International Dose Effect Alliance
November 2016 Workshop Proceedings
International Dose Effect Alliance
November 2016 Workshop Proceedings

Final Report, March 2017

EPRI Project Manager
D. Cool

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The Electric Power Research Institute (EPRI) prepared this report:

Principal Investigator
D. Cool

This report describes research sponsored by EPRI.
ABSTRACT

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
EXECUTIVE SUMMARY

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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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PROGRAM: Radiation Safety, 41.09.01

IMPLEMENTATION CATEGORY: Strategic Long-Term
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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 multidisciplinarity; 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 dosemetric 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
EPRI Workshop
International Dose Effect Alliance

Donald A. Cool
Technical Executive

9 November 2016

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

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-Nabuls, 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
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

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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
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
EPRI Workshop Welcome

Mike Howard, Ph.D.
EPRI CEO
International Dose Effect Alliance Workshop
November 9, 2016

Together...Shaping the Future of Electricity

EPRI’s Mission

Advancing *safe*, *reliable*, *affordable* and *environmentally responsible* electricity for society through global collaboration, thought leadership and science & technology innovation
**EPRI 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
EPRI Principles

- Independent
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- Nonprofit
  - Chartered to serve the public benefit
- Collaborative
  - Bring together scientists, engineers, academic researchers, industry experts

Together...Shaping the Future of Electricity
4
MANAGING RISKS FROM LOW-DOSE RADIATION: HOW TO DECIDE
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

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.
Joint Undertakings

- **Information System on Occupational Exposure (ISOE)**
  - Collect and analyse occupational exposure data from NPPs, share exposure management experiences

- **Working Group on Data Analysis (WGDA)**
  - Analysis ISOE data for trends

- **Working Group on Radiological Protection Aspects of Decommissioning Activities at Nuclear Power Plants (WGDECOM)**
  - Occupational exposure management experience and good practice for units in decommissioning

**Upcoming Workshops**

- **Workshop on Management of Non-Nuclear Waste**
  - Legnaro, ITALY, May 2017

- **Workshop on Post-Accident Food Safety Science**
  - (Fukushima, JAPAN, 8-10 November 2016)

**Activities Under Development**

- **International School of Radiological Protection (ISRP)**
  - Sharing Social Media Experience
  - Evacuation Decisions
  - Building Human capital in RP

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

  - 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

  - 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
5
EPRI RADIATION SAFETY PROGRAM
EPRI
Radiation Safety Program

Donald A. Cool
Technical Executive

9 November 2016

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

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.

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.
EPRI Radiation Safety – Technical Strategy Groups

Radiation Management and Source Term (RMST TSG)
Carola Gregorich, cgregorich@epri.com, +1 (650) 855 8917

Groundwater (GW TSG)
Karen Kim, kkim@epri.com, +1 (650) 855 2190

Low Level Waste (LLW TSG)
Karen Kim, kkim@epri.com, +1 (650) 855 2190

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 once (1) per membership period
• Access to
  • Deliverables
  • Collaboration SharePoint
  • Webcasts
  • Workshops

Interactive & Collaborative Peer Groups

Deliverable Types

• Technical Reports
• Technical Updates

• Key Issue Review
• Publication Summary
• Comment Summary
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

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
**EPRI Low Dose Program Research 2016 – 2019**

<table>
<thead>
<tr>
<th>Low Dose Rate Cancer Risks</th>
<th>Emerging Issues Non-Cancer Risks</th>
<th>Global Research Coordination</th>
<th>Communication Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Meta-analysis of influential human data</td>
<td>• Transient Release</td>
<td>• Scientific Advisory Committee</td>
<td>• Focus on messages and presentation of results</td>
</tr>
<tr>
<td>• Animal Data analysis</td>
<td>• Cardiovascular</td>
<td>• International Dose Effect Alliance</td>
<td>• New Deliverables</td>
</tr>
<tr>
<td>• Cancer Risk Modeling</td>
<td>• Lens Dose Workshop</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Adverse Outcome Pathways</td>
<td>• Monitor activities on:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Cellular and Intracellular environment</td>
<td>- CNS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Individual Sensitivity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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
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.
### IDEA Vision

**Mission**
- 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.

**Goals**
- 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.

**Phases**
- Phase 1:
  - Initiate discussions, identify organizations.
  - Organize a first workshop to explore current programs and the possibilities for collaborