm$ 2.67	218.1 $\pm$ 3.93
	400	396	1	393.2 $\pm$ 7.28	241.5 $\pm$ 7.83

TABLE II  
Experiment II—Radiation Doses, Sample Sizes, and Mean Ages at Death of RFM and BALB/c Female Mice Exposed to  $\gamma$  Rays at 40 rad/min or 0.0069 rad/min

Strain and sex	Dose rate (rad/min)	Dose (rad)	No. of mice exposed	No. lost to follow-up*	Mean age at death (days $\pm$ SE)	Life shortening (days $\pm$ SE)
RFM $\varphi$ $\varphi$	40	0 <sup>b</sup>	749	2	641.4 $\pm$ 5.96	—
		50	775	17	573.9 $\pm$ 5.97	67.5 $\pm$ 8.44
		200	766	2	480.5 $\pm$ 6.45	160.9 $\pm$ 8.78
	0.0069 <sup>a</sup>	50	1468	11	614.7 $\pm$ 4.15	26.7 $\pm$ 7.26
		100	1531	9	598.7 $\pm$ 4.36	42.7 $\pm$ 7.38
		200	1526	13	564.1 $\pm$ 4.29	77.3 $\pm$ 7.34
		400	866	2	499.4 $\pm$ 5.86	142.0 $\pm$ 8.36

Storer, 1979 ([link](#))

A limited pool of animals was used for “animal contribution” to DDREF estimate:

## Oak Ridge Lifespan Data

Acute

- RFM Mice at ORNL were exposed to gamma rays at 0.45 Gy/min (Table 1)

Protracted

- Others were exposed to 0.084 Gy/day over several days (Table II).

Analyzed

- Red boxes indicate the groups used to estimate DDREF.

# Other archived data

European Radiobiology Archives (ERA) overview on the information that is available in the archives					
	Labs	Studies	Groups	Animals total	Animals with data
ERA	21	149	4,623	232,587	93,445
NRA	11	143	1,861	190,471	115,801
JRA	14	39	367	29,537	3,396
Sum	46	331	6,851	452,595	212,642

European Radiobiology Archives ([link](#))

$\gamma|n^0$  Janus Tissue Archive

Home Documentation Sample Requests Data Treatments Help

Janus Radiobiology Archives ([link](#))

Oak Ridge studies are only a subset of all historic studies

- Hundreds of animal radiobiology studies have been conducted.
- Data from many of these studies is available online from the European Radiobiology and Janus Archives.

## Radiation health risk estimates



Contemporary US citizens (and people world-wide) are exposed to non-therapeutic ionizing irradiation accumulating several hundreds of milliSieverts per person over the entire lifetime, generally with no more than 20 mSv per exposure.

However, the health risks of low dose and protracted exposures are still estimated based on the health consequences observed following acute, high dose exposures and a model of the relationship between dose, risk, and protraction.

The BEIR VII report and most contemporary radiation protection guidelines use the linear-quadratic model that was originally developed to describe effects of high dose rate therapeutic radiation exposures.

## DDREF estimate per BEIR VII



Seventh report of the Biological Effects of Ionizing Radiation (BEIR) committee estimates a 3-12% absolute increase in the risk of fatal cancer development per Sievert of exposure (National Research Council, 2006).

To reach this conclusion the BEIR VII committee used as data:

- atomic bomb survivor data to evaluate dose and dose rate effectiveness factor for the life span study of atomic bomb survivors;
- dose-response data from a selection of large mouse studies carried out at the Oak Ridge National Laboratory in the late 1970s involving whole body gamma exposures from a cesium-137 source

We decided to re-evaluate methodology (use of LQ model) and completeness of the animal datasets (Haley et al., 2015).

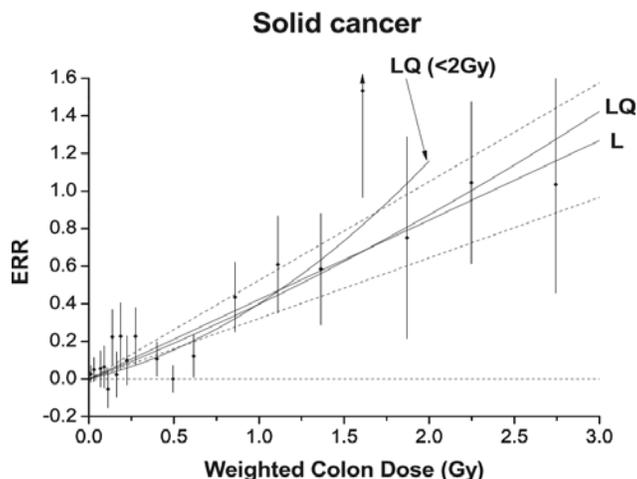
## DDREF estimate by BEIR VII - remaining questions



- Evaluation of DDREF varies based on dose range “limits” – is LQ model the best one to use?
- LSS data may need to be re-evaluated based on new dosimetry
- Animal data were not fully utilized! The European Radiobiology Archives (ERA) and Janus tissues archives contain 16 animal mortality studies that fit BEIR VII’s inclusion criteria, 15 of which were not included in the original BEIR VII analysis.

Could a better estimate of DDREF be obtained by simply including more animal data in the analysis?

## Excess relative risk of solid cancers (DDREF proxy) L and LQ fits and different dose cutoffs in atomic bomb survivors



(Ozasa et al Radiat Res. 2012;177: 229–43. )

Estimated excess relative risk (ERR - equal to relative risk minus one) of solid cancer development vs. mean total colon dose for atomic bomb survivors. Black points represent central estimates for each exposure group. Vertical bars represent 95% confidence intervals. Linear (L) and linear-quadratic (LQ) dose response models were both fit to the data and appear as labeled. A linear-quadratic model fit to doses below 2 Gy is shown as well (LQ (<2Gy)).

# Re-evaluation of DDREF with animal archives

Total doses up to 1.5 Gy



## World-wide irradiated animal data archives

- (Western) European archives – virtual collection at <https://era.bfs.de>
- Japan – very little on line so far
- Russia – some materials digitized but not online
- US – most data and materials collected into Northwestern University Radiation Tissue Archives (NURA)
  - (there are paraffin embedded dog, mouse and rat tissue samples from ANL (JANUS experiments) as well as ITRI, PNNL and UCDavies)
  - two websites with ANL mouse, ANL dog and (still in work) Lovelace dog data:  
[http://janus.northwestern.edu/dog\\_tissues/introduction.php](http://janus.northwestern.edu/dog_tissues/introduction.php)  
<http://janus.northwestern.edu/janus2/index.php>



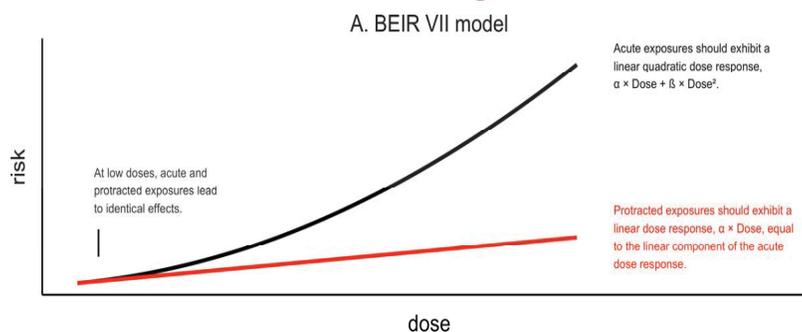
# DDREF re-estimate using wider set of animal mortality data



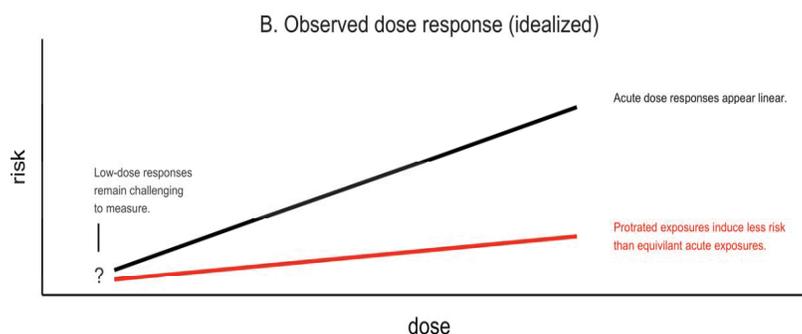
- The European Radiobiology Archives (ERA) and Janus tissues archives contain 16 animal mortality studies that fit BEIR VII's inclusion criteria, 15 of which were not included in the original BEIR VII analysis.
- These data were curated and developed into a dataset suitable for analysis and analyzed following the approach used by BEIR VII committee.
- The goal of this effort was to re-evaluate the precision of BEIR VII's estimate and also test the validity of the dose-response model this committee used.

Haley et al., 2015

# Replicating DDREF evaluation using more of the existing animal data



Each panel shows dose (x-axis) vs. risk (y-axis) where risk represents the excess risk of carcinogenesis or organism mortality.



Black lines represent the response to acute exposures. Red lines represent the response to protracted exposures.

Haley et al, 2015

## Replicating DDREF evaluation using more of the existing animal data: included data



Studies	Treatments	Animals	Criteria
302	6,810	452,595	All animal data from ERA and Janus archives
124	2,611	205,758	Individual-level animal data available
35	827	116,542	External radiation exposures
35	457	76,096	Low-LET, whole body exposures
34	230	45,730	Total dose equal to or below 1.5 Sv
32	175	43,043	No other treatments (e.g. no chemical exposures)
26	119	34,439	Digitized data on treatment and lifespan confirmed by primary literature
16	91	28,289 <sup>a</sup>	At least three distinct treatment groups per stratum so that a linear-quadratic model could be fitted
9	71	20,325 <sup>b</sup>	At least three distinct treatment groups after stratifying by study ID

Inclusion criteria based on the BEIR VII analysis were used as well as additional criteria (e.g. only individual animal data were used for analysis); eventually the complete animal dataset used covers 20,325 mice in 71 treatment groups.

Haley et al 2015

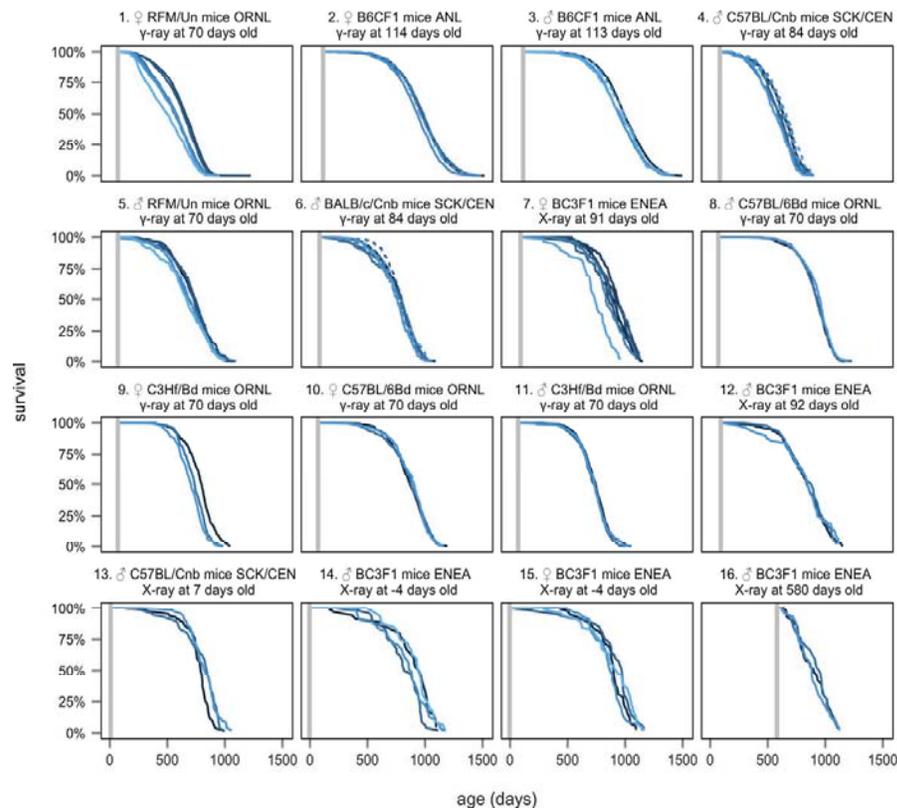
## Replicating DDREF evaluation using more of the existing animal data: excluded data



Treatment group ERA identifier	Reason for exclusion
1003-21-6	This treatment group was abandoned. Cause of death is listed as 'abandon' or 'remove to another experiment'.
11-2-79 11-2-80 11-2-81	Some mice in these treatment groups had impossibly long lifespans, e.g. 6993. This seems to be a coding error in the data. No access to the correct data was available.
1007-3-8 1007-3-16	Mean lifespans differed from those reported in Table 1 of [45] by more than 1 standard deviation. Moreover, there are fewer mice in the ERA dataset than listed by Ullrich and Storer.
3-4 (all treatments)	These groups are identical to those listed in study 3-2.
11-1 (all treatments)	No external data source was found to confirm the treatments and lifespans in this study.
11-2 (all treatments)	No external data source was found to confirm the treatments and lifespans in this study.
3-2 (all treatments)	No external data source was found to confirm the treatments and lifespans in this study. The only source found that details this study [47] was limited to neutron exposures.
1003-xx	No external data source was found to confirm the treatments and lifespans in this study.
9-8	No external data source was found to confirm the treatments and lifespans in this study.

Haley et al 2015

## Survival vs. dose in animal datasets included



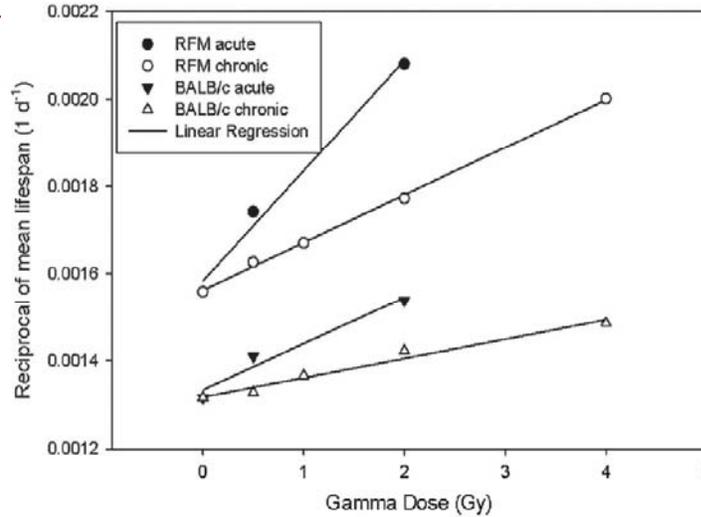
Note that the uppermost leftmost stratum contains data used in the original BEIR VII analysis. This is only the acute exposure data from that analysis, as the data from protracted exposures was not available for individual mice. (Haley et al 2015)

## Replicating DDREF evaluation using more of the existing animal data

$$\begin{aligned}
 DDREF &= \frac{\text{acute risk}}{\text{protracted risk}} \\
 &= \frac{\alpha \cdot \text{dose} + \beta \cdot \text{dose}^2}{\alpha \cdot \text{dose}} \\
 &= 1 + \frac{\beta}{\alpha} \cdot \text{dose}
 \end{aligned}$$

By definition, DDREF is a function of the ratio between quadratic and linear coefficients,  $\beta/\alpha$ , and dose. As formulated, it can be derived from direct comparisons of protracted and acute exposures. However, because acute exposure risk depends on linear and quadratic terms both, DDREF can also be derived using the linear quadratic model from acute exposure data alone. This is done by estimating  $\alpha$  and  $\beta$  terms based on a quadratic fit to the data and then by extrapolating the risk of protracted exposures from the  $\alpha$  term. The more curved the graph of risk from an acute dose is, the higher the DDREF estimate will be. Notably most of the data that BEIR VII used to estimate DDREF came only from acute exposures.

# OTHER INVESTIGATORS: re-evaluations of DDREF estimates from BEIR VII animal dataset

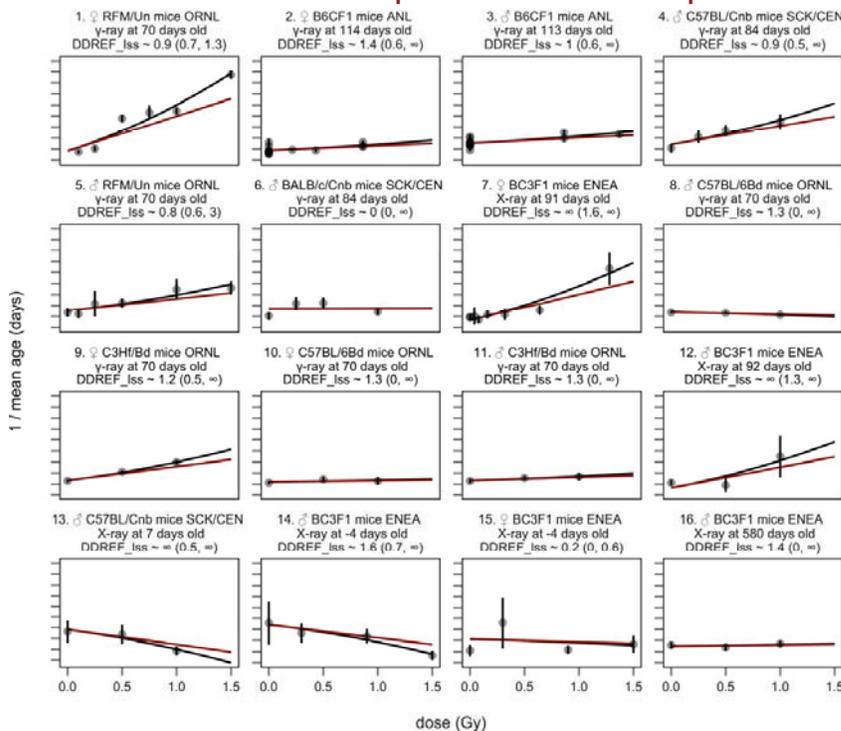


**Fig. 4.** Linear fits to the reciprocal mean lifetimes of the gamma exposed RFM and BALB/c female mice. Both acute and chronic exposures are shown.

...still – limited archive use and no protracted data on individual mice...

Hoel, Health Physics 2015 108(3)

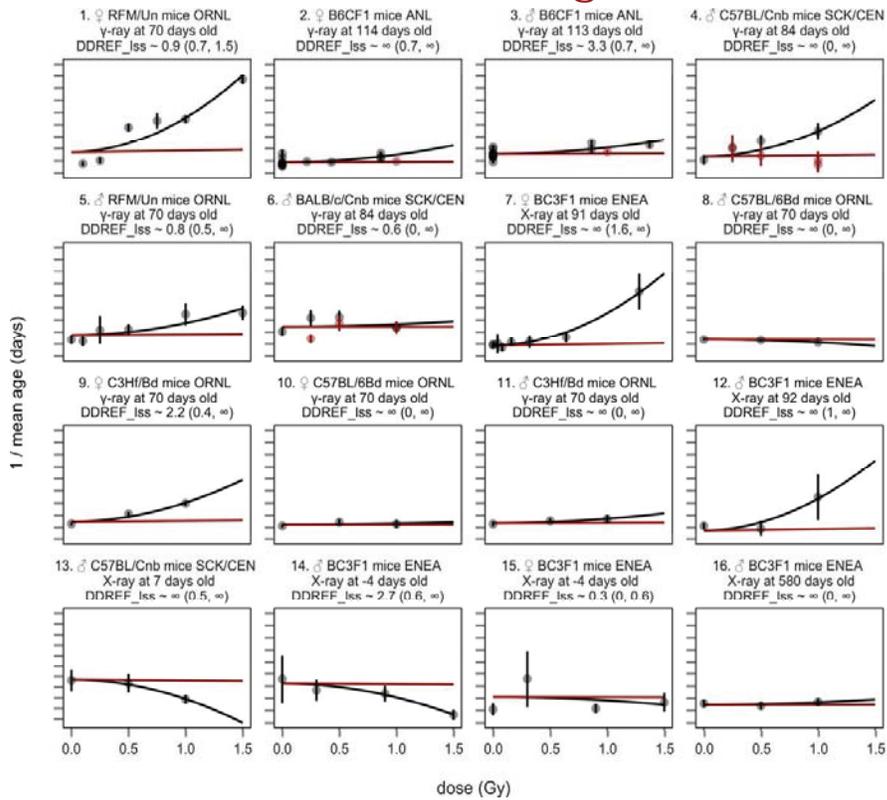
# Re-estimated DDREF using the BEIR VII method acute exposures extrapolation



— acute  
— protracted

BEIR VII model applied to acute exposures only— protracted were estimated based on acute

# Re-estimated DDREF using the BEIR VII method

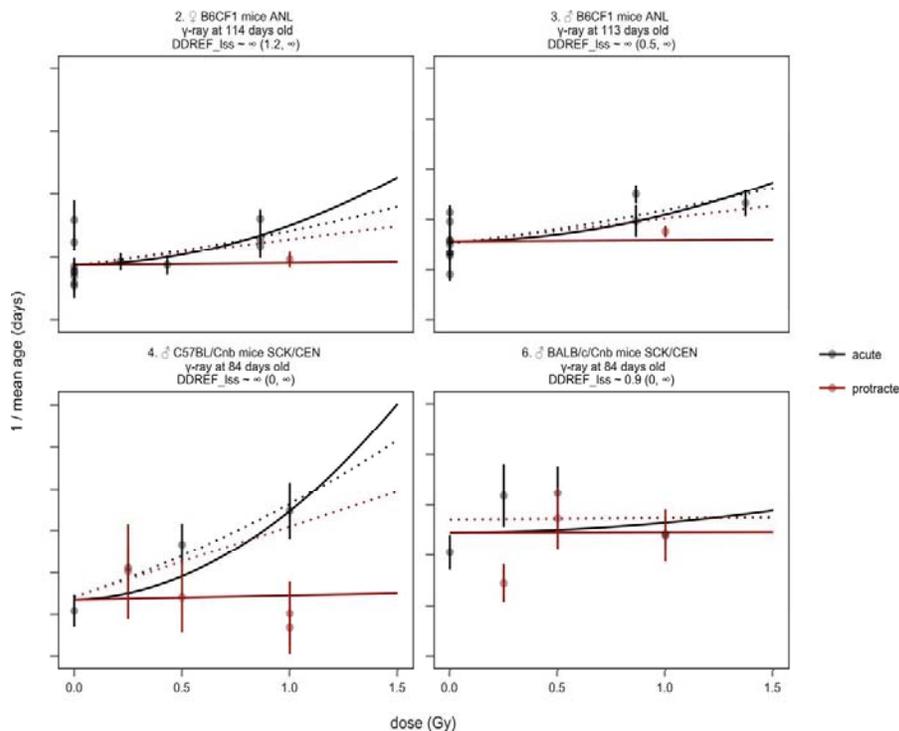


DDREF estimates (ranging from 0 to infinity) from each stratum in isolation are listed in each facet label with 95% confidence intervals in parentheses.

(Fitting all curves was done for constant beta/alpha values.)

(Haley et al 2015)

# BEIR VII model applied only to protracted-acute exposure comparisons



The data are restricted to strata that received both acute and protracted exposures. This is similar to BEIR VII's original animal mortality analysis however these animal studies were not used by BEIR VII.

(Haley et al., 2015)

## DDREF evaluation based on additional animal data: BEIR VII model alone and with several possible corrections



Model	All data	Acute data	Comparison data
<i>BEIR VII model</i>	$\infty$ (2.9, $\infty$ )	1.3 (0.9, 3.0)	$\infty$ (4.8, $\infty$ )
<i>Hormetic correction</i>	$\infty$ (2.3, $\infty$ )	1.2 (0.9, 3.4)	$\infty$ (4.8, $\infty$ )
<i>Heterogeneity correction</i>	1.3 (0.9, 5.5)	0.9 (0.8, 1.3)	$\infty$ (2.0, $\infty$ )
<i>Stratification by study</i>	1.0 (0.8, 1.6)	1.0 (0.8, 1.2)	$\infty$ (2.2, $\infty$ )
<i>Survival analysis</i>	4.8 (1.5, $\infty$ )	0.9 (0.7, 1.5)	$\infty$ (2.5, $\infty$ )

Model	Central estimate	Acute atomic bomb survivor data	Acute animal carcinogenesis data	Comparison animal mortality data
<i>Original BEIR VII analysis using only original datasets</i>	1.5 (1.1, 2.3)	1.3 (0.8, 2.4)	1.4 (1.1, 2.6)	2.0 (1.3, 7.7)

DDREF estimates for a variety of models. Central estimates are shown with 95% confidence intervals in parentheses. The details of each model, named in the first column, are described in the text. Each model was applied to three different data sets to produce three distinct DDREF estimates. "All data" refers to DDREF estimates based on all of the available data. "Acute data" refers to DDREF estimates based only on the apparent curvature of acute exposure data in each stratum, excluding protracted exposure data. "Comparison data" refers to DDREF estimates based on strata that included both acute and protracted exposures, excluding strata that only included acute exposures. Haley et al., 2015

## DDREF re-estimate using wider range of animals - CONCLUSIONS



- Inclusion of greater animal mortality dataset, rather than establishing a better estimate of DDREF, showed that BEIR VII's dose response model did not fit the observed data.
- DDREF based on the curvature of acute exposure data was never significantly greater than 1, implying that protracted and low-total-dose exposures have a similar risk per Sievert as acute exposures. By contrast, estimates of DDREF based on data that directly compared acute and protracted exposures were infinitely high, implying that low dose exposures are neutral with respect to carcinogenesis or life shortening.
- The component of DDREF that pertains to protracted (but not low-total-dose) exposures, the so-called dose rate effectiveness factor (DREF) should be estimated based on direct comparisons of acute and protracted exposures.

# Re-evaluation of DREF with animal archives

Total doses up to 4 Gy

DREF evaluation based on additional animal data:

Data	DREF <sub>LSS</sub> estimate	Effect of age at exposure per 13% increase in age
Primary analysis 0 – 4 Sv	2.1 (1.7, 2.7)	0.80 (0.55, 1.01)
Sensitivity analysis 0 – 3 Sv	2.6 (1.8, 4.4)	0.78 (0.29, 1.13)
Sensitivity analysis without strata showing radiation poisoning	2.1 (1.7, 2.9)	0.80 (0.54, 1.03)
Delayed analysis: censor 6%	2.2 (1.7, 2.8)	0.82 (0.61, 1.09)
Delayed analysis: censor 13%	2.2 (1.7, 2.9)	0.97 (0.72, 1.23)
Delayed analysis: censor 26%	2.2 (1.8, 2.8)	0.97 (0.73, 1.25)

DDREF estimates for several variations on linear-linear model. Central estimates are shown with 95% confidence intervals in parentheses. The details of each variation are named in the first column.

DDREF values are centered close to 2 regardless of approach used.

Age of exposure has significant effect on DDREF – its value increases (effect of protracted exposure becomes more substantial) with age.

## DREF re-estimate using wider range of doses - CONCLUSIONS



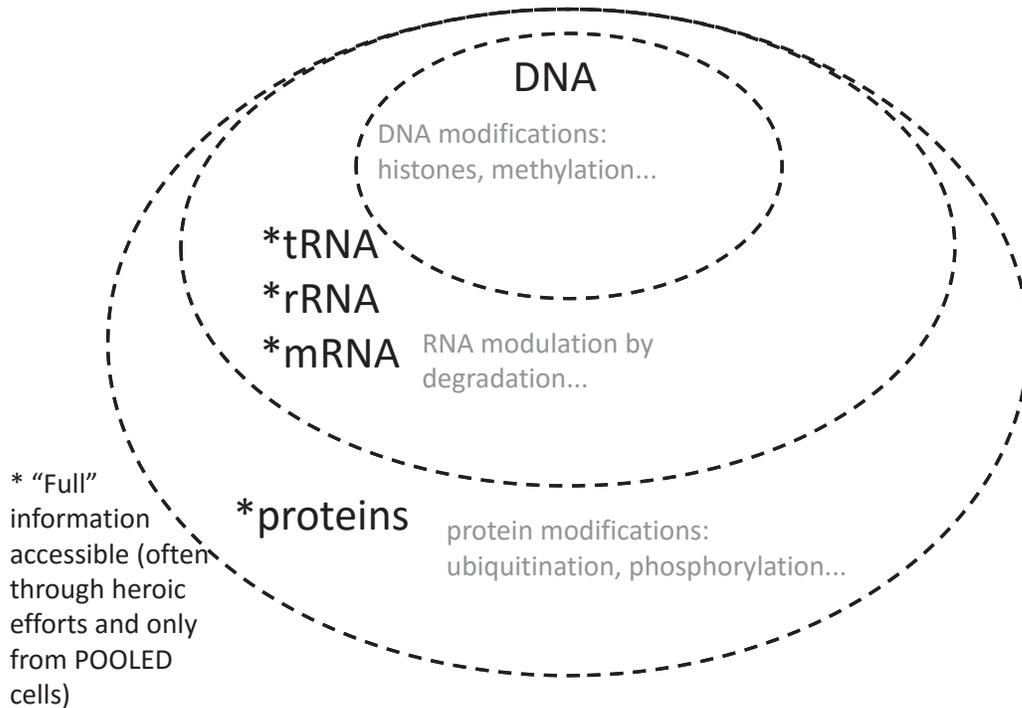
- Until recently, no effort has been made to incorporate all world-wide animal irradiation data that exist in the public domain, nor to use “best fit” approaches to evaluate these data using formalisms other than LQ. Our recent publication Haley et al., 2015 used all publically available animal irradiation archives to re-evaluate DDREF and found that a dose rate effectiveness factor – DREF calculated from all existing animal archives is still inaccurate if LQ model is used as a basis for calculation.
- We have extended this work to intra- and inter-species comparisons, and extended the range of doses under consideration to 4Gy, which matches skin dose maximum considered for human A-bomb survivor studies conducted by RERF. Evaluation of DREF was done using a “linear – linear” model (similar to Hoel 2015)
- New evaluation of DREF value is close to 2 – value also proposed by ICRP

## New Knowledge Leads to New Understanding of Biology

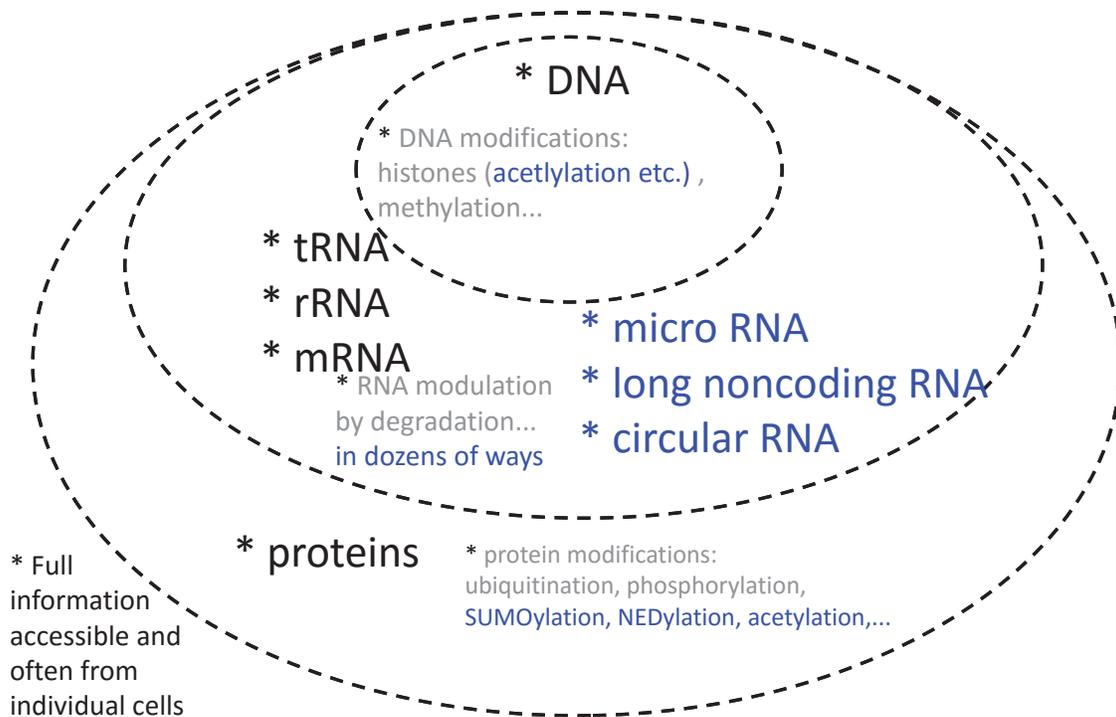


- Concepts never before considered became “standard”
  - discoveries of new molecules and new means for “intracellular” control – subtle changes are detectable and understood as things occur in unison
  - discovery of qualitatively new types of cell to cell communication as means for “intercellular” control – subtle changes ripple through the whole organism

# Key Biological Molecules 1996



# Key Biological Molecules 2016



## Conclusions and Summary

- Uncertainties about low dose and low dose rate radiation remain; these can be aided by additional animal studies
- Regulation involves combinations of cellular, animal and human studies
- Animal studies suggest that we may be over-protecting the population at low doses and low-dose rates
- International collaboration has enhanced dataset availability and conclusions that can be drawn.



Lab picnic, 2012

# 16

## RESEARCH NEEDS IN THE LOW-DOSE RADIATION FIELD

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# Research Needs in the Low-dose Radiation Field

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Presentation at the  
International Dose Effect Alliance Workshop 2016,  
EPRI, Charlotte, NC, USA  
on November 9-10, 2016

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Version 1.01

Disclaimer: Opinions expressed in this presentation are my own professional opinion,  
and do not necessarily represent those of my employer. 1

# Research Needs in the Low-dose Radiation Field

Considerable amount of data on low-dose radiation (LDR) health effects is indeed available, as it has been studied for a long time. But, there is still disagreement in the scientific community with two opposing views:

- The linear no-threshold (LNT) model
  - Endorsed by advisory bodies
  - Accepted and used by regulatory agencies.
- Radiation Hormesis

## Research Needs in the Low-dose Radiation Field

The persistence of the low-dose radiation cancer risk controversy, after so much study, is of very much concern since:

- Actions taken based on the wrong hypothesis can be very harmful, as such actions can **increase** rather than **decrease** cancer risk.

Hence *the* most important research need is to resolve the low-dose radiation cancer risk controversy.

3

## What is the effect of low-dose radiation on cancer?

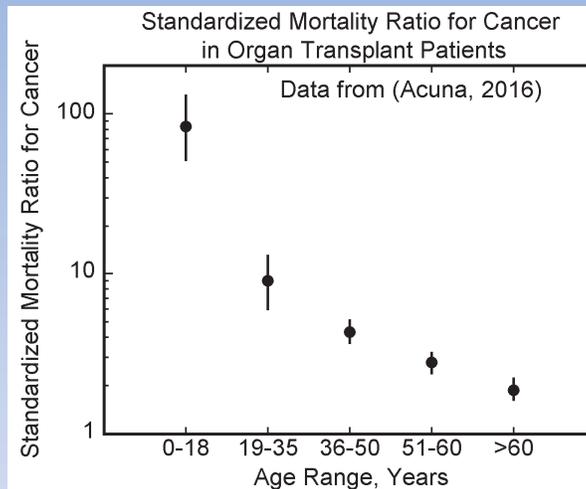
To understand this, we need to first understand what causes cancers.

The prevalent model of cancer is the somatic mutation model of cancer, and we have been fighting the war on cancer based on this model. Is this model valid? Are cancerous mutations the primary cause of cancers? No, since almost everyone has cancerous or pre-cancerous mutations (covert cancers) but lifetime risk of being diagnosed with cancer is only ~30%. ([Greaves, 2014](#)).

If mutations are not the primary cause of cancers, what is?

4

## What is the Primary Cause of Cancer?



The tremendous increase in cancers when the immune system is suppressed indicates immune suppression may be the primary cause of most cancers. Hence, an alternative model of cancer is the **Immune Suppression Model of Cancer**.

(See “Changing the Paradigm of Cancer Screening, Prevention, and Treatment”, Doss, Accepted for publication in Dose-Response, 2016)

## Evidence supporting the immune suppression model of cancer

Immune system response reduces rapidly with age ([Levin, 2012](#)) and cancer risk rises rapidly with age (e.g. [WHO](#)).

Females have stronger immune system than males ([Furman, 2014](#)) and have lower risk of cancer compared to males ([Siegel, 2015](#))

Allergy sufferers have overactive immune system and have lower risk of cancer ([Wang, 2005](#))

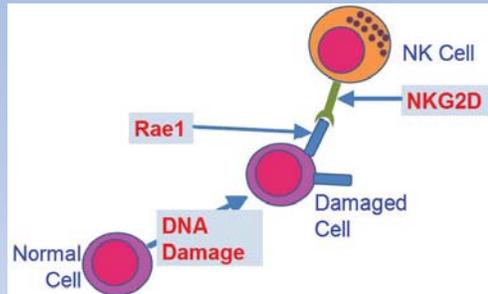
Breastfeeding enhances immune system in infants ([Turfkruyer, 2015](#)) and it reduces childhood leukemias ([Amitay, 2015](#))

Exercise ([Woods, 2009](#)) and infections ([Karbach, 2012](#)) stimulate the immune system and reduce cancers ([Orsini, 2008](#)), ([Richardson, 1999](#))

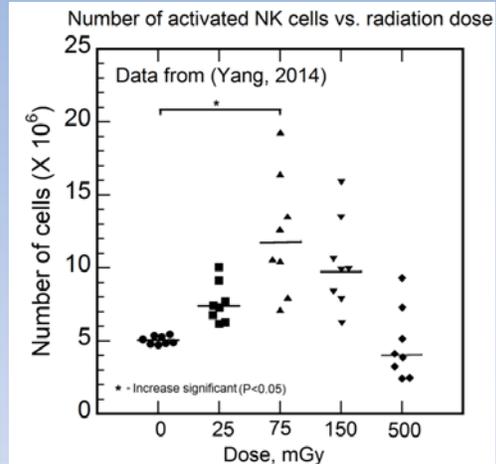
High-dose radiation ([Liu, 2003](#)), cigarettes ([Stämpfli, 2009](#)), and alcohol ([Molina, 2010](#)) suppress the immune system and they all increase cancer risk ([Ozasa, 2012](#)), ([Stämpfli, 2009](#)), ([Nelson, 2013](#))

## Effect of low-dose radiation on the immune system

The DNA Damage Response Arouses the Immune System ([Gasser and Raulet, 2006](#))



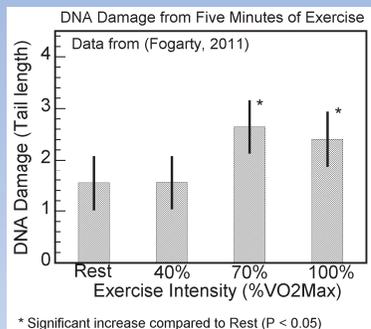
Up-regulation of Rae1 and other ligands of the NKG2D receptor. Activates NK cells.



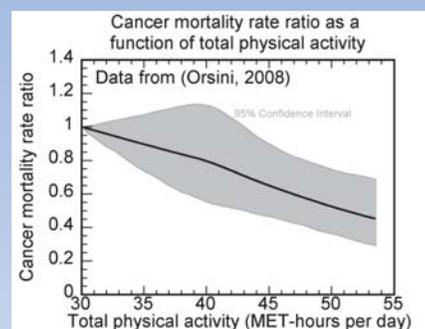
LNT model supporting publications (e.g. BEIR VII Report) ignore or dismiss the importance of the immune system in preventing cancers and the enhancement of the immune system from low-dose radiation.

The enhanced immune system response would reduce cancers. 7

## Increased DNA Damage Observed Shortly After Five Minutes of Vigorous Exercise or Low-dose Radiation Exposure



Even five minutes of vigorous exercise resulted in increased DNA damage.



Vigorous exercise reduces cancer mortality significantly. The benefit from exercise is due to the enhanced defenses.

Since vigorous exercise reduces cancers, it would be extremely unwise to not exercise based on the observed DNA damage from vigorous exercise.

**BEIR VII Report has used similar logic to raise concerns about the DNA damage from low-dose radiation and has dismissed the beneficial effects of enhanced defenses.**

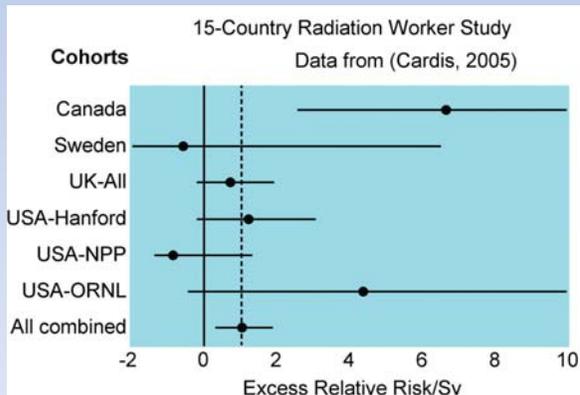
# What does the evidence say regarding the cancer risk of LDR?

9

## 15-Country Study of Radiation Workers

### Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries

E Cardis, M Vrijheid, M Blettner, E Gilbert, M Hakama, C Hill, G Howe, J Kaldor, C R Muirhead, M Schubauer-Berigan, T Yoshimura, F Bermann, G Cowper, J Fix, C Hacker, B Heinmiller, M Marshall, I Thierry-Chef, D Utterback, Y-O Ahn, E Amoros, P Ashmore, A Auvinen, J-M Bae, J Bernar Solano, A Biau, E Combalot, P Deboodt, A Diez Sacristan, M Eklof, H Engels, G Engholm, G Gulis, R Habib, K Holan, H Hyvonen, A Kerekes, J Kurtinaitis, H Malke, M Martuzzi, A Mastauskas, A Monnet, M Moser, M S Pearce, D B Richardson, F Rodriguez-Artalejo, A Rogel, H Tardy, M Telle-Lamberton, I Turai, M Usel, K Veress



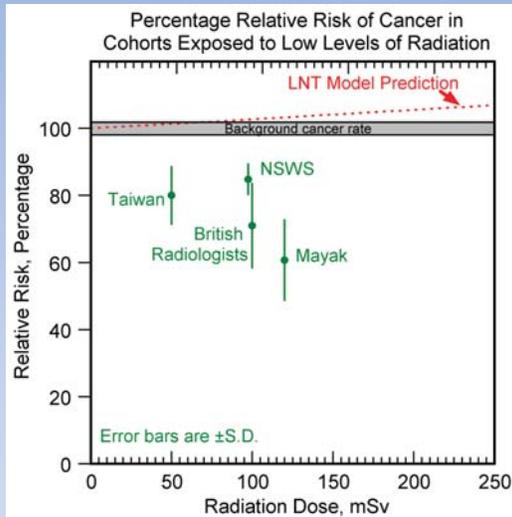
Canadian data are clearly inconsistent with most other data.

BEIR VII Report , instead of asking for a re-examination of the Canadian data, utilized these results to support the LNT model in an Addendum to the Report which was already finalized.

In 2011, [CNSC withdrew Canadian data](#) because of faults identified in them, negating the conclusion of the 15-Country Study.

10

## Effect of prolonged low-dose radiation exposures on cancer



LNT model Prediction - [BEIR VII Report \(2006\)](#)

Taiwan - Residents of radio-contaminated apartments in Taiwan ([Hwang, 2006](#))

NSWS - Radiation workers in Nuclear Shipyard Worker Study ([Sponsler, 2005](#)) This study excluded the possibility of Healthy Worker Effect since the comparison is to non-radiation workers.

British Radiologists - British Radiologists who entered service during the period 1955-1979 ([Berrington, 2001](#))

Mayak - Evacuated residents of villages near Mayak Nuclear Weapons Facility ([Kostyuchenko, 1994](#))

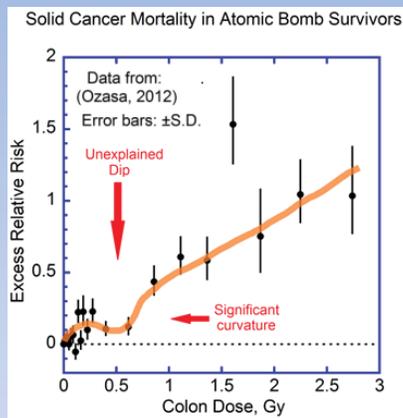
Low-dose radiation exposures have resulted in reducing cancers contradicting the LNT model prediction

BEIR VII Report ignored British Radiologists and Mayak studies which were available at the time of the report. [BEIR VIII Scoping meeting in 2014](#) ignored results from Taiwan and NSWS studies.

11

## Atomic Bomb Survivor Cancer Mortality Data

(the most important data according to BEIR VII Report & others)



Excess Relative Risk rises with dose from 0 to  $\sim$ 0.25 Gy, decreases with dose from  $\sim$ 0.25 to  $\sim$ 0.5 Gy, and then rises with dose, resulting in a significant curvature.

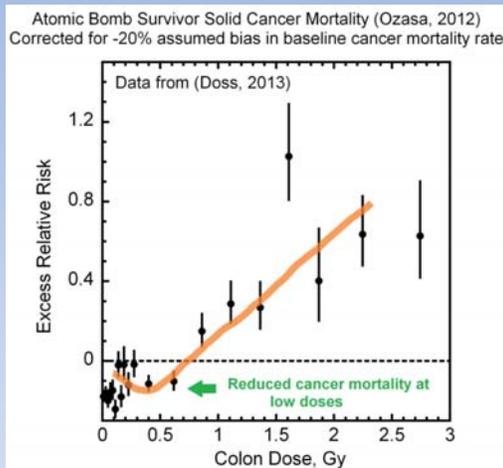
Ozasa et al. state: "The curvature over the 0-2 Gy range has become stronger over time, ....., and has become significant with longer observation"

The significant curvature in the dose-response of the atomic bomb survivor cancer mortality data is inconsistent with the LNT model.

Since Ozasa et al. utilized cancer rates of lowest dose cohorts, extrapolated to zero dose, as the baseline cancer rates in the process of extracting the Excess Relative Risks, and since low radiation doses reduce cancer risk as seen earlier, the baseline cancer rates used would have a negative bias.

12

## Atomic Bomb Survivor Data Corrected for Negative Bias in Baseline Cancer Rate

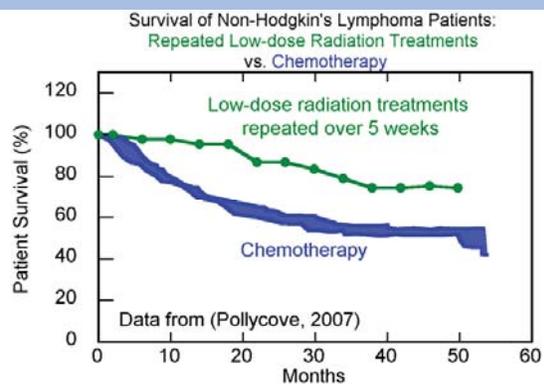
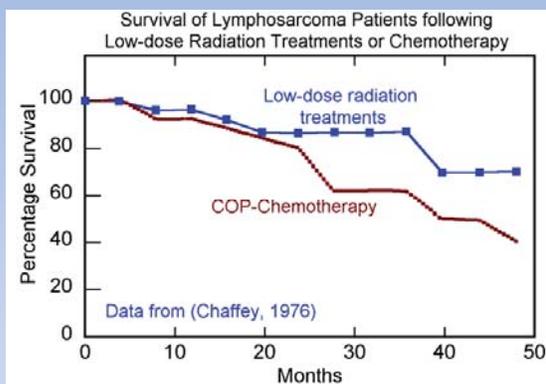


Correcting for the negative bias in the baseline cancer rate results in a J-shaped dose-response curve consistent with radiation hormesis. ([Doss, 2012](#)), ([Doss, 2013](#))

Since the publication of the ([Ozasa, 2012](#)) update, many LNT model supporters, have stopped referring to the atomic bomb survivor data when discussing low-dose radiation cancer risk, e.g. Mark Little in his opening statement in Medical Physics “Point/Counterpoint: low-dose radiation is beneficial, not harmful” ([Doss, 2013](#))

13

## Survival of Cancer Patients Treated Repeatedly with Low-Dose Radiation

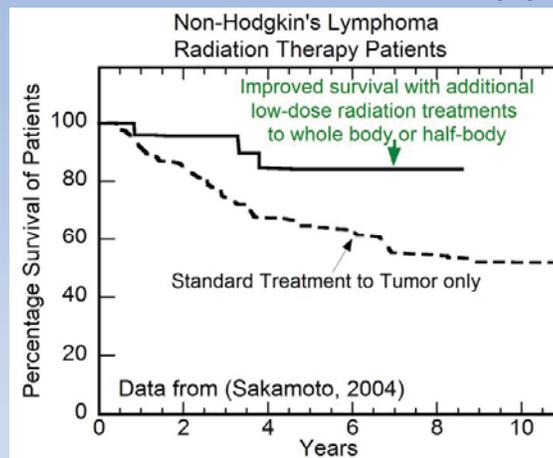


Difference in survival between these two curves is not significant.

Repeated whole-body low-dose radiation treatments (10 cGy X 15 over 5 weeks = 1.5 Gy total) had a cancer therapeutic effect, performing as well as or better than chemotherapy, contradicting the LNT model. There were very few adverse side effects from the low-dose radiation treatments (temporary suppression of blood cells).

14

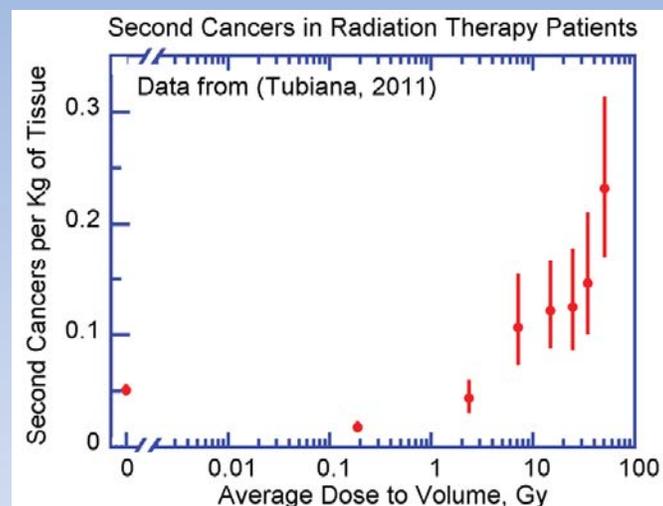
## Effect of Adjuvant Low-dose Radiation Treatments on the Survival of Radiation Therapy Patients



Interspersed low-dose radiation treatments to the whole body or half-body (10 cGy x 15 over 5 weeks = total 1.5 Gy) between the standard radiation therapy treatments to the tumor led to better survival and had a cancer therapeutic effect, contradicting the LNT model.

15

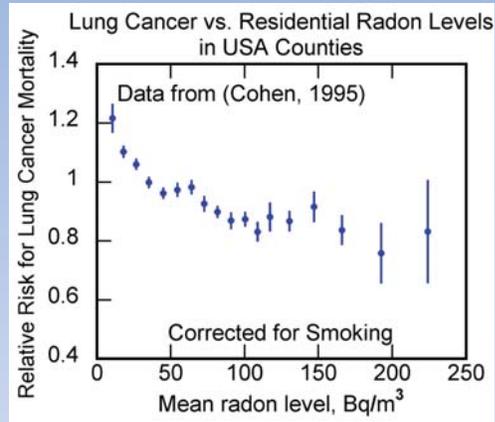
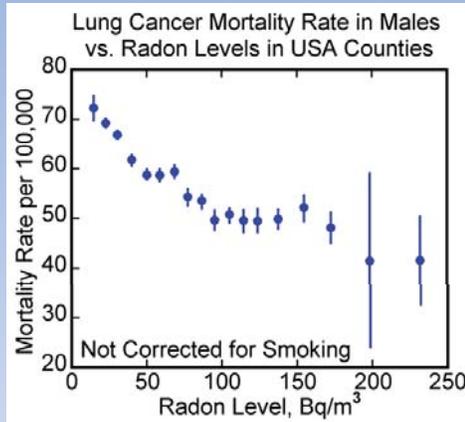
## Second Cancers per Kg of Tissue vs. Radiation Dose



Tissues having ~0.2 Gy radiation dose had reduced second cancers per kg of tissue in comparison to tissues having no radiation dose from the radiation therapy, contradicting the LNT model prediction.

16

## Residential Radon and Lung Cancer

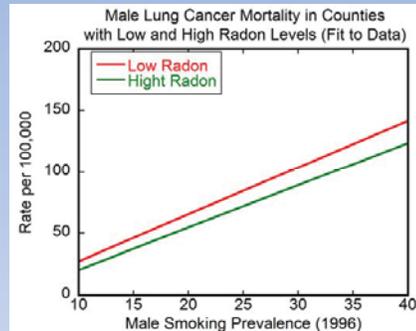
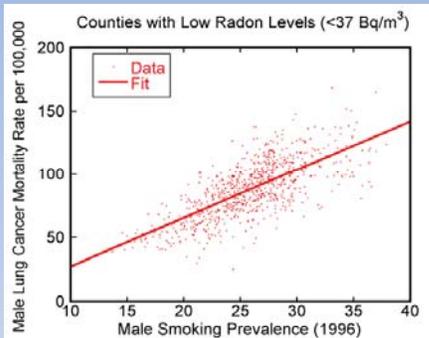


Smoking data at County level were not available. State level data were used to estimate County level data. Led to uncertainties.

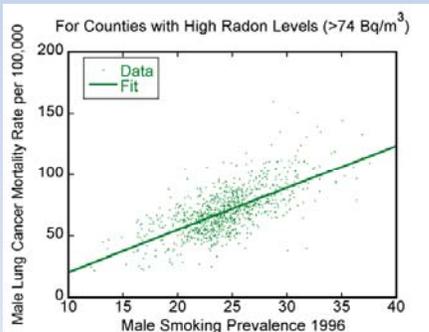
Cohen study was criticized for incorrect accounting of Smoking  
([Heath, 2004](#), [Puskin, 2003](#))

County level smoking prevalence data are now available, e.g.:  
Cigarette smoking prevalence in US counties: 1996-2012, ([Dwyer-Lindgren, 2014](#))

## Lung Cancer Mortality Rate (2000-2009) vs. Smoking Prevalence in 1996 for Males in Low and High Radon Counties of USA



Analysis not published yet

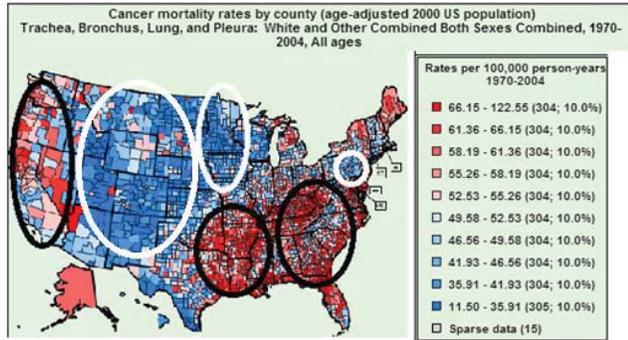
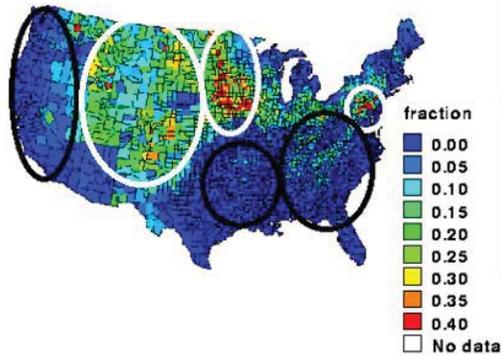


Radon levels: USEPA 1993b. EPA/State Residential Radon Surveys, 1987-1992, Volumes 1-5.: U.S. Environmental Protection Agency. Lung cancer mortality rates: <https://gis.cancer.gov/geoviewer/app/>

Lung cancer mortality rates were lower in high radon counties in comparison to low radon counties for the same level of smoking. Therefore, confounding by smoking cannot explain the reduction of lung cancers observed in high radon counties. Multiple linear regression of entire dataset confirms the reduction of lung cancers with increasing radon levels.

## Radon Levels and Lung Cancer in USA

Predicted fraction of homes over 4 pCi/L



Higher radon counties (green, yellow, red) correspond to mostly lower rates of lung cancer (blue). Higher lung cancer counties (red) correspond mostly to lowest radon areas (blue).

Radon levels: <http://energy.lbl.gov/ie/high-radon/frac4.htm>

Lung, Trachea, bronchus, pleura cancer mortality: <http://ratecalc.cancer.gov/ratecalc/>

Similar pattern observed for: UK, Canada, Ireland, France, Germany, Spain, Switzerland, Sweden, Portugal.

19

How about publications that claim increased cancer risk from low-dose radiation?

20

## Publications that claim to support the LNT model

- Have major flaws in study design, data, analysis, and/or interpretation.
- Utilize 90% CI to claim increased cancer risk when 95% CI (which they previously used) would show no increased cancer risk.
- Use evidence that is of marginal significance and do not consider important confounding factors.
- Have insufficient statistics to distinguish between radiation hormesis and LNT models but calculate radiation risk coefficient using a linear model.
- Generally do not discuss other publications that show reduced cancer risk from low-dose radiation.
- Discuss increased cancer risk from a single type of cancer (which could result from chance, considering the lower statistics) while ignoring the overall reduction in cancers.

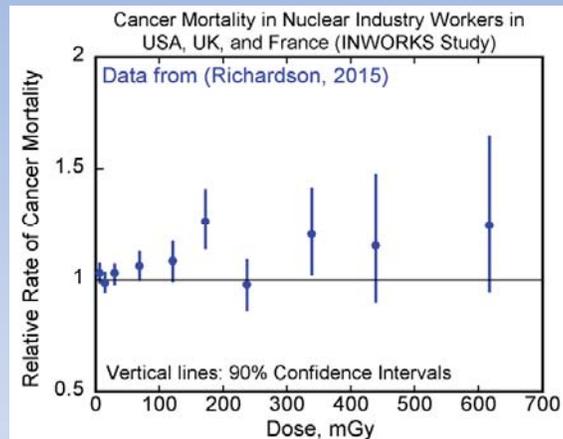
21

## Publications claiming cancer risk from low-dose radiation

Study	Criticism
<a href="#">(Leuraud, 2015)</a> , <a href="#">(Richardson, 2015)</a> – INWORKS studies	<a href="#">(Doss, 2015)</a> , <a href="#">(Sacks, 2016)</a> : Ignored medical radiation dose, which was small compared to occupational dose in early years but was much higher in later years. <b>Used 90% CIs.</b>
<a href="#">(Kendall, 2013)</a> Childhood Leukemias vs. Natural Background Radiation	<a href="#">(Doss, 2014)</a> , <a href="#">(Sacks, 2016)</a> : Data are of marginal significance. All cancers RR=1.03 (1.00-1.07 95%CI). Did not consider confounding by breastfeeding & daycare attendance, which result in 20% and 30% cancer reduction respectively.
<a href="#">(Pearce, 2012)</a> <a href="#">(Mathews, 2013)</a> Cancers following childhood CT scans	<a href="#">(Cohen, 2013)</a> , <a href="#">(Walsh, 2014)</a> , <a href="#">(Boice, 2015)</a> , <a href="#">(Sacks, 2016)</a> : Potential for Reverse causation; data not consistent with present knowledge on radiation-induced cancers, not consistent with A-bomb survivor data.
<a href="#">(Hwang, 2008)</a> Taiwan apartment residents	One cancer type had higher incidence ( <b>90% CI</b> ), quite likely due to chance. <a href="#">(Doss, 2013)</a> : Reduction of all cancers (95% CI).
<a href="#">(Schonfeld, 2013)</a> Techa River solid cancer mortality	Statistics not sufficient to determine dose-response shape; LNT model was used for analysis. <a href="#">(Jargin, 2014)</a> : Possible medical examination bias in higher dose population.
<a href="#">(Krewski, 2006)</a> , <a href="#">(Darby, 2005)</a> Radon lung cancer	<a href="#">(Fornalski, 2011)</a> : Bayesian analysis of 28 studies shows no dose-dependence can be determined.

22

## INWORKS Study of Cancers in Nuclear Industry Workers in USA, UK, and France (Richardson, 2015)



Criticism of the study ([Doss, 2015](#)), ([Sacks, 2016](#))

90% confidence intervals (CIs) used. Data points have very large errors, and almost all data points are consistent with no increased cancer risk if 95% CI were used. Obtaining shape of dose response from this poor quality data is senseless.

23

## Discussion of Recent Publications Claiming Increased Cancers following Childhood CT scans as described in ([Boice, 2013](#))

([Pearce, et al, 2012](#)) UK Study:

### Brain Cancers:

- ERR/Gy for glioma increased with age at exam – this is reverse of prior studies. The risk is expected to decrease for higher ages when brain development nears completion
- ERR/Gy = 23 much higher than 0.88, observed in A-Bomb survivors <10 y

### Leukemias and MDS:

- ERR/Gy Leukemia and Myelodysplastic Disease (MDS) – 36, much higher than 6.5 in A-Bomb Survivors <20y

([Mathews, 2013](#)) Australian Study:

**All cancers:** Risk estimate for All cancers (excluding brain cancers) was 27 vs 3 for A-bomb survivors

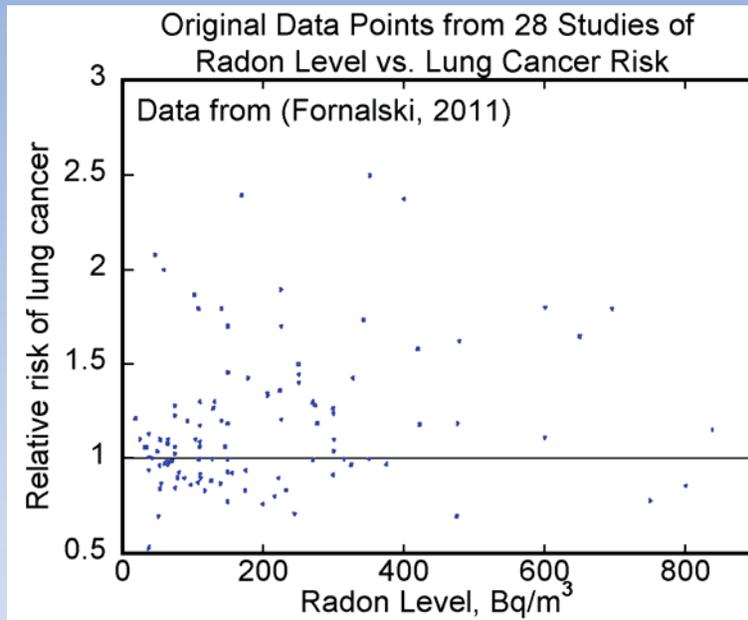
**Latency period:** Study of cancers one year after CT scans increased the likelihood of reverse causation

**Implausible tumors associated with CTs:** Excesses seen for melanoma and Hodgkin's lymphoma, not known to be associated with radiation, and not for breast cancer, a radiosensitive site

**Inconsistent Age at exposure effect:** Excess leukemias observed for later age exposure but not for early age

Both studies were subject to reverse causation because of study design. Considering the large inconsistencies with previous studies, the conclusions of these studies are in doubt, and so these studies do not provide evidence for causal link between CT scans and cancers ([Boice, 2013](#)). The conclusions of these publications are not credible.

24



A Bayesian analysis of 28 ecological and case-control studies indicates no conclusion on shape of dose-response can be drawn. The original data span a wide range of dose-response shapes.

25

## Challenge to LNT Model Proponents

1. Explain the significant reduction of cancer mortality rates in atomic bomb survivors as radiation dose increases from  $\sim 0.25$  Gy to  $\sim 0.5$  Gy
2. Explain the cancer therapeutic effect of repeated applications of LDR in cancer patients
3. Explain the reduction of second cancers/kg of tissue in radiation therapy patients for tissues with  $\sim 20$  cGy dose
4. Explain the reduction of cancers with low-dose rate radiation exposures in evacuated residents of villages near Mayak, British Radiologists who joined service between 1955-79, Nuclear Shipyard Radiation Workers, and Taiwan apartment residents
5. Explain the negative correlation universally observed between residential radon levels and lung cancers
6. Stop using obviously faulty data and data that are already discredited because of major flaws.

26

## Overall Conclusion:

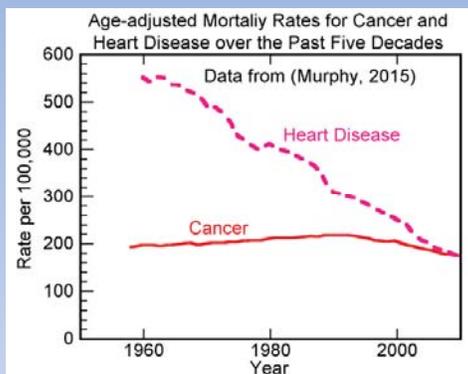
### Low-dose radiation reduces cancer risk.

But, we have been using the LNT model for radiation safety since the 1950s. What are the consequences of using the LNT model?

A **No-Threshold** model is intrinsically **more dangerous** to the public as it inflates the risk by giving significance to unmeasurable changes in risk, thereby inducing governments and the public into fleeing the imagined risk and running into real risk.

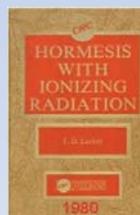
27

## LNT model is responsible for ~30% of recent cancer deaths

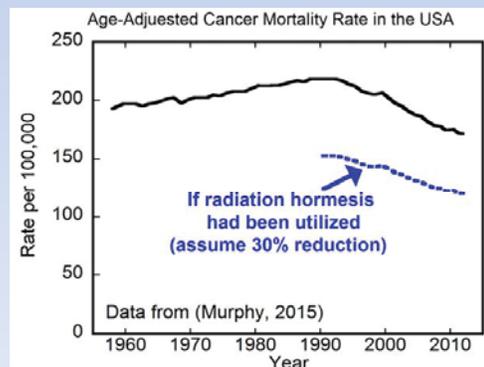


The war on cancer has not been successful as age-adjusted cancer mortality rates continue to be high in spite of tremendous advances in cancer screening, prevention, and treatment based on the mutation model of cancer.

**LNT Model** blocked study of radiation hormesis in the 1980s when it was proposed as a method of reducing cancers (Hormesis with Ionizing Radiation, TD Luckey, 1980).



About 30% of cancer deaths in the past few decades could have been avoided if radiation hormesis had been studied in the 1980s & utilized.



## Research Needs in the Low-dose Radiation Area

- Prospective studies to resolve the LDR cancer risk controversy
- Prospective studies to optimize cancer prevention from LDR
- Clinical trials of LDR treatments for different types of cancers
- Study of lung cancer rates in residents of radon-mitigated homes, before and after radon mitigation, to determine definitively the effect of residential radon on lung cancers.

### Benefits to the Public:

- Significant reduction of cancer mortality rates, much more than has been achieved in the past 50 years
- Eliminate the harm caused by the use of the LNT model in diagnostic imaging, in case of nuclear accidents, dirty bombs, etc.
- Reduced costs for all uses of radiation

# **17**

## **INTERNATIONAL DOSE EFFECT ALLIANCE WORKSHOP: LOW DOSE EFFECTS RESEARCH – OPG'S PERSPECTIVE**

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## International Dose Effect Alliance Workshop Low Dose Effects Research – OPG’s Perspective

Loc Nguyen, M.Sc., CHP  
Senior Scientist, Science & Technology  
Health Physics Laboratory  
Whitby, Ontario, CANADA



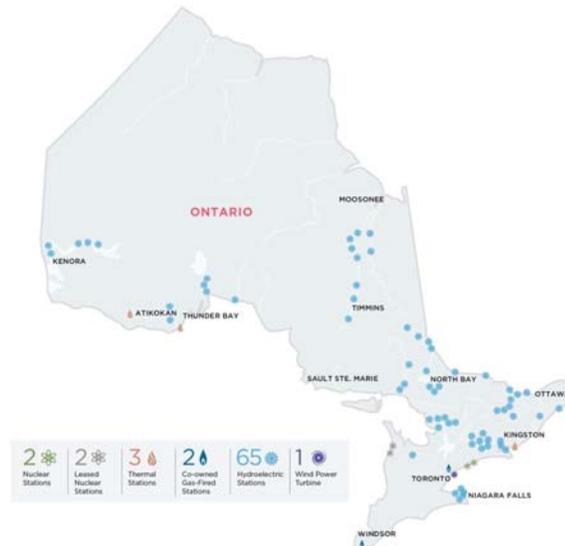
### Agenda

- Introduction
- Low Dose Research (LDR) Portfolio being pursued
- Other Needed Research Areas
- Summary



## Ontario Power Generation (OPG) Overview

- Produces about 50% of Ontario's electricity (at 40% less cost)
- 65 hydro, 2 nuclear, 2 biomass station
  - 2 leased nuclear stations
  - 2 co-owned gas plants
- Closed last coal plant in 2014
- 99 percent Green House Gas emission-free
- 9,200 employees (20% reduction since 2011 levels)
- Ontario's low-cost electricity producer



**ONTARIO**POWER  
GENERATION

3



## OPG Nuclear

- Pickering Nuclear Generating Station
- Darlington Nuclear Generating Station (Refurbishment in progress)
- Health Physics Laboratories + Waste Facility



Pickering NGS is 40 km East of Toronto



Darlington NGS is 70 km East of Toronto

4

**ONTARIO**POWER  
GENERATION



## OPG's Communication Activities

- Provide regular updates to the Regulator, Canadian Nuclear Safety Commission, and the public of abnormal event(s), radiological releases and emission from the operations via:
  - i. Environmental monitoring reports.
  - ii. Participating in Community Forums (i.e. Durham Nuclear Health Committee chaired by Region's Commissioner and Medical Officer of Health).
  - iii. Neighbours Newsletters to the community to provide updates on community issues.
  - iv. Community Information Sessions
  - v. As requested by members of the public, including the media.



## Research & Development Organization

- OPG has a dedicated R&D organization and budget (\$16M/y) to strategically review and address contemporary issues via the CANDU Owner Group (COG):
  - New scientific findings and recommendations from ICRP, UNSCEAR, IAEA, etc. (e.g. new eye dose limits)
  - Changes in regulatory requirements (e.g. RP or environmental protection)
  - Improvement of work practices and equipment
- OPG collaborates with national, international agencies and educational institutions to address common industry issues via COG.



## Low Dose Effects Research Portfolio (COG Projects)

- **Completed project: 1**
  - Studies on the toxicity of Tritium (HTO and OBT)
- **Ongoing Projects: 3**
  - Provide funding to maintain the Biological Research Facility (BRF) at Chalk River Nuclear Laboratory (CNL) to conduct current and future LDR on animals.
  - Provide funding to the educational institutions to carry out LDR.
  - Effect of low dose radiation on cancer: a mouse model mechanistic study. Expect completion: 2018/19.

7

P r e s e n t a t i o n   T i t l e

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## Low Dose Effects Research Portfolio (Cont'd)

- **Proposed Project: 3**
  - In-vivo Study on the Relative Biological Effectiveness of HTO and OBT in inducing double strand breaks.  
**Expect: Feb 2019.**
  - The Biological and Immunological Effect of Low Dose Radiation on Aged Population.  
**Expect: Mar 2020.**
  - Effects of Tritium Exposure on Immune System and Implications in Breast and Lung Cancer Development.  
**Expect: Mar 2020.**

8

P r e s e n t a t i o n   T i t l e

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## Other Needed Research Areas

- Research on non-cancer effects including epidemiological studies on:
  - Cardiovascular disease
  - Radiation induced opacity (Cataracts)
- Risk Communication Methodology and Strategy:
  - What is the actual risk?
  - How do we balance it?
  - What are the benefits from accepting certain risks?
  - How do we communicate/convey our message to members of the public?
  - Communication approach to our regulators?
- Probability of Causation for radiation induced diseases or cancer

9

Presentation Title

ONTARIOPOWER  
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## Summary

- OPG supports the low dose research that improve our understanding of health risks associated with exposure to low dose radiation.
- Interested in future research on non-cancer effects (i.e. cardiovascular disease, cataracts, etc.)
- Interested in the development of a better risk communication strategy/methodology to the public and regulator(s) regarding radiation health effects.

10

Presentation Title

ONTARIOPOWER  
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## Questions and Answers

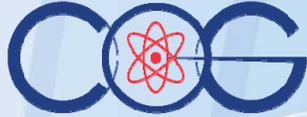




# 18

## LOW DOSE RESEARCH AT CANDU OWNERS GROUP

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*Excellence through Collaboration*

## **LOW DOSE RESEARCH AT CANDU OWNERS GROUP**

Peter Ernst  
Program Manager  
Research & Development

EPRI IDEA Workshop  
November 10, 2016



## **TOPICS ADDRESSED**



- **COG Overview**
- **COG R&D Program Overview**
- **Low Dose Research at COG**



## COG OVERVIEW



COG is a private not for profit corporation funded voluntarily by its Members:

- Five Canadian and six offshore Members
- Programs on collaborative research, information exchange, joint projects and regulatory affairs
- Mission is to provide programs for cooperation, mutual assistance and exchange of information for the successful support, development, operation, maintenance, and economics of CANDU technology
- COG overall budget of ~\$70M dollar per year with ~\$40M going to its R&D program.



3

## COG Interfaces / Linkages



- **WANO** (World Association of Nuclear Operators)
  - Weekly OPEX review
  - Some joint initiatives such as performance measures
- **NEI** (Nuclear Energy Institute)
  - Formal member of NEI's Inter Group Coordination Committee reviewing items of common interest
- **EPRI** (Electric Power Research Institute)
  - Hold a Canadian CANDU license
  - Work closely to avoid duplication and influence programming
- **CNSC** (Canadian Nuclear Safety Commission)
  - Facilitate Member / CNSC discussion & alignment
- **IAEA** (International Atomic Energy Association)
  - COG sits on the Nuclear Safety Standards Committee (NUSSC)
  - Provide an interface between IAEA and the CANDU industry
- **CSA** (Canadian Standards Association)
  - COG sits on the CSA Nuclear Strategic Steering Committee.
  - Fund 'seed documents' and technical expertise for environmental standards



4

## COG R&D PROGRAM OVERVIEW



### The COG R&D Program:

- addresses current and emerging operating issues to support the safe, reliable and economic operation of CANDU reactors
- is sponsored by Ontario Power Generation, Bruce Power LP, New Brunswick Power Nuclear, SNN-SA (Romania), and by Atomic Energy of Canada Limited.

### COG R&D Program is managed under five areas:

- Chemistry, Materials and Components
- Fuel Channels
- Safety & Licensing
- **Health, Safety and Environment**
- Industry Standard Toolset



## LOW DOSE RESEARCH AT COG



- LDR projects are managed by the Health, Safety and Environment R&D Program (HS&E).
- The elements of LDR have been included in the HS&E Strategic Plan for many years.
- HS&E has contributed considerable funding for LDR related projects in collaboration with CNL and others.
- COG also supports Radiation Biology work at universities, both to improve our understanding and provide means of training personnel
- COG is mandated to pursue collaborations with other organizations wherever possible. This is especially important for LDR work.



## COG Supported LDR Research Projects



- Support for the Biological Research Facility (ongoing)
  - COG co-funded the construction of the BRF at CNL in 1998, and has, for several years, contributed to its maintenance to help ensure that this state-of-the-art facility is available for LDR projects on animals
- Relative Toxicity of Gamma-Rays and H-3 Beta-Particles in Mice. (completed)
  - This project was an essential precursor to the larger CNL studies to determine the relative toxicity of  $^3\text{H}$  and gamma-rays. The project provided the  $^3\text{H}$  retention data necessary for the dosimetry needed to create equivalent gamma-irradiation schedules.



## COG Supported LDR Research Projects



- Studies on the Toxicity of H-3 (Tritium) (ongoing)
  - In this project COG collaborated with CNL, CNSC and IRSN to carry out the life-span study comparing the toxicity of gamma and tritium beta radiation using 3300 mice as referred to by CNL in their previous presentation. COG continues to collaborate with CNL to examine the histology of the deceased animals and obtain relative OBT data.
- Effect of low dose radiation on cancer: a mouse model mechanistic study. (ongoing)
  - This project, supported by COG, forms part of the overall CNL project on the effects of low dose internal and external radiation on the development of cancer. This work will examine the effects of chronic tritium and gamma-radiation on intestinal cancer progression, animal life span and associated molecular and cellular mechanisms.



## COG Supported LDR Research Projects



- National Science and Engineering Research Council (NSERC) Industrial Research Chairs (IRC) in Radiation Science (completed)
  - COG supported this IRC at McMaster University for 10 years which provided research funding for radiation biology and dosimetry. Among the areas studied were the biological effects of low doses of different isotopes, and understanding the low dose mechanisms which subsequently drive the dose response. These mechanisms included radiation-induced genomic instability, bystander effects, hereditary effects, and adaptive response.
- NSERC Consolidated Research and Development (CRD) Grant in Radiation Science (Ongoing)
  - Following on the successes of the IRC above COG funded two projects in Radiation Science at McMaster which were successful in receiving a CRD Grant. This work will continue the research on low dose mechanisms as above.
  - The team involved is at the forefront in radiation measurement and biology, and have a wide network of international collaborators.



## COG Proposed New LDR Projects



- In vivo study on the relative biological effectiveness of HTO and OBT in inducing double strand breaks (DSB). (2 years)
  - This project will determine RBE for DSB induction following acute HTO and OBT exposures in tissues of laboratory mice. Two independent methods of DSB measurement will be utilized and several tissue and cell types will be analyzed.
- Effects of tritium exposure on immune system and implications in breast and lung cancer development (3 years)
  - This project will answer the question of whether tritium radiation alters immune parameters and how that may contribute to breast and lung cancer development and metastasis.
- The biological and immunological effect of low dose radiation on aged population (3 years)
  - Recent findings suggest that the radiation sensitivity, measured in terms of carcinogenic events, increases with age among adults after age of 40-45. This project will explore this hypothesis using DNA damage in mice of different ages following exposure to low dose gamma radiation.





# ***QUESTIONS?***





# 19

## AFTER FUKUSHIMA: WHAT WE DID AND HOW WE SHOULD DO FOR THE FUTURE

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## After Fukushima What we did & How we should do for the future

**Masako Bando**

Yukawa Inst., Kyoto-Univ. /RCNP,Osaka Univ. /NPO EINSTEIN

**EPRI conference** 2016 9 – 10 November 2016

@Mathematical Institute, University of Oxford, Andrew Wiles Building

Woodstock Road, Oxford, OX2 6GG,

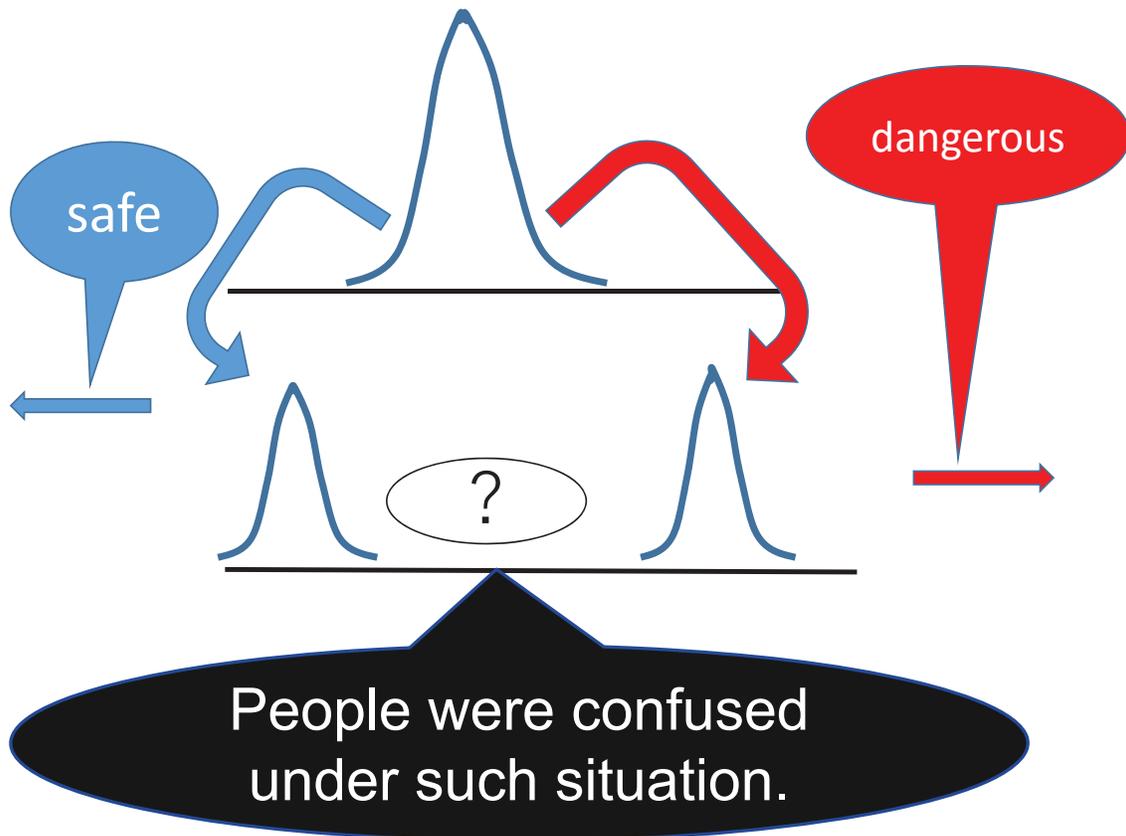
<https://www.phe-toxactionservices.org.uk/cms/article.php?article=3539&course=127&details=true>

In collaboration with

**T. Wada/H.Toki/Tanihata/ Y. Manabe/T.Higuchi/ S.Hirota/T. Shima/ H.Toki**

## After 3 · 1 1 Confusion after Fukushima

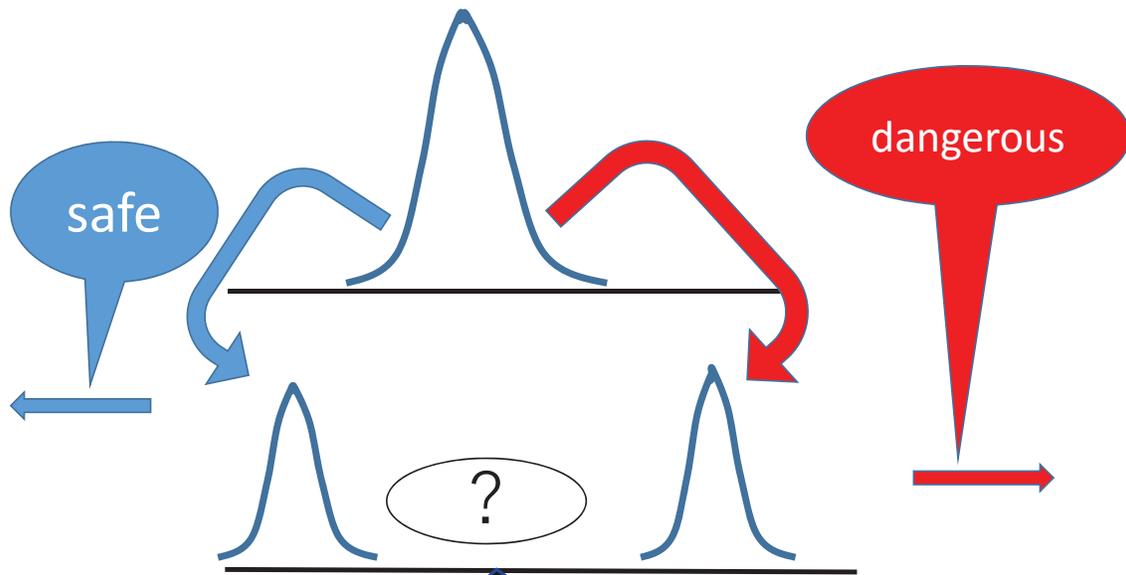
**Distribution of opinions  
on the biological effects  
caused by low dose and low dose rate  
radiation exposure**



**The fundamental cause of this  
in science**

**Not only mass media and extreme  
views expressed by some people**

**but also among the  
scientists themselves!**



Majority of Scientists  
Had to keep silent

# What we did

1

Collaboration with  
citizens and students

# Meeting with students



## Unit conversion sheet for Japanese citizens

### conversion

放射能の単位

**Bq(ベクレル)**

放射線を「出す」

1Bqは、1秒間に1つの割合で原子核が崩壊して別の原子核に変化する**能力**のことです。



覚え方は  
「1秒1発1ベクレル」

影響の単位

**Sv(シーベルト)**

人体が「受け取る」

放射線を浴びた時、体がどのくらいの**影響**を受けるのかを表す単位です。

どんな放射線を体のどこに受けるかで影響は違ってくるけれど、**数字が同じなら影響もだいたい同じだよ!**



# Students citizens scientists



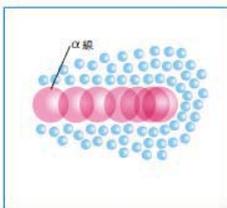
## 知っておくとよわかる!

### ●放射線の、なにが問題か

放出された放射線は、物質を構成している原子のまわりの電子をはね飛ばします。これは電離と呼ばれます。電離した電子は、物質中の原子同士のつながりを乱します。

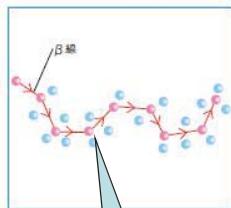
### ● $\alpha$ 線、 $\beta$ 線、 $\gamma$ 線の違い

粒子が高速で飛んでいるものを、放射線といいます。発見されたときは正体がわからなかったのですが、次々いろいろな種類が発見され、その順に $\alpha$  $\beta$  $\gamma$ （ギリシャ文字のABC）と名付けられました。その後、 $\alpha$ 線は高速で運動している陽子2つと中性子2つのかたまり、 $\beta$ 線は高速で運動している電子、 $\gamma$ 線は光速の光の粒だとわかりました。



$\alpha$ 線

青い丸は、水中を $\alpha$ 線が通ったときの電離の様子。α線は重いのでゆっくり進み、まわりの電子をはね飛ばしながら、ほぼまっすぐ進む。電離のたびにエネルギーを失い、進む距離は2、3cm程度、体内では細胞を壊す。紙一枚で遮へいできる。

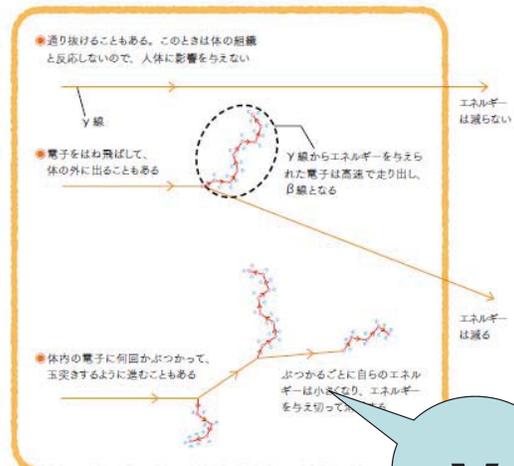


$\beta$ 線

青い丸は、水中で $\beta$ 線が通ったときの電離の様子。β線は軽いのでまわりの電子をはね飛ばしながら、変な方向に進む。電離のたがえ、エネルギーが少なくて、体内では数mm進む。アルミニウム、10mm程度のプラスチックで遮へいできる。

### ● $\gamma$ 線は人体をどんなふうに通過するか

$\alpha$ 線と $\beta$ 線は体の中を通り抜けることはできませんが、 $\gamma$ 線は通り抜けることができます。しかし、厚い鉛や鉄で遮へいできます。



$\alpha$

$\beta$

$\gamma$

Different rays  $\alpha\beta\gamma$

\* $\gamma$ 線にエネルギーの違いは、周囲への影響が異なるように、 $\alpha$ 線にもエネルギーの違いがあります。エネルギーが高いほど、周囲への影響が大きい。

# Interdisciplinary symposium



**What we did**

②

Multidisciplinary  
research meetings

# We reviewed science and history of radiations

Scientists from various fields;

physics, epidemiology, biology,  
animal experiment, immunology,  
medical doctors, sociologists . . . .  
. . . .

13



## Yukawa(Copenhagen) Spirit

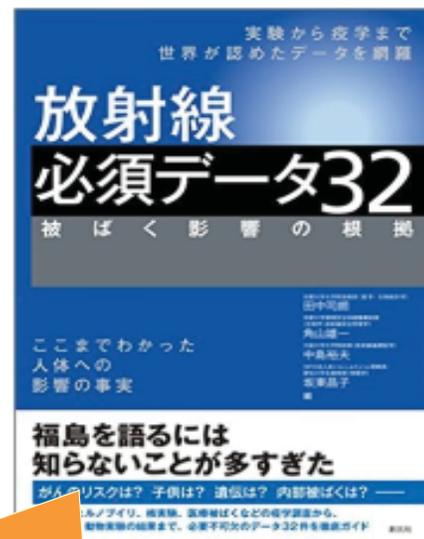
Inter-  
discipli  
nary



Research Institute for Fundamental Physics  
→not "Elementary Particles" or "Nuclear Physics"  
implying that Yukawa had a wider scientific scope in mind.

## Book providing a review for citizens

データ32完成！



32 Essential data of biological  
effects caused by irradiation

# What we did

③

Start Research from physical point of view  
biological effects  
caused by Low dose irradiation<sup>17</sup>

Research  
Whack-A-Mole

Construction of  
a mathematical model



## Further for Research Whack-A-Mole

Construction of  
Mathematical model

Qualitatively

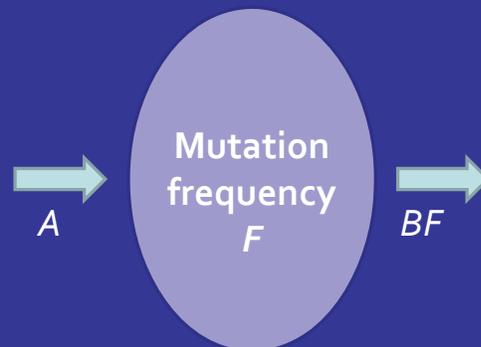
Unified  
understanding

## Mutation Frequency

- Mutation rate is very low

$N_m$  is almost constant  $\rightarrow N_n = \text{const.}$   $N_m/N_n = F(t)$

$$\frac{dF(t)}{dt} = A - BF(t)$$



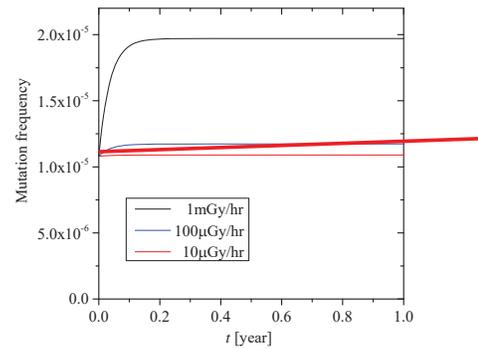
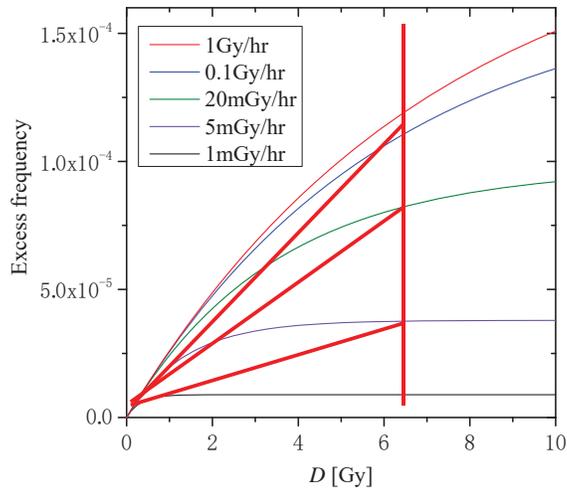
$$A = a_0 + a_1d, \quad B = b_0 + b_1d$$

$d$  : dose rate of artificial irradiation

$$a_0 + a_1d = a_1(d_{\text{eff}} + d)$$

$d_{\text{eff}}$  : effective dose rate

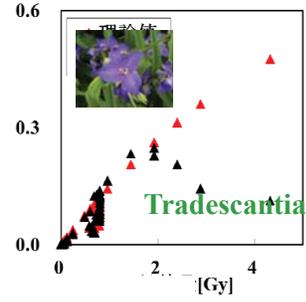
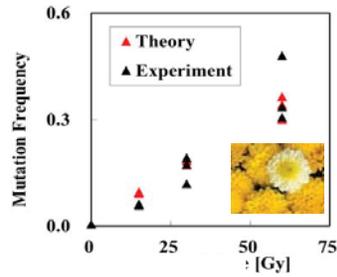
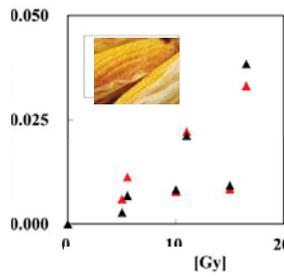
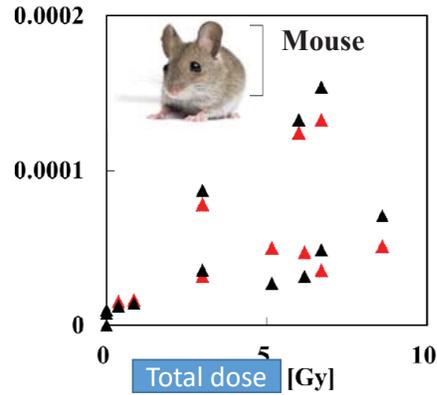
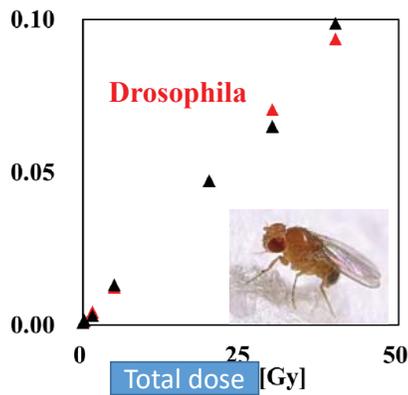
# Characteristic feature



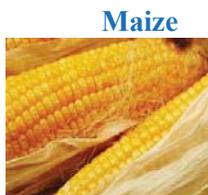
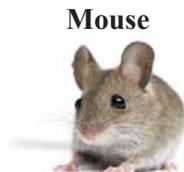
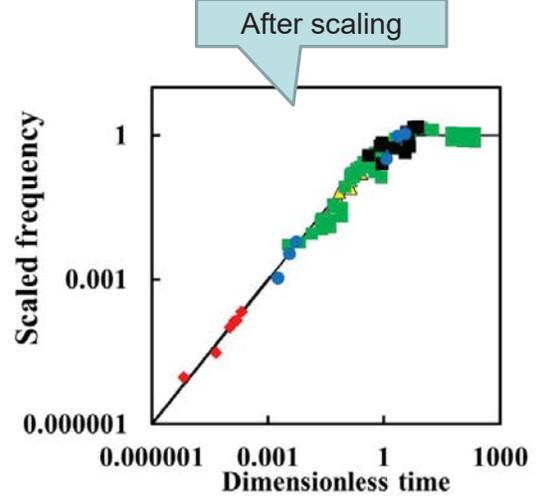
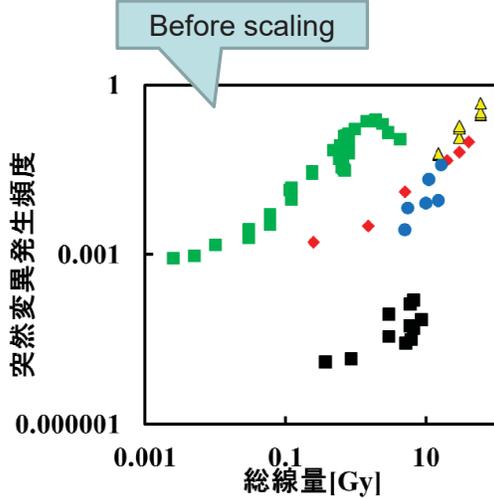
## DDREF depends on $D$

“DDREF”	Total dose $D$			
Dose rate $d$	20 mGy	50 mGy	0.2 Gy	1 Gy
0.1 Gy/hr	1.00	1.00	1.00	1.01
20 mGy/hr	1.00	1.00	1.01	1.07
5 mGy/hr	1.01	1.01	1.06	1.32
1 mGy/hr	1.03	1.08	1.33	3.06
0.1 mGy/hr	1.33	1.93	5.96	28.1
10 $\mu$ Gy/hr	6.01	15.0	59.2	280
1 $\mu$ Gy/hr	59.9	149	592	2800

# Comparison WAM with data



# Whack-A-Mole Model





# Towards Next Step

①

Thyroid Cancer Survey  
in Fukushima

# Recent Research

## Survey of Childhood Thyroid Ultrasound Examinations in Fukushima



First round  
367,672

↓  
300,476  
81.7%

↓  
115

Second round  
381,286

↓  
267,769  
70.2%

↓  
57

People aged 18 years or younger as of April 1, 2011, living in Fukushima

underwent thyroid ultrasound screening

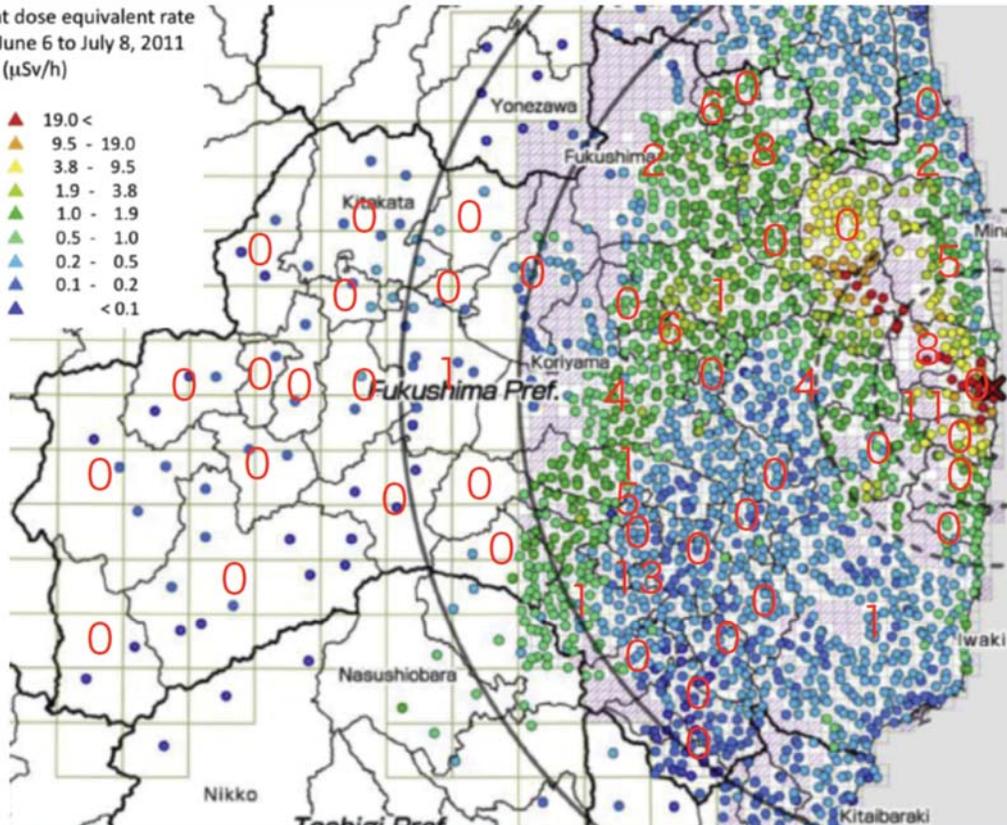
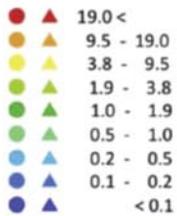
Surely physicists contribute everywhere!

Tow more collaborators Have joined us!

Dose dependence



Ambient dose equivalent rate from June 6 to July 8, 2011 ( $\mu\text{Sv/h}$ )





The high prevalence can be attributed to mass screening. Not meaningful because of differences in methodology

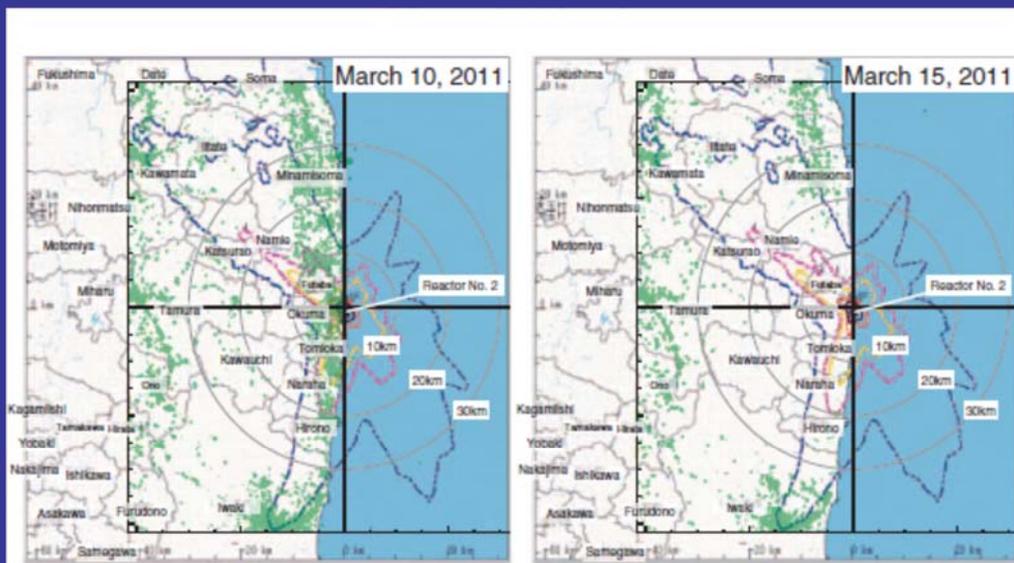
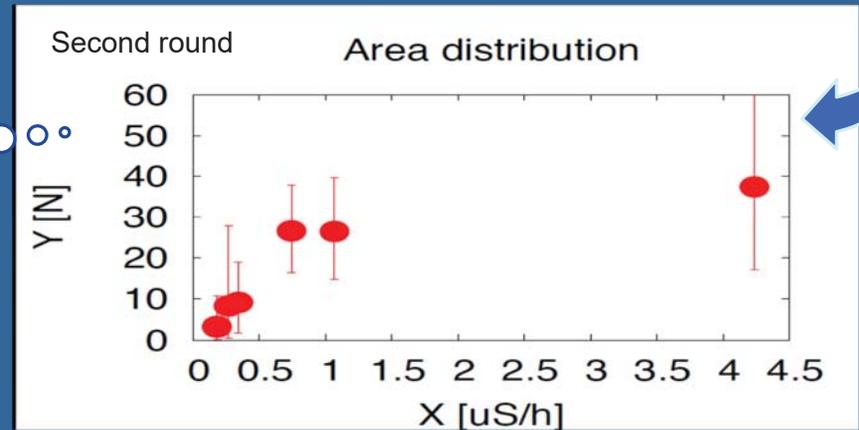
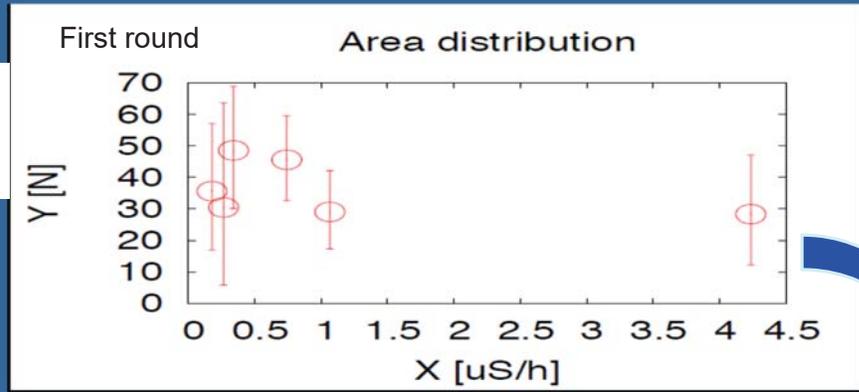
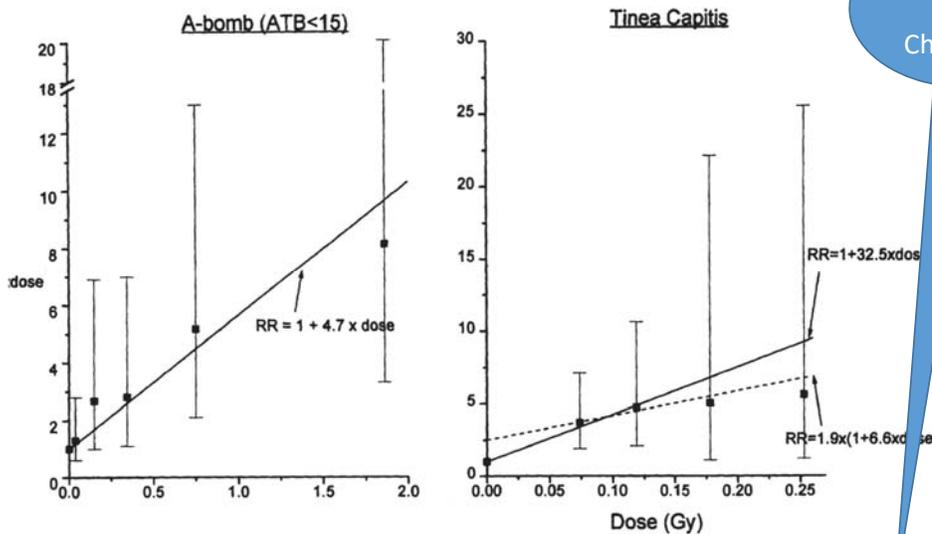


Fig. 2. The 24-hour integrated distribution of people on March 10, 2011 (left) and on March 15, 2011 (right).



“Thyroid Cancer after Exposure to External Radiation: A Pooled Analysis of Seven Studies” E. Roy et al, Radiation Research 141,259-277(1995)  
 The thyroid gland of children is especially vulnerable to the carcinogenic action of ionizing radiation. —————> 120000 people

**Remind the importance of**

**Principles of science research**

Three principles for atomic energy research

1. Non-secrecy (公開)

2. Democratic management (民主)

3. Freedom in research (自主)

# Towards Next Step

②

Multidisciplinary Low dose  
initiative

35

Prof. Wolfgang Weiss encouraged us

- People now distrust science, scientists.
- To recover such situation needs time and power
- Encourage young scientists to join the project
- The project should be made on the basis of fundamental purpose of long term strategy



**JMELODI!**

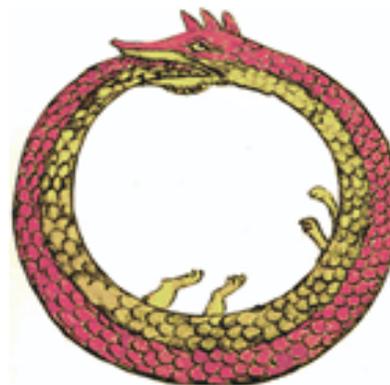
## Biology and Physics

**Low Dose radiation effect 2015  
Biological and medical science  
based on Physics**

**Together with medical  
physicists, epidemiologists**

• • • •

**Low Dose Radiation Effect 2015**  
Biological & Medical Science based on Physics 2015  
special session.



**Research Institute of Fundamental Physics  
Yukawa Institute**

# Common Platform for the study of Biological effects caused by Irradiation

**1<sup>st</sup> Step to our aim**

Multidisciplinary research committee was organized by  
JSPS(Japan Society for the promotion of Science) committee



chaired by

**Mutual  
Intensive  
Discussion**

**Wada**

**Animal exp.  
data**

放射線影響に関する  
知見の統合

**Epidemiological  
data**

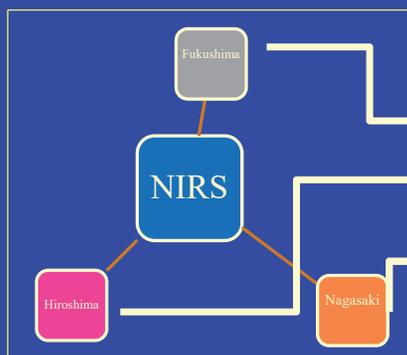
**Integrated Mathematical Science  
Exact Information of Dosimetry**

**National Institute for Quantum and Radiological  
Science and Technology by merging NIRS and some  
institutes of Japan Atomic Energy Agency(JAEA).**

We  
Jap  
the

**International and  
Interdisciplinary collaboration**

orce for



Fuku... of  
Management Survey

1 To properly take care of the health  
of the residents of Fukushima  
Prefecture for a long time (Medical  
care-motivation)

2 To clarify the question regarding the  
health effect caused by long term with  
very low dose rate radiation exposure

# Towards

③

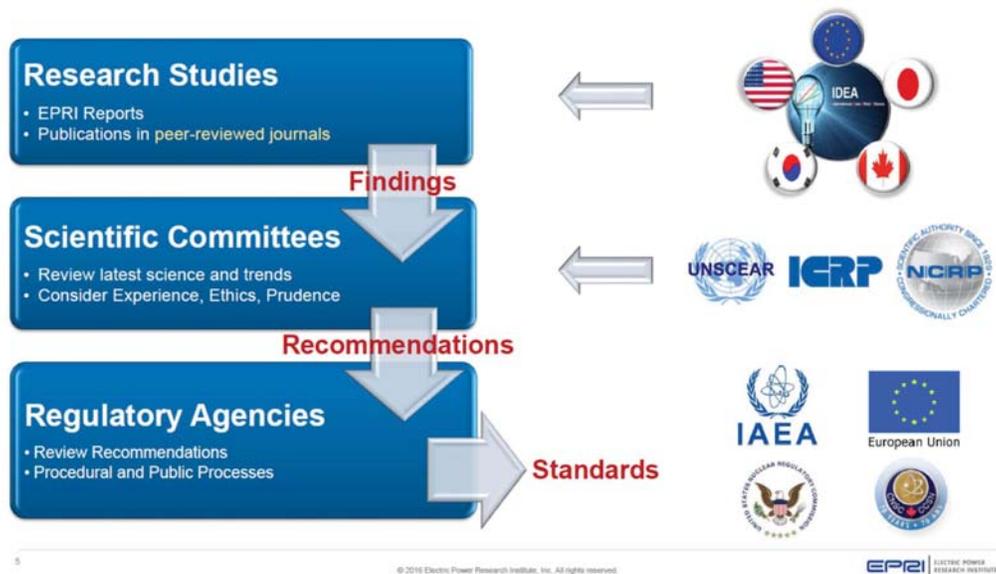
Multidisciplinary Low dose  
initiative

## PLANET +JMELODI

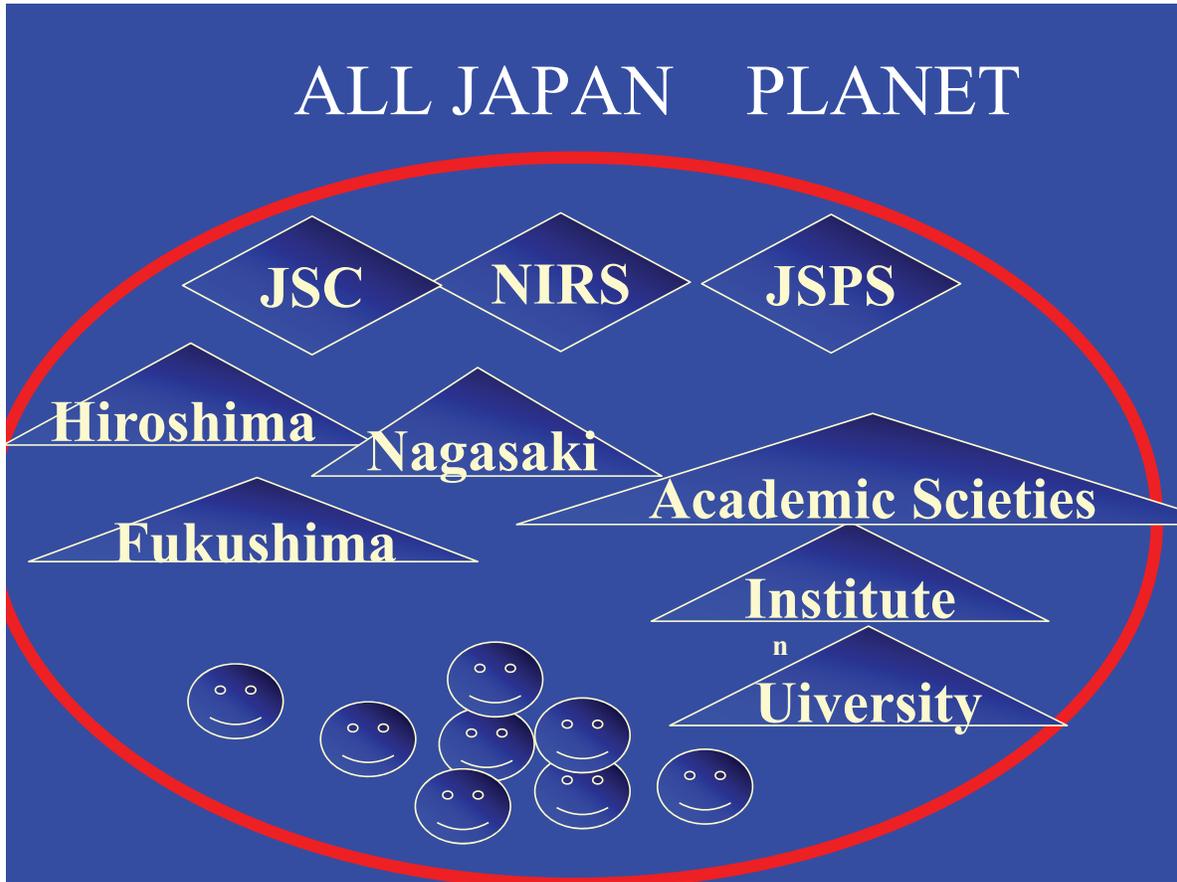
- The time has come for the Japanese scientists to launch a long term project cutting through various institutions and disciplines.
- The project must be truly international, under the Yukawa spirit.
- We should learn from the history of Chernobyl.



**Copenhagen spirit.**



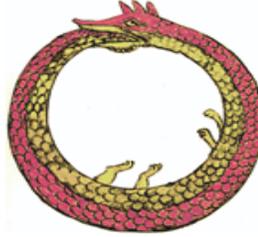
# International and multidisciplinary Collaboration



# Low Dose Radiation Effect 2015

Biological & Medical Science based on Physics 2015  
special session.

Autumn, 2015  
Yukawa Institute  
for Theoretical  
Physics,  
Kyoto, Japan



## First Circular

Biological risks of low-dose radiation in radiation biology are being extensively investigated and the study of biological defense systems has been developed especially during the last 20 years. However, those findings are shared only to those of limited fields. As a result, extreme opposite opinions divided scientists into two sides, which caused confusion to people in Japan especially after the Fukushima dai-ichi nuclear power plant accident. It is seriously needed scientific discussion independent of political bias, among the scientists cross over the disciplines..

The purpose of this special session is to exchange the scientific views among scientists from different fields, biology, physics, epidemiology, medical science and so on. It would enhance the scientific understanding and reduce uncertainties on the effects of exposure to low dose radiation, providing the society with important information to improve risk protection management. Physicists tend to understand different phenomena in a unified way and to estimate quantitatively by using mathematical modelling and analysing accumulated data of radiation biology and epidemiology.

Let us gather multidisciplinary scientists and have hot discussion on low dose radiation risk in this conference, attempting to obtain the consensus among different fields.

We expect that it will lead new scopes of study of an academic area.

In the USA and Europe, national projects are already processed.

We, Japanese scientists who we experience a nuclear power plant accident of Fukushima, should make efforts to Promote such project in Japan.

We hope that this conference may become the first step of making purely scientific network.

**The title of the first session of  
the First Pugwash Conf.**

**The reference value of Radiation Dose**

**We should make clear distinction between judgement  
from the humanitarian standpoint and scientific truth**

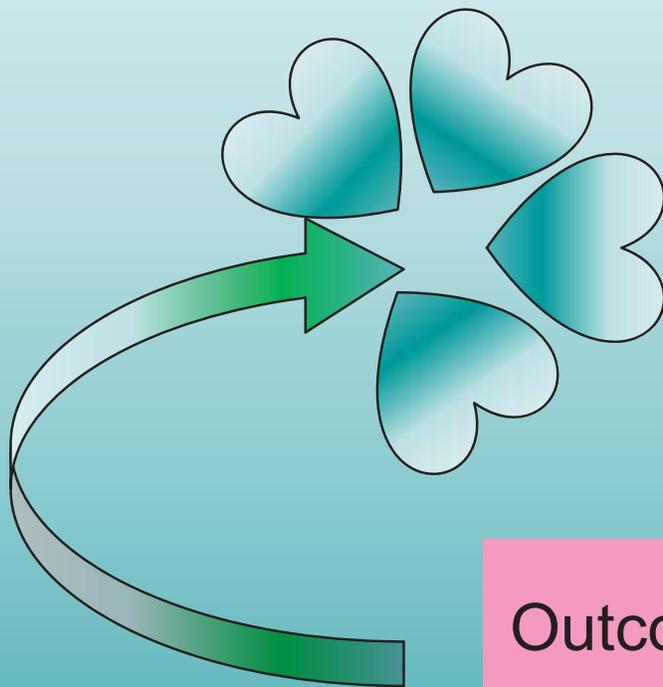
**Prof. Yukawa  
attended this  
session!**

**How is the Biological effects  
caused by irradiation in  
Fukushima area**

# Goal

Not only radioprotection purpose

47



Outcome

# Radiology



# Energy for our Future



# Evolutionary Biology



# Radiatin Biology as Science

What is Life?

Dellbruck

Bohr

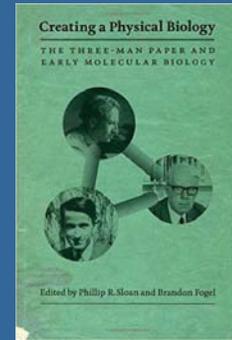
Hit theory

Shrodinger Lea

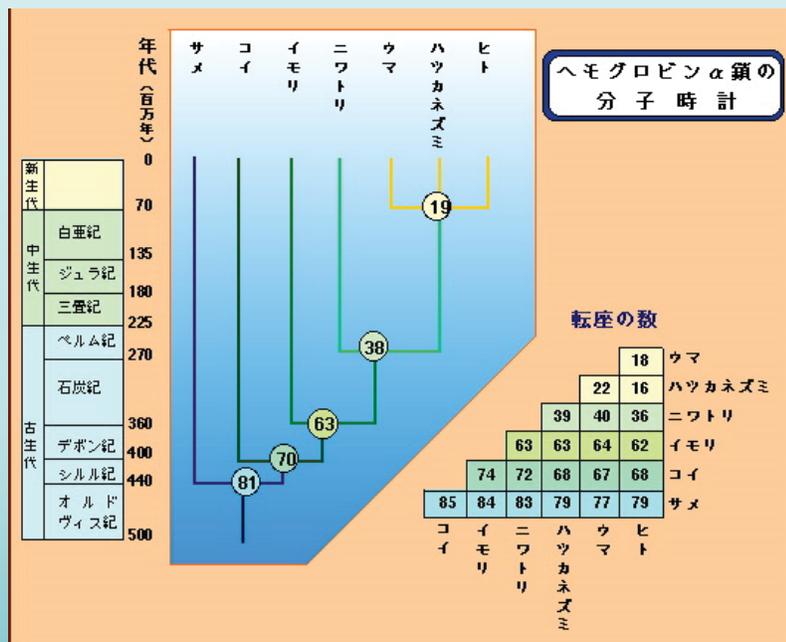
## Landmark of Molecular Biology

### COPENHAGEN Geist

- 1 Attempt to tackle a biological problem with a new set of tools
- 2 Conscious collaboration between a geneticist, a biophysicist and an atomic physicist



1935 Gottingen Academy of Science  
 "On the nature of gene mutation and gene structure"

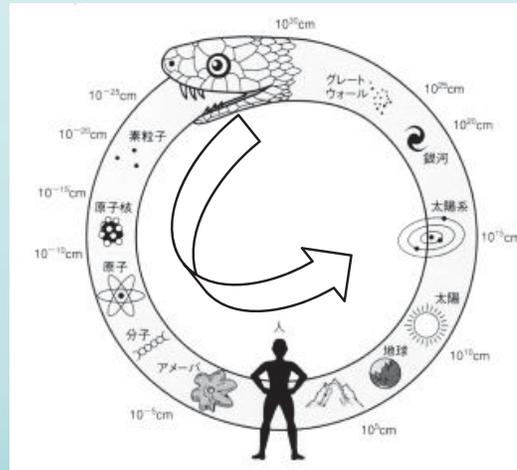


Molecular Biology

・ Kimura Ohta ・

Evolution

Japan National Institute for Genetics



**Nuclear physics**

**Yukawa Institute**

Evolution of Universe

**Molecular Biology**

**Institute for Genetics**

生物の進化

## Space adventure





# Dyson Culture

**THE END**



# **20**

## **LOW DOSE RESEARCH AT QST-NIRS**

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# Low Dose Research at QST-NIRS

Yutaka Yamada,  
Shizuko Kakinuma, Imaoka Tatsuhiko, Kazuhiro Daino, Takamitsu  
Morioka, Mayumi Nishimura, Tetsuo Nakajima, Michiya Sasaki, Hiroshi  
Takeshita, Takeo Shimomura, Jun Ohtake, Atsuro Ishida,  
Yoshiya Shimada

National Institute of Radiological Sciences (NIRS)  
National Institutes for Quantum and Radiological Science and Technology (QST)

1



## NIRS → QST-NIRS (2016)

**National Institutes for Quantum and Radiological Science and Technology (QST):**  
a new national corporation

✓ **Composed of three institutes/directorates**

- [National Institute of Radiological Sciences \(NIRS\)](#)
- Quantum Beam Science Research Directorate\*
- Fusion Research and Development Directorate\*

} **Former NIRS**  
} **Moved from JAEA**

✓ **Mission of QST includes:**

- **Medical application of radiation**
- **Radiation effects, radiation protection and radiation emergency medicine**
- Development and application of quantum beams and laser technologies
- Research and development of nuclear fusion



**Toshio Hirano, MD PhD**  
President, QST



**Yoshiya Shimada, PhD**  
Executive Director, QST

2

# Dept. of Radiation Effects Research, QST-NIRS

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## ✓ Research Plan 2016–2022

- Development of a risk model based on epidemiology and animal studies including:
  - **Radiation carcinogenesis experiments** on the effect of **age, low dose rate exposure, radiation type** and **lifestyle factors**
  - **Mechanistic studies** using **next generation genomics** and methodology of **stem cell biology**
- Construction of an **animal experiment data archive (J-SHARE)**
- Launching a **platform of experts** that identifies and solves important low dose radiation risk issues (**PLANET**)



**Shizuko Kakinuma, PhD**  
Director, Dept of Radiation Effects Research

3

# Dept. of Radiation Effects Research, QST-NIRS

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## ✓ Organization 2016

- 13 tenured researchers
- 6 research teams
  - **Radiobiology for Children's Health** (Shizuko Kakinuma, PhD)
  - **Stem Cells and Cancer** (Tatsuhiko Imaoka, PhD)
  - **Chronic Exposure, Cancer and Pathology** (Yutaka Yamada, DVM PhD)  
Including low dose research for Fukushima project
  - **Stress and Lifestyle Effects** (Tetsuo Nakajima, PhD)
  - **Dietary Effects** (Bing Wang, MD PhD)
  - **Children's Environmental Health** (Shizuko Kakinuma, PhD)

## ✓ Budget 2016

- Internal 18 million JPY (US\$173,000) + external funds
- Internal 60 million JPY (US\$577,000) for Fukushima project 2016, 2017

4

# Low dose research

---

5

## Radiation carcinogenesis animal experiments

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**Low Dose Effects  
Research Building  
QST-NIRS**



**Fast neutron source**

$^9\text{Be}(d,n\gamma)^{10}\text{B}$   
2 MeV (mean)



**Low dose rate  
gamma-ray source  $^{137}\text{Cs}$**

1–500 mGy/day  
(0.04–20 mGy/hr)



**SPF animal facility**

11,000 mice  
3,000 rats



# Radiation carcinogenesis animal experiments

## Wild-type cancer models

Mortality, liver, lung, lymphoma, etc.



B6C3F1 mouse

AML



C3H mouse

Breast



SD rat

Lung



WM rat

## Heterozygotic cancer models

Brain



*Ptch1*<sup>+/-</sup> mouse

Intestine



*Apc*<sup>Min/+</sup> mouse

Intestine



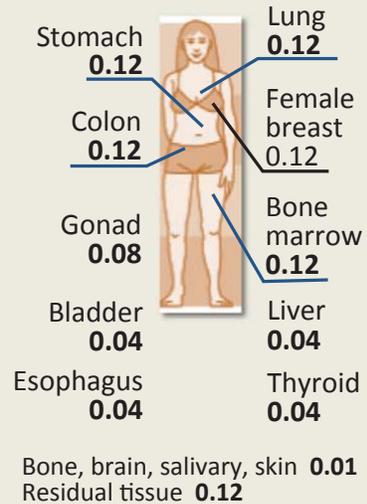
*Mlh1*<sup>+/-</sup> mouse

Kidney



*Tsc2*<sup>Eker/+</sup> rat

## Tissue weighting factors (ICRP, 2007)



# Low dose rate exposure animal experiments

Chronic exposure

1Gy (0.0263mGy/min x27days) irradiation

4Gy (0.1052mGy/min x27days) irradiation

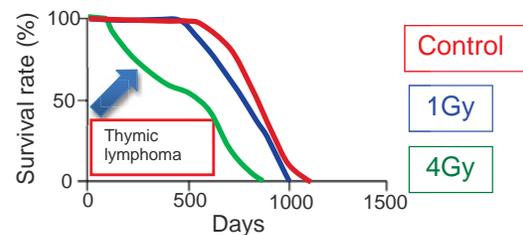
1 → 4 weeks

7 → 10 weeks

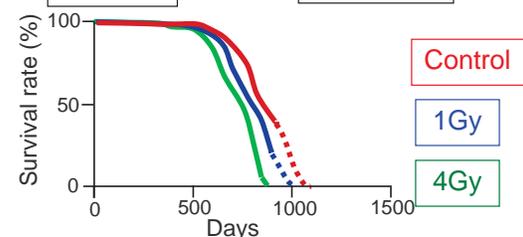
15 → 18 weeks

Life span shortening  
Lymphomas  
Liver tumors  
Lung tumors  
Other solid tumors

Acute 1 week

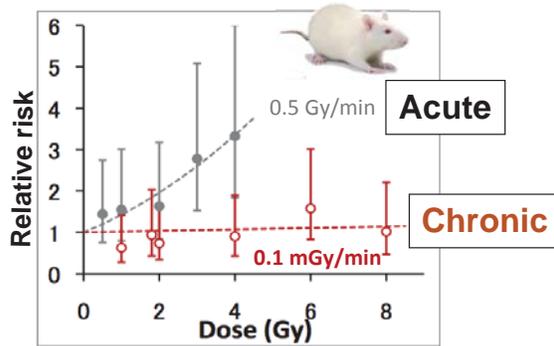


Chronic 1-4weeks



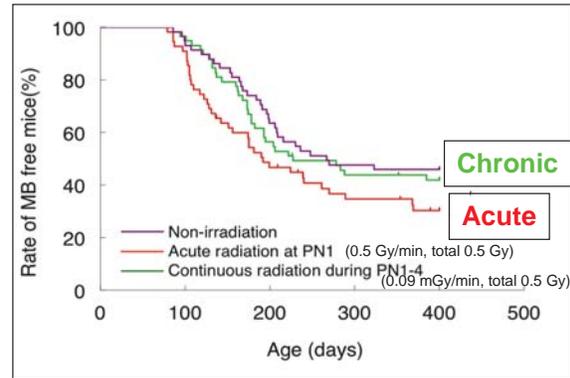
# Low dose rate exposure animal experiments

## Mammary tumor



SD female rats  
Irradiation at 7 ages of the weeks  
(Imaoka et al)

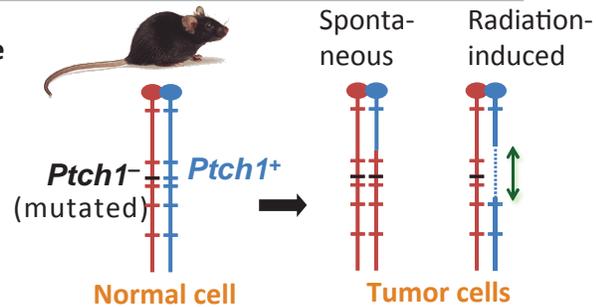
## Brain tumor (Medulloblastoma)



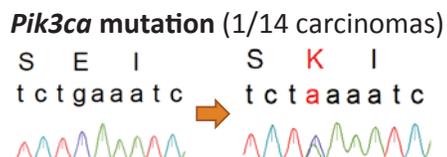
*Ptch*<sup>-/-</sup> mice  
Irradiation at one day old  
(Tsuruoka et al)

# Oncogenic mutations in radiation-induced cancer

## Deletion mutations in MB of *Ptch1*<sup>+/-</sup> mouse (Ishida, Takabatake et al.)



## Mutations screening in mammary tumor of SD rat (Showler, Nishimura, Daino et al.)



**Needs: Further identification of oncogenic mutations in radiation-induced cancer models**

# Japan-Store House of Animal Radiobiology Experiments: J-SHARE

---

## Background and aim of J-SHARE

A project to evaluate the effects of radiation on children was launched within the NIRS in 2006, which has since focused on risk analyses for life shortening and cancer prevalence using laboratory animals.

As well as the economic and practical limitations to repeating such large-scale experiments, ethical considerations make it vital that we **store and share the pathological data and samples of the animal experiments for future use**.

We are now constructing such an archive called the Japan-Storehouse of Animal Radiobiology Experiments (J-SHARE).

# Outline of J-SHARE

## What does J-SHARE do?

Provide animal experiment **database and biological materials** of NIRS for collaborative research with the international community.

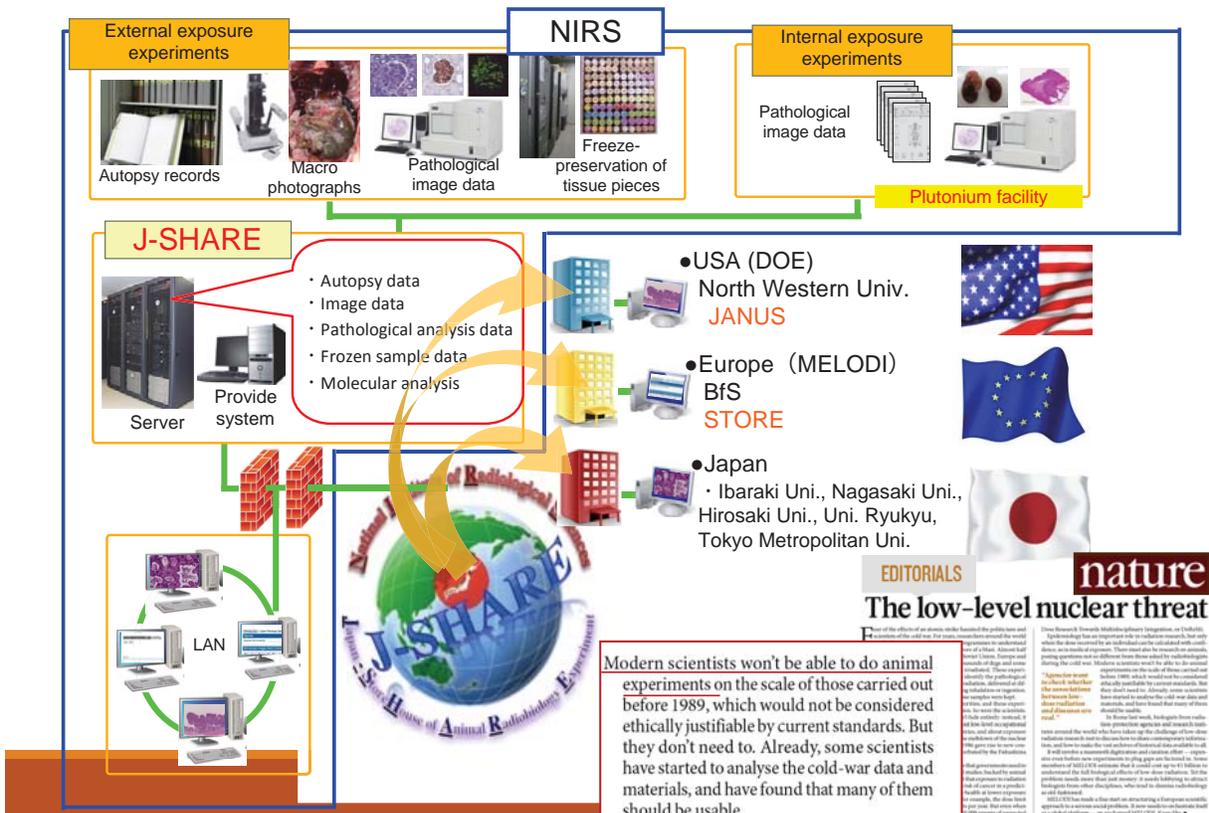
### Integrating:

- Autopsy data (spreadsheets)
- Image data (Macro photos, virtual slides – zoomable images)
- Pathological analysis data
- Cellular analysis data (Blood cell examination, FACS scans)
- Molecular analysis (Sequences, CGH, expression, etc.)
- Frozen samples (Ear, spleen, liver, tumors)
- Histopathological slides and paraffin blocks
- Publish reports

### Outputs:

- To an HTML web browser
- To other clients using web services

# Overview of J-SHARE



## Number of samples to be stored in J-SHARE

Animals	Radiation	Number of animals	Age at exposure (E:Fetal days, W:Weeks)
B6C3F1 mice Female, Male Life span study	Gamma (acute)	2300	E3, E13, E17, 1W, 3W, 7W, 15W
	Gamma (fractionated)	1460	1W, 7W, 15W
	Gamma (low dose rate)	1400	1W, 7W, 15W
	Carbon ions	1800	E3, E13, E17, 1W, 3W, 7W, 15W
	Carbon ions (fractionated)	960	1W, 7W
	Neutron	2300	E3, E13, E17, 1W, 3W, 7W, 15W
<b>Total</b>		<b>10220</b>	
Sprague Dawley rats Female Breast cancer study	Gamma (acute)	600	E3, E13, E17, 1W, 3W, 7W, 15W
	Gamma (low dose rate)	500	3W, 7W
	Carbon ions	600	E3, E13, E17, 1W, 3W, 7W, 15W
	Neutrons	500	3W, 7W
<b>Total</b>		<b>2200</b>	
Wistar rats Female Lung cancer study	X-rays	757	1W, 5W, 15W
	Neutrons	480	5W, 15W
	Neutrons (fractionated)	192	5W, 15W
<b>Total</b>		<b>1429</b>	

All experiment include non-irradiated animals.

## Samples to be stored in J-SHARE

### Genetically-modified animal experiments

- Brain tumors: *Ptch1*<sup>+/-</sup> mice
- Digestive tract tumors: *Apc*<sup>Min/+</sup>, *Mlh1*<sup>+/-</sup> mice
- Kidney tumors: Eker rats

### Combined effect of radiation and chemicals

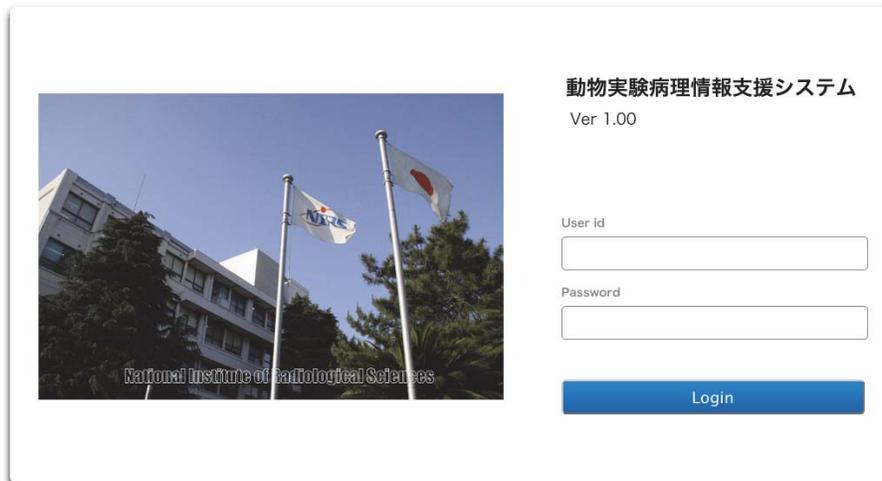
- Thymic lymphoma: MNU, ENU, B6C3F1 mice

### Cancer prevention

- Calorie restriction: B6C3F1 mice
- Antioxidant nutrients, phytochemicals: *Apc*<sup>Min/+</sup> mice

# Access to J-SHARE

- User's registration (user ID, password)
- Free
- Download and utilize only the disclosed data



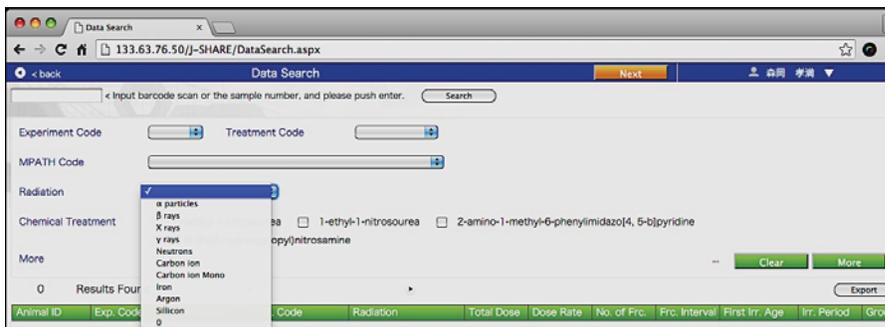
動物実験病理情報支援システム  
Ver 1.00

User id  
[input field]

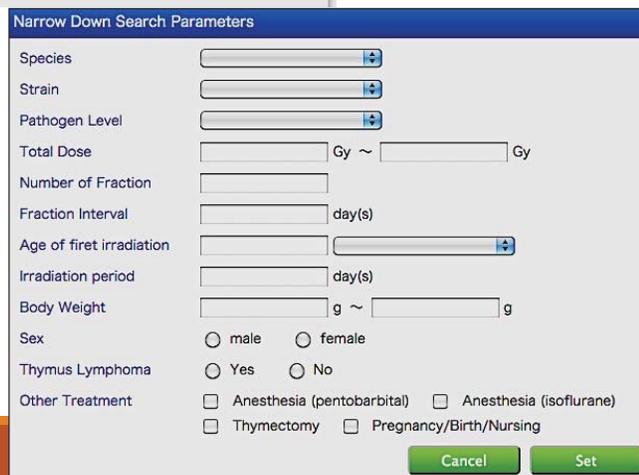
Password  
[input field]

Login

## Data search and parameters



- Experiment Code
- MPATH Code
- Species
- Strain
- Sex
- Radiation
- Dose
- Age at exposure  
etc.



# Results of data search

< back Data Search Next 山田 裕

< Input barcode scan or the sample number, and please push enter. Search

Experiment Code: 6AB-A Treatment Code: C-0.2-1-1w

MPATH Code: 268 : adenocarcinoma

Radiation: Carbon ion

Chemical Treatment:  1-methyl-1-nitrosourea  1-ethyl-1-nitrosourea  2-amino-1-methyl-6-phenylimidazo[4, 5-b]pyridine  N, N-Bis(2-hydroxypropyl)nitrosamine

More ... Clear More

44 Results Found 1 - 44 Export

Animal ID	Exp. Code	Animal No.	Trm. Code	MPATH Code	Radiation	Total Dose	Dose Rate
S8498	6AB-A	36	C-0.2-1-1w		Carbon ion	0.2Gy	
S9137	6AB-A	26	C-0.2-1-1w		Carbon ion	0.2Gy	
S9235	6AB-A	21	C-0.2-1-1w		Carbon ion	0.2Gy	
S9356	6AB-A	6	C-0.2-1-1w		Carbon ion	0.2Gy	
S9472	6AB-A	37	C-0.2-1-1w		Carbon ion	0.2Gy	
S9542	6AB-A	1	C-0.2-1-1w		Carbon ion	0.2Gy	
S9803	6AB-A	31	C-0.2-1-1w		Carbon ion	0.2Gy	
S9844	6AB-A	2	C-0.2-1-1w		Carbon ion	0.2Gy	
S10104	6AB-A	27	C-0.2-1-1w		Carbon ion	0.2Gy	
S10465	6AB-A	11	C-0.2-1-1w		Carbon ion	0.2Gy	
S10466	6AB-A	22	C-0.2-1-1w		Carbon ion	0.2Gy	
S10483	6AB-A	40.1	C-0.2-1-1w		Carbon ion	0.2Gy	
S10520	6AB-A	38	C-0.2-1-1w		Carbon ion	0.2Gy	
S10526	6AB-A	7	C-0.2-1-1w		Carbon ion	0.2Gy	
S10619	6AB-A	12	C-0.2-1-1w		Carbon ion	0.2Gy	
S10629	6AB-A	3	C-0.2-1-1w		Carbon ion	0.2Gy	
S10640	6AB-A	16	C-0.2-1-1w		Carbon ion	0.2Gy	
S10682	6AB-A	40.2	C-0.2-1-1w		Carbon ion	0.2Gy	
S10716	6AB-A	28	C-0.2-1-1w		Carbon ion	0.2Gy	
S10785	6AB-A	40.3	C-0.2-1-1w		Carbon ion	0.2Gy	
S10818	6AB-A	29	C-0.2-1-1w		Carbon ion	0.2Gy	
S10825	6AB-A	17	C-0.2-1-1w		Carbon ion	0.2Gy	
S10840	6AB-A	32	C-0.2-1-1w		Carbon ion	0.2Gy	
S11065	6AB-A	8	C-0.2-1-1w		Carbon ion	0.2Gy	

# View of individual data

< back Autopsy Data Entry Submit 森岡 孝典

Experiment Code : 6AB-A / Animal Number : 70 / Treatment Code : C-2-1-1w / Group Size : 40  
 Radiation : Carbon ion / Total Dose : 2.0 / Number of Fraction : 1 / Fraction Interval : 0 / Age of First Irradiation : 1W / Irradiation Period : 0

Animal ID : S11273

Autopsy Primary

Autopsy Performed By: [dropdown] Autopsy Date: 2007/05/07 Autopsy Reason: Moribund  
 Tissues Prepared By: [dropdown] Preparation Date: [dropdown] Block Count: [input]  
 Parts Extract By: [dropdown] Birth Date: 2005/01/22 Sex:  Male  Female  
 Reproductive History:  Yes  No

Weight

Body: 19.8 g  
 Brain: [input] mg Thymus: [input] mg Lung: r. [input] mg L  
 Pituitary: [input] mg Heart: [input] mg Adrenal: r. [input] mg L  
 Saliv.gi.: [input] mg Liver: [input] mg Kidney: r. [input] mg L  
 Thyroid: [input] mg Spleen: [input] mg Testis/Ovary: r. [input] mg L

Other

Pleural effusion: 0.000000 ml Pleural effusion Status: [dropdown] Thymic Lymphoma:   
 Ascites: [input] ml Ascites Status: [dropdown] WBC: [input]  
 Blood Type: [dropdown] RBC: [input] ×10<sup>6</sup>/mm<sup>3</sup> Serum Status: [input]  
 Breast Tissue: [dropdown] Smear Status: [dropdown]  
 Hit: [input] %  
 Feed: [dropdown]  
 Frozen Sample: [dropdown] Box Number: [input]  
 Notes: [input]



Autopsy sheet

# View of pathological diagnosis

Slide No.	Organ	MPATH Code	Main	Sub
1	Femur	MPATH 458 : normal	<input type="checkbox"/>	<input checked="" type="checkbox"/>
1	Sternum	MPATH 458 : normal	<input type="checkbox"/>	<input checked="" type="checkbox"/>
1	Pituitary	MPATH 458 : normal	<input type="checkbox"/>	<input checked="" type="checkbox"/>
1	Others	MPATH 397 : osteosarcoma	<input checked="" type="checkbox"/>	<input type="checkbox"/>
2	Brain	MPATH 119 : hemorrhage and non-specified extravasation	<input type="checkbox"/>	<input checked="" type="checkbox"/>
2	Eye	MPATH 458 : normal	<input type="checkbox"/>	<input checked="" type="checkbox"/>
2	Testis	MPATH 458 : normal	<input type="checkbox"/>	<input checked="" type="checkbox"/>
2	Thyroid	MPATH 458 : normal	<input type="checkbox"/>	<input checked="" type="checkbox"/>

Organ	MPATH Code	Remarks
Others	MPATH 397 : osteosarcoma	Cervical pleura: Osteosarcoma.
Adrenal	MPATH 377 : pheochromocytoma	Adrenal gland
Harderian	MPATH 280 : Harderian gland adenoma	Harderian gland

MPATH codes

Confirmed diagnosis

# Virtual slide (Image Scanner 'NanoZoomer')



## Hi-speed, Hi-resolution Digital slide scanner

Hamamatsu Photonics K.K.'s Web Site said...

The NanoZoomer 2.0-HT series is a system that converts glass slides into digital slides by scanning them quickly at high resolutions. It processes up to max. 210 slides automatically using its dedicated slide cassettes. You can save time by processing large amounts of samples overnight. The NanoZoomer 2.0-HT can also automatically read a slide's barcode information and use it to name the slide file.

Tissue slide

# International partnership

NIRS

Related projects



$\gamma|n^0$  Janus Tissue Archive



Chernobyl Tissue Bank  
[www.chernobyltissuebank.com](http://www.chernobyltissuebank.com)



Washington State University College of Pharmacy  
United States Transuranium & Uranium Registries



Collaborative Researches

Integration of data and samples



[yamada.yutaka@qst.go.jp](mailto:yamada.yutaka@qst.go.jp)

## Japanese activities for low dose/ low dose-rate research network

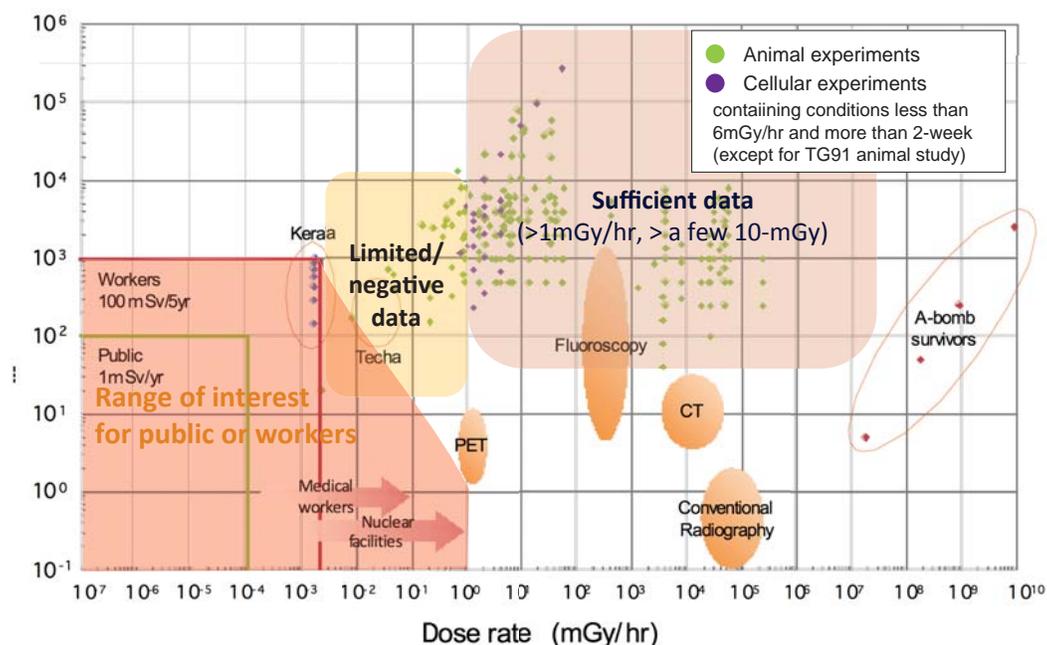
# Background

## Needs

- Social concern (fear) on health effects by long-term chronic exposure (existing situation) after Fukushima Daiichi nuclear accident
- Uncertainty of risk estimation of low dose/low dose-rate chronic/fractionated exposures
- Absent of consensus among experts at the accident
- Decreasing experts and courses/labs on radiation biology and RP also in Japan

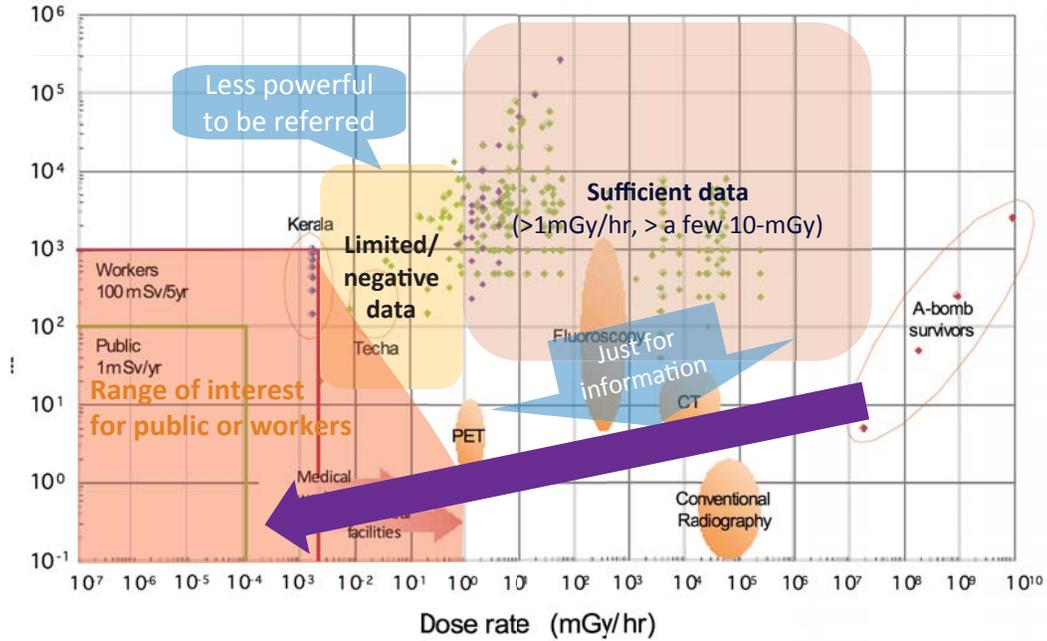
25

## Current status of low dose/low dose-rate biological research

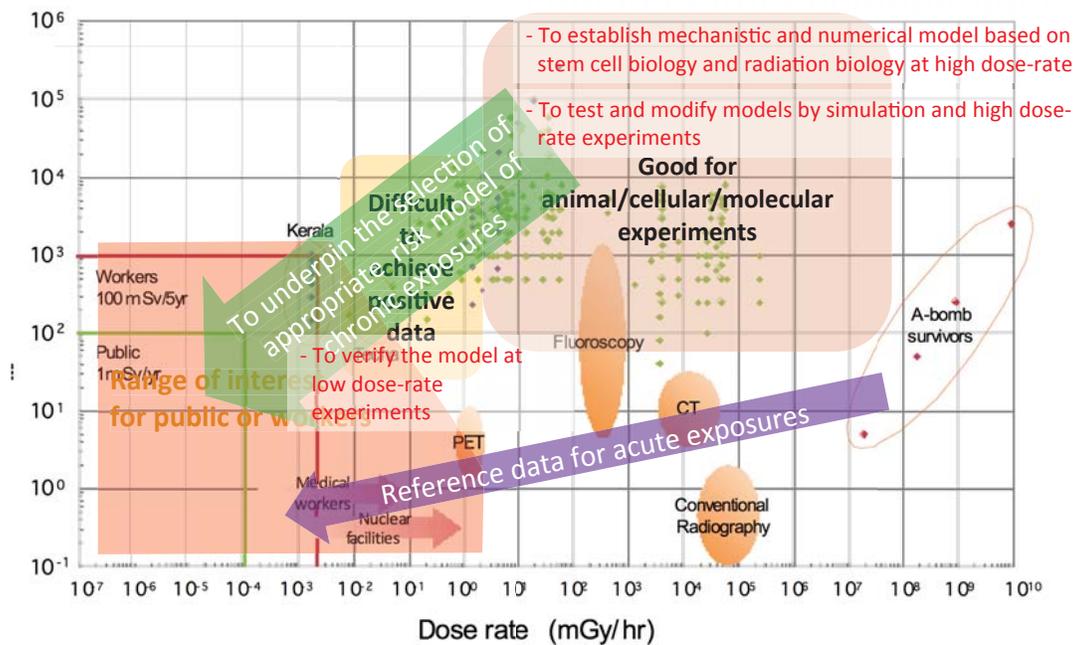


26

# Current status of extrapolation



# Desirable approach



# Prospectus

---

To establish all-Japan network among regulators, academia and research institutes, and other stakeholders (incl. industries)

- To propose strategies to improve quantitative estimation of low dose/low dose-rate risk
  - Top down approach from needs
  - Rolling annually
- To propose support system for cooperation among related experts and institutes

# Schedule

---

## Preparatory committee in NIRS

- Appoint 9 specialists from radiation protection, radiation biology, epidemiology, dose assessment
- Chairman: Dr Michiaki Kai
- 1<sup>st</sup> meeting, 26<sup>th</sup> July
- 2<sup>nd</sup> meeting, 26<sup>th</sup> Sep
- Introduction in JRRS annual meeting, 26<sup>th</sup> Oct
- Comment from high level experts (Jan, 2017)
- Publish a report (Mar, 2017)

## PLANET (tentative name)

- April, 2017?



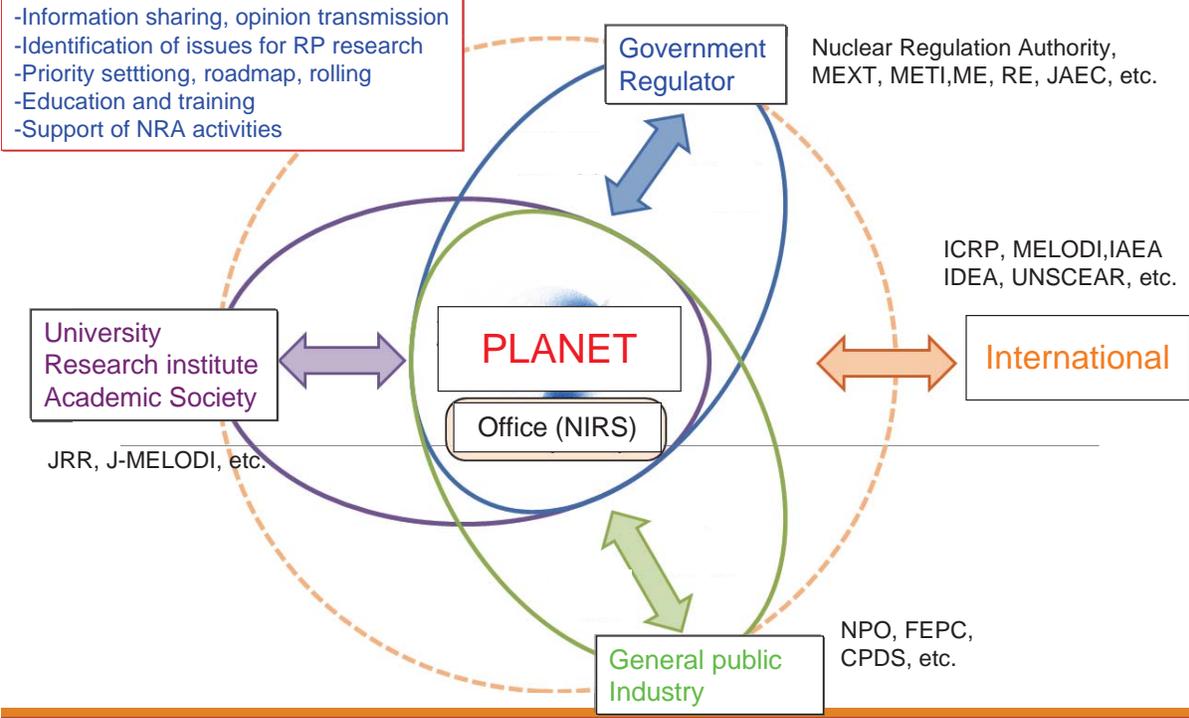
## Issues for research (tentative)

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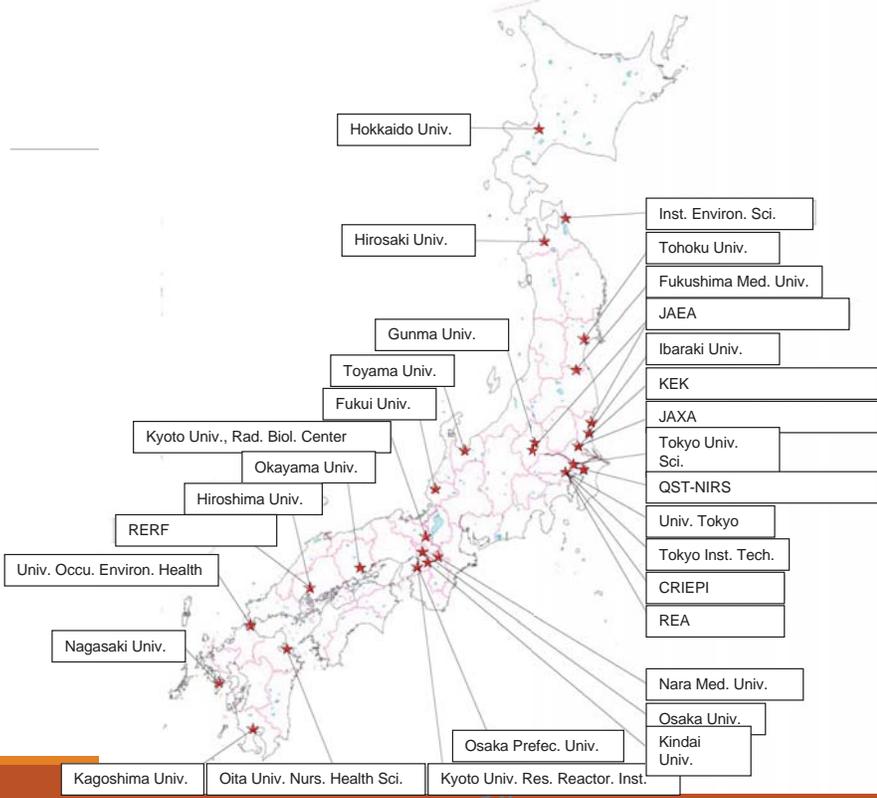
### Target

- Low dose-rate (<6 mGy/hr) and low dose (<100 mGy)
  - Especially (far) less than 1 mGy/hr
    - Range of limited or controversial data
- To improve risk estimation
  - Identify indices relevant to health effects
  - Identify approaches for the indices
    - Epidemiology
    - Animal experiments
    - Molecular and cellular experiments
    - Numerical/mathematical modeling approach
  - Identify priorities from issues/needs strategically

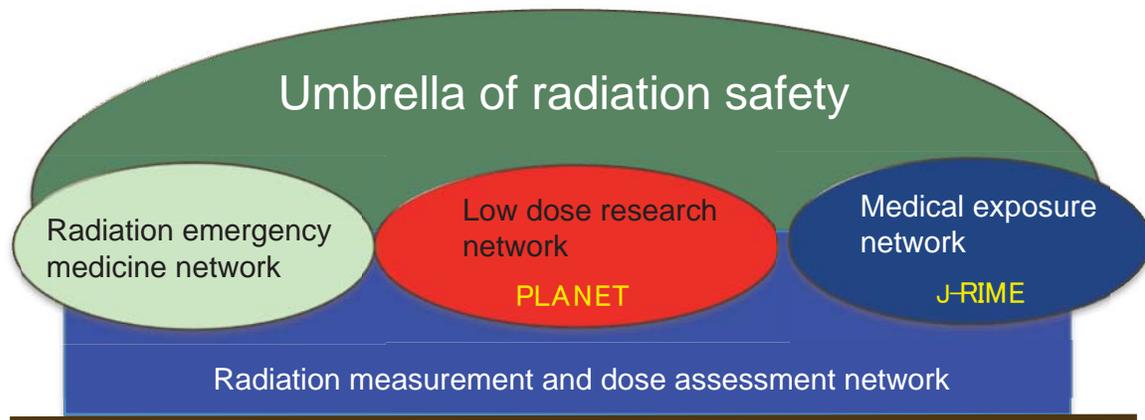
# System of PLANET (tentative)



## Universities and Research Institutes of Radiation Research in Japan



# Future plan of radiation network in Japan



J-RIME: Japan Network for Research and Information on Medical Exposure

## Acknowledgements

Ayaka Hosoki	Masami Ootawara	Shusuke Tani
Ayako Ootsuka	Masaru Takabatake	Toshiaki Kokubo
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Fumiko Watanabe	Mayumi Shinagawa	Yi Shang
Harumi Osada	Misuzu Fujita	Yoshika Kin
Hitomi Seo	Mutsumi Kaminishi	Yoshiko Amasaki
Humiko Mizumoto	Rika Yamada	Yuka Ishida
Kazuhiro Daino	Seiji Kito	Yumiko Sugawara
Kazuko Hirasawa	Shino Takeda	
Kyoko Kadono	Shizue Sasaki	
Mari Ogawa	Shunsuke Yamazaki	
Masaaki Sunaoshi		

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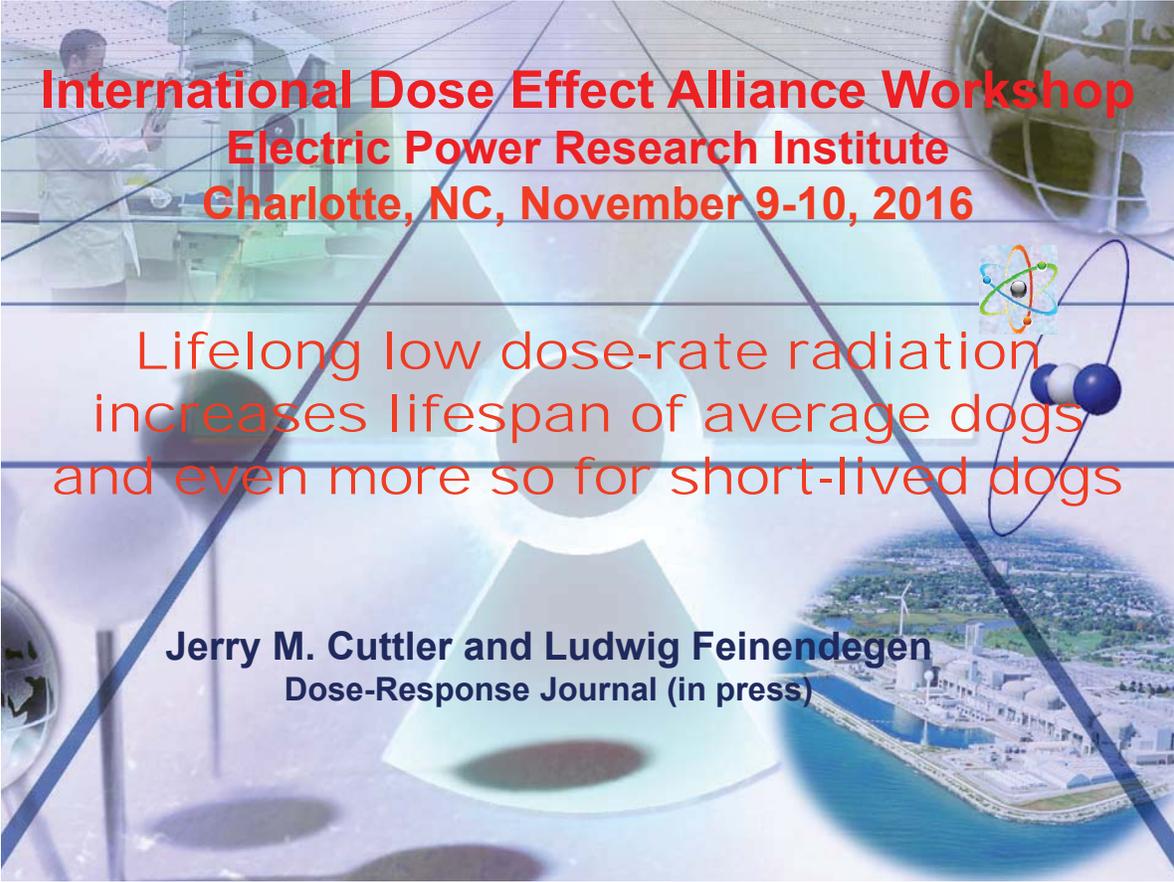
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Thank you for your attention  
and good collaboration with IDEA.

# **21**

**LIFELONG LOW DOES-RATE RADIATION INCREASES  
LIFESPAN OF AVERAGE DOGS AND EVEN MORE SO  
FOR SHORT-LIVED DOGS**

---



**International Dose Effect Alliance Workshop  
Electric Power Research Institute  
Charlotte, NC, November 9-10, 2016**

**Lifelong low dose-rate radiation  
increases lifespan of average dogs  
and even more so for short-lived dogs**

**Jerry M. Cuttler and Ludwig Feinendegen**  
Dose-Response Journal (in press)

**Letter to the Editor**

**The high price of public fear of low-dose  
radiation\***

**Alan E Waltar<sup>1</sup>, Antone L Brooks<sup>2</sup>, Jerry M Cuttler<sup>3</sup>,  
Ludwig E Feinendegen<sup>4,7</sup>, Abel J González<sup>5</sup> and  
William F Morgan<sup>6</sup>**

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<sup>2</sup> DOE Low Dose Radiation Research Program, Washington, DC, USA

<sup>3</sup> Canadian Nuclear Society, Toronto, Canada

<sup>4</sup> Nuclear Medicine, Heinrich-Heine-University, Dusseldorf, Germany

<sup>5</sup> United Nations Scientific Committee on the Effects of Atomic Radiation,  
Buenos Aires, Argentina

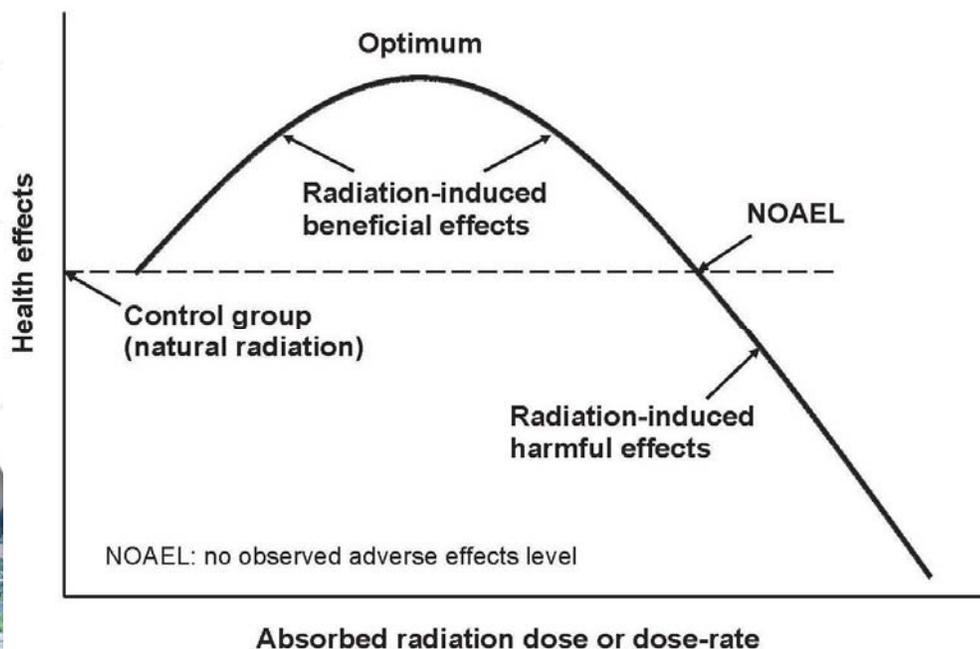
<sup>6</sup> Pacific Northwest National Laboratory, Richland, WA, USA

<sup>7</sup> BECS Department, Brookhaven National Laboratory, Upton, NY, USA

## The basic problem of nuclear energy

- People are *afraid* of nuclear power plants.
- We tell everyone that any *radiation* they receive raises their risk of fatal *cancer*.
- This is the 1950s antinuclear health scare. It is *false*.
- *Low radiation stimulates* adaptive *protection* systems
- The APSs are > 150 genes in humans.
- *High radiation inhibits* or *damages* these systems.
- There is **threshold** for harm for every type of exposure
- Therefore, low dose is beneficial; high dose is harmful
- **Longevity**, not cancer, is best measure of health effect

## Radiation dose-response model



## Longevity is best measure of health effects

- Cancer is the ideal nuclear scare. **We dread it**
- **Cancer** is very complex; has many causes, confounding factors, uncertainties, poorly understood, unpredictable
- **Longevity** is best measure of radiation health effects
- Cameron: early radiologists, nuclear shipyard workers
- Calabrese-Baldwin: gamma radiation **increases median lifespan** of low-dose group by **10 to 30%** over “controls”
- Radiation stimulates the **adaptive protection systems**, which act against the enormous **spontaneous** rate of cell damage **and** against damage by all the other causes

## Nuclear Shipyard Workers Study

John Cameron, APS, Physics and Society, Oct 2001

Table 1

Deaths from All Causes, Person-years and Death Rates<sup>1</sup> for high-dose nuclear workers (NW<sub>>0.5 rem</sub>); low-dose nuclear workers (NW<sub><0.5 rem</sub>); and non-nuclear workers (NNW) (after Matanoski 1991 p. 333)

	High dose	Low dose	Zero dose
Workers in Subset	27,872	10,348	32,510
Person-years	356,091	139,746	425,070
Deaths	2,215	973	3,745
Death Rates Per 1,000 <sup>2</sup>	6.4	7.1	9.0
Death Rate (SMR) <sup>3</sup>	0.76	0.81	1.00
95% C.I. <sup>4</sup>	(0.73, 0.79)	(0.76, 0.86)	(0.97, 1.03)

1 Rates calculated per 1000 person-years.

2 Adjusted for deaths excluded from analysis due to unknown date of death.

3 Using age-calendar time specific rates for U.S. white males.

4 C.I. = 95% Confidence intervals.

## Blood system is very radiation sensitive

### HEMOPOIETIC RESPONSE TO LOW DOSE-RATES OF IONIZING RADIATION SHOWS STEM CELL TOLERANCE AND ADAPTATION

Theodor M. Fliedner Dieter H. Graessle □ Radiation Medicine Research Group and WHO Liaison Institute for Radiation Accident Management, Ulm University, Germany

Viktor Meineke □ Bundeswehr Institute of Radiobiology Affiliated to the University of Ulm, Germany;

Ludwig E. Feinendegen □ Heinrich-Heine-Universität Düsseldorf, Germany, and Brookhaven National Laboratory, Upton, NY, USA

□ Chronic exposure of mammals to low dose-rates of ionizing radiation affects proliferating cell systems as a function of both dose-rate and the total dose accumulated. The lower the dose-rate the higher needs to be the total dose for a deterministic effect, i.e., tissue reaction to appear. Stem cells provide for proliferating, maturing and functional cells. Stem cells usually are particularly radiosensitive and damage to them may propagate to cause failure of functional cells. The paper revisits 1) medical histories with emphasis on the hemopoietic system of the victims of ten accidental chronic radiation exposures, 2) published hematological findings of long-term chronically gamma-irradiated rodents, and 3) such findings in dogs chronically exposed in large life-span studies. The data are consistent with the hypothesis that hemopoietic stem and early progenitor cells have the capacity to tolerate and adapt to being repetitively hit by energy deposition events. The data are compatible with the "injured stem cell hypothesis", stating that radiation-injured stem cells, depending on dose-rate, may continue to deliver clones of functional cells that maintain homeostasis of hemopoiesis throughout life. Further studies perhaps on separated hemopoietic stem cells may unravel the molecular-biology mechanisms causing radiation tolerance and adaptation.

## Blood system responds to chronic radiation

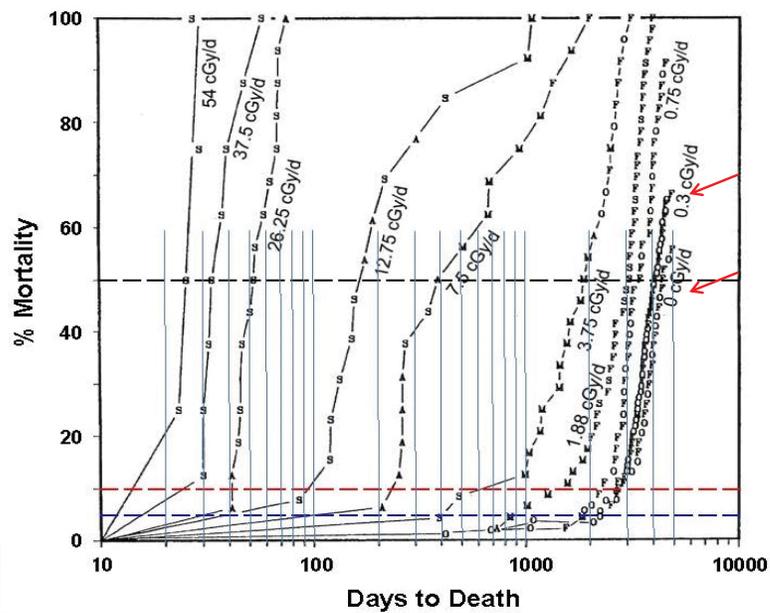
- This paper reviewed histories of **humans** in 10 radiation accidents, 28,000 in Tcha and 1,800 in Mayak, also studies on rats and dogs
- Found that health effect is a function of **dose-rate** and **total dose**
- Blood stem cells tolerate and adapt to *chronic* radiation
- They adapt better at *lower* dose rate
- Radiation clones functioning cells that maintain a lifetime of service
- Beagle dogs in 110 rad/year had same cancer rate as control dogs
- ICRP's 1934 standard: tolerance dose of 0.2 r/day or 50 rad/y is **okay**
- ICRP's LNT & ALARA recommendations are **not** justified

# Continuous Co-60 irradiation of dogs

0.3 cGy/d = 110 cGy/year = 110 rad/year

Blood counts of 0.3 cGy/d same as controls

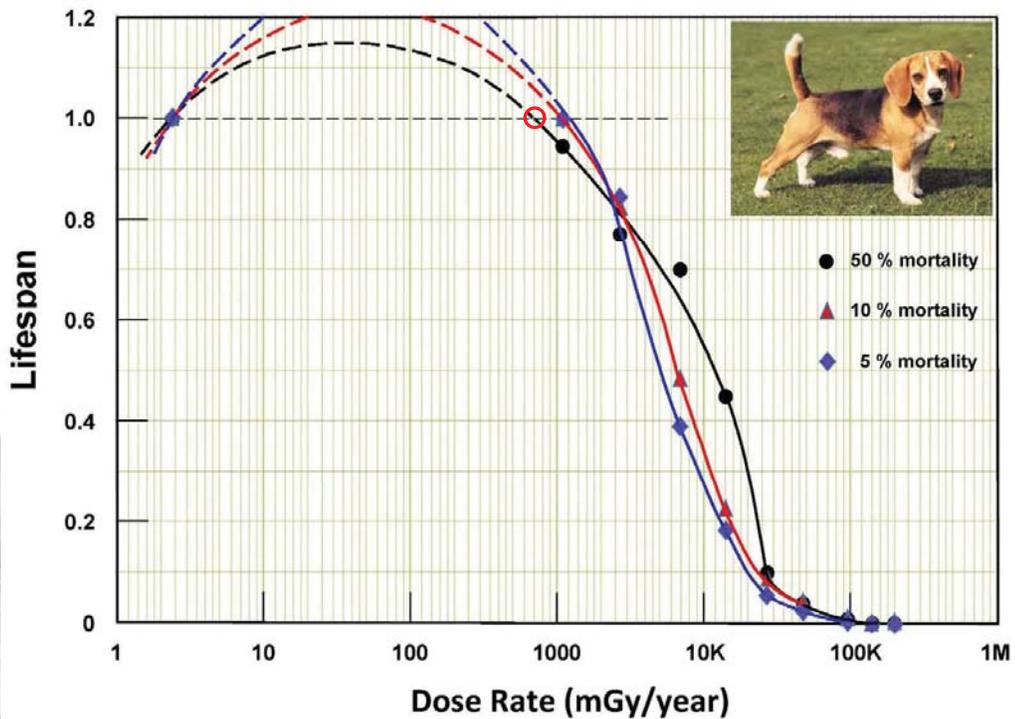
Fatal tumors of 0.3 cGy/d same as controls



Dose Rate (cGy/day)	Dose Rate (mGy/year)	Lifespan (days)			Lifespan (normalized)		
		50% mortality	10% mortality	5% mortality	50% mortality	10% mortality	5% mortality
background	$2.4 \times 10^0$	4300	2700	2150	1.00	1.00	1.00
0.3	$1.1 \times 10^3$	4050	2700	2150	0.94	1.00	1.00
0.75	$2.7 \times 10^3$	3300	2200	1800	0.77	0.82	0.84
1.88	$6.9 \times 10^3$	3000	1300	850	0.70	0.48	0.386
3.75	$1.4 \times 10^4$	1900	600	400	0.44	0.222	0.182
7.5	$2.7 \times 10^4$	400	220	95	0.093	0.081	0.043
12.75	$4.7 \times 10^4$	150	91	40	0.035	0.034	0.0182
26.25	$9.6 \times 10^4$	51	40	30	0.012	0.0148	0.0136
37.5	$1.4 \times 10^5$	32	23	15	0.0074	0.0085	0.0068
54	$2.0 \times 10^5$	24	13	11	0.0056	0.0048	0.0050

## Median lifespan versus Co-60 radiation level

Threshold for shorter lifespan ~ 700 mGy/year



## The key assumption in these analyses

- The exposed dogs at 50, 10 and 5% mortality levels in each dose-rate group would have had the same lifespans as the corresponding control dogs at 50, 10 and 5% mortality levels, if they had not been exposed.
- In other words, we assumed that the chronic exposure to radiation determined lifespan, regardless of the specific cause of death.

## Radiotoxicity of Inhaled $^{239}\text{PuO}_2$ in Dogs

Bruce A. Muggenburg,<sup>a</sup> Raymond A. Guilmette,<sup>a</sup> Fletcher F. Hahn,<sup>a</sup> Joseph H. Diel,<sup>a</sup> Joe L. Mauderly,<sup>a</sup>  
Steven K. Seilkop<sup>b</sup> and Bruce B. Boecker<sup>a,1</sup>

<sup>a</sup>Lovelace Respiratory Research Institute, Albuquerque, New Mexico 87108; and<sup>b</sup>SKS Consulting Services, Siler City, North Carolina 27344

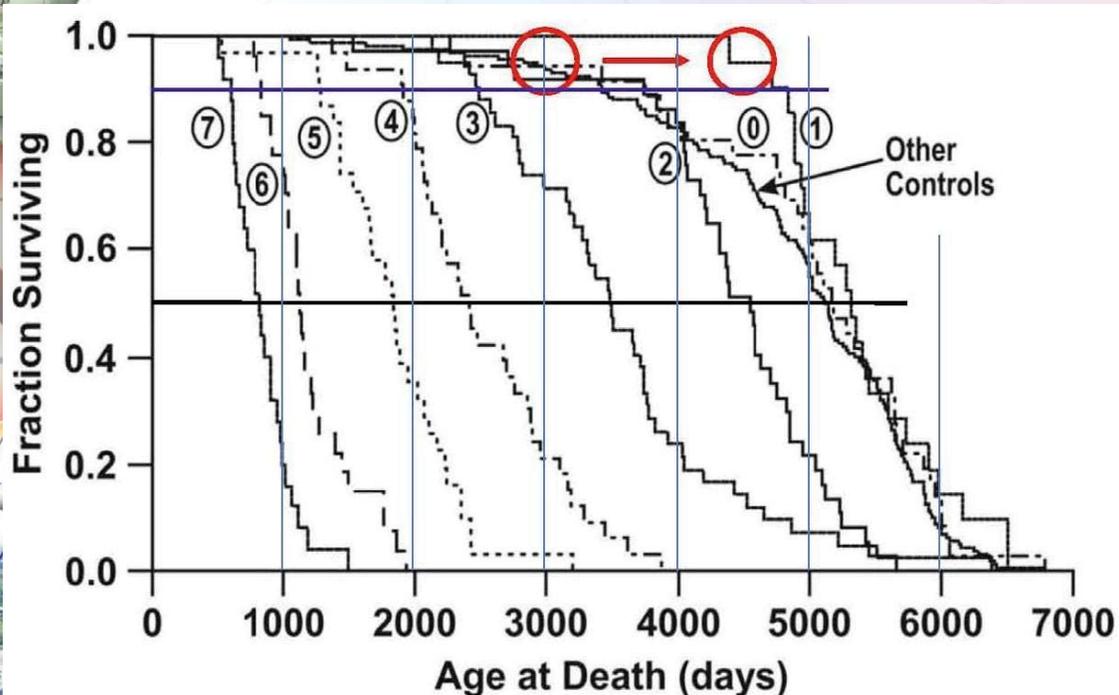
Muggenburg, B. A., Guilmette, R. A., Hahn, F. F., Diel, J. H., Mauderly, J. L., Seilkop, S. K. and Boecker, B. B. Radiotoxicity of Inhaled  $^{239}\text{PuO}_2$  in Dogs. *Radiat. Res.* 170, 736–757 (2008).

Beagle dogs inhaled graded exposure levels of insoluble plutonium dioxide ( $^{239}\text{PuO}_2$ ) aerosols in one of three monodisperse particle sizes at the Lovelace Respiratory Research Institute (LRRRI) to study the life-span health effects of different degrees of  $\alpha$ -particle dose non-uniformity in the lung. The primary noncarcinogenic effects seen were lymphopenia, atrophy and fibrosis of the thoracic lymph nodes, and radiation pneumonitis and pulmonary fibrosis. Radiation pneumonitis/pulmonary fibrosis occurred from 105 days to more than 11 years after exposure, with the lowest associated  $\alpha$ -particle dose being 5.9 Gy. The primary carcinogenic effects also occurred almost exclusively in the lung because of the short range of the  $\alpha$ -particle emissions. The earliest lung cancer was

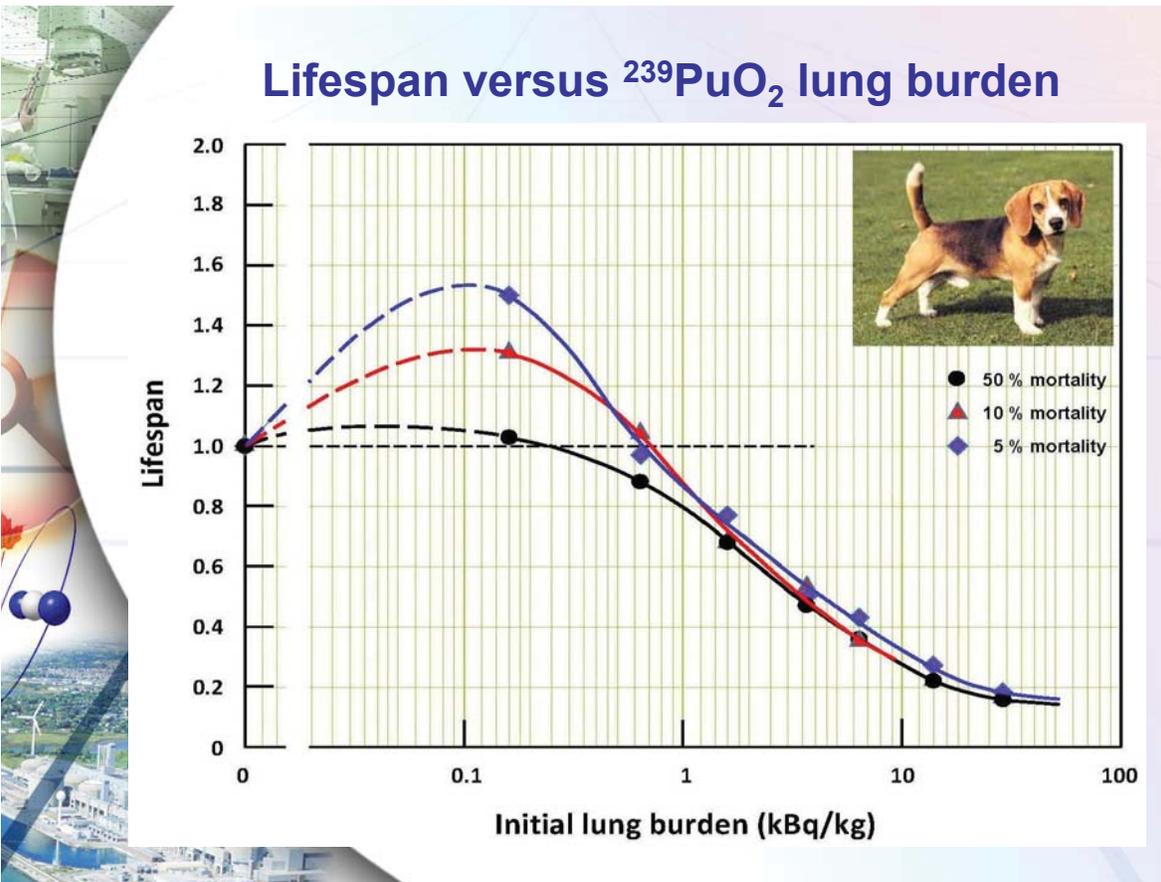
erations, the possibility of plutonium environmental exposure exists through a severe reactor accident such as that at Chernobyl, various nuclear weapons testing activities, and waste disposal practices at various nuclear sites. Of increasing concern is the possible use by terrorists of  $^{239}\text{Pu}$  in an improvised nuclear device (IND) or in a radiological dispersal device (RDD). The inventories of  $^{239}\text{Pu}$  that exist around the world are mainly in the metallic or dioxide form.  $^{239}\text{Pu}$  has a radioactive half-life of about 24,000 years and decays primarily by  $\alpha$ -particle emissions. Due to its abundance and long half-life, accidental and intentional human exposures continue to be important concerns.

In the early years after plutonium was discovered, data on the possible long-term health effects in humans were absent. Therefore, numerous studies of the dosimetry and health effects of internally deposited  $^{239}\text{Pu}$  were conducted in laboratory animals since its discovery more than 60

## Radiotoxicity of inhaled $^{239}\text{PuO}_2$ in beagle dogs



Group	Initial Lung Burden (kBq/kg)	Lifespan (days)			Lifespan (normalized)		
		50% mortality	10% mortality	5% mortality	50% mortality	10% mortality	5% mortality
Control	0	5150	3610	3000	1.00	1.00	1.00
1	0.16	5316	4760	4500	1.03	1.32	1.50
2	0.63	4526	3780	2910	0.88	1.05	0.97
3	1.6	3482	2500	2310	0.68	0.69	0.77
4	3.7	2421	1940	1500	0.47	0.54	0.50
5	6.4	1842	1280	1280	0.36	0.35	0.43
6	14	1122	840	810	0.22	0.23	0.27
7	29	807	625	530	0.16	0.17	0.18



## Hormesis by Low Dose Radiation Effects: Low-Dose Cancer Risk Modeling Must Recognize Up-Regulation of Protection

Ludwig E. Feinendegen, Myron Pollycove, and Ronald D. Neumann

### Contents

1	Introduction.....
2	The Meaning of Absorbed Dose in the Low Dose Region.....
3	Primary Biological Interactions.....
4	Damage to DNA and its Repair.....
5	Hierarchy Level Responses in Biological Systems.....
6	Three Categories of Physiological Defenses of Complex Biological Systems.....
7	Low-Dose Induced Adaptive Protections.....
8	Physiological Defenses Against Cancer.....
9	Damage and Protection in the "Dual-Probability- Model" of Cancer Risk.....
10	Chronic Irradiation.....
11	Conclusion.....
	References.....

### Abstract

Ionizing radiation primarily perturbs the basic molecular level proportional to dose, with potential damage propagation to higher levels: cells, tissues, organs, and whole body. There are three types of defenses against damage propagation. These operate deterministically and below a certain impact threshold there is no propagation. Physical static defenses precede metabolic-dynamic defenses acting immediately: scavenging of toxins;—molecular repair, especially of DNA;—removal of damaged cells either by apoptosis, necrosis, phagocytosis, cell differentiation-senescence, or by immune responses,—followed by replacement of lost elements. Another metabolic-dynamic defense arises delayed by up-regulating immediately operating defense mechanisms. Some of these adaptive protections may last beyond a year and all create temporary protection against renewed potentially toxic impacts also from nonradiogenic endogenous sources. Adaptive protections have a maximum after single tissue absorbed doses around 100–200 mSv and

## Beneficial effects of low radiation

Medical practitioners used radiation ~1900 to ~1960, to:

- Eliminate metastases or slow cancer growth
- Accelerate healing of wounds
- Stop infections: gas gangrene, sinus, inner ear, boils
- Treat arthritis and other inflammatory conditions
- Treat swollen lymph glands
- Cure pneumonia, asthma

with no apparent increase of cancer incidence

**New: Treatment of Alzheimer disease (dementia)**

# Treatment of Alzheimer Disease With CT Scans: A Case Report

Dose-Response:  
An International Journal  
April-June 2016:1-7  
© The Author(s) 2016  
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sagepub.com/journalsPermissions.nav  
DOI: 10.1177/1559325816640073  
dos.sagepub.com



Jerry M. Cuttler<sup>1</sup>, Eugene R. Moore<sup>2</sup>, Victor D. Hosfeld<sup>3</sup>,  
and David L. Nadolski<sup>4</sup>

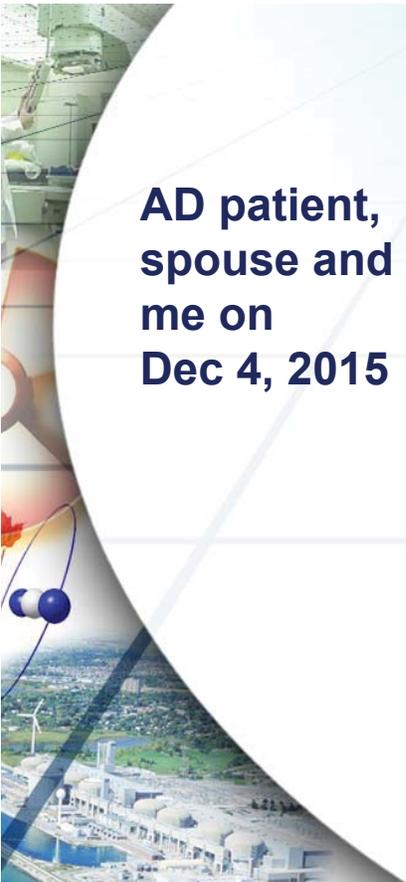
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4826954/> <http://dos.sagepub.com/content/14/2/1559325816640073.full>

## Abstract

Alzheimer disease (AD) primarily affects older adults. This neurodegenerative disorder is the most common cause of dementia and is a leading source of their morbidity and mortality. Patient care costs in the United States are about 200 billion dollars and will more than double by 2040. This case report describes the remarkable improvement in a patient with advanced AD in hospice who received 5 computed tomography scans of the brain, about 40 mGy each, over a period of 3 months. The mechanism appears to be radiation-induced upregulation of the patient's adaptive protection systems against AD, which partially restored cognition, memory, speech, movement, and appetite.

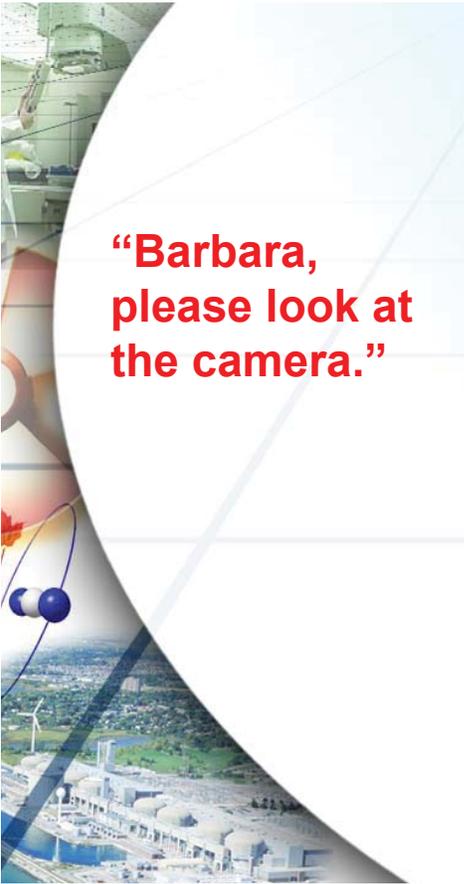
## Keywords

Alzheimer disease, CT scan, adaptive protection systems, ionizing radiation



**AD patient,  
spouse and  
me on  
Dec 4, 2015**



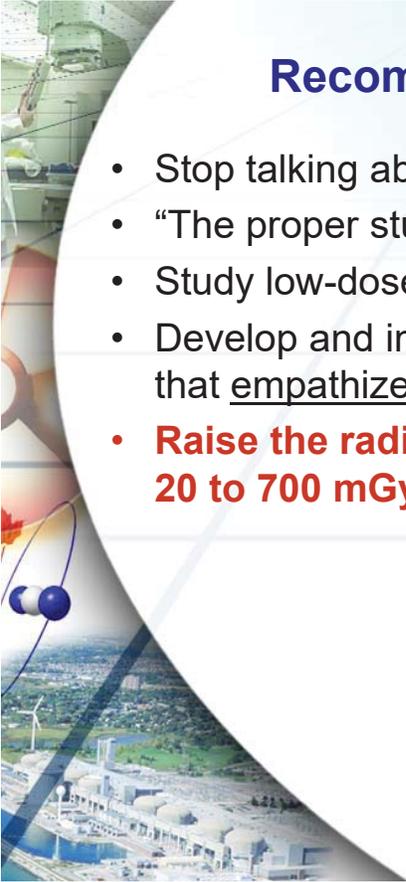


**“Barbara,  
please look at  
the camera.”**



## **Conclusions**

- Short-lived dogs are more radiation sensitive vs. average dogs
- Average and rad-sensitive dogs live longer in a low dose-rate
- Rad-sensitive dogs benefit more from low rad vs. average dog
- Alphas in lungs send signals to stimulate the entire dog's life
- There are dose-rate thresholds for both gammas and alphas
- If dogs are assumed to model humans, then rad-sensitive people would benefit more than average people from radiation



## Recommendations for the future

- Stop talking about cancer risk. Study low-dose stimulation.
- “The proper study of mankind is man.” Alex Pope, 1734
- Study low-dose human health **benefits**, e.g. Alzheimer
- Develop and implement public communication programs that empathize with human fears about radiation effects
- **Raise the radiation level threshold for evacuation from 20 to 700 mGy/year (2 to 70 rad/year)**

Subsequent to the workshop, a paper on dog longevity containing the figures used in the presentation was published, available at <http://journals.sagepub.com/doi/pdf/10.1177/1559325817692903>





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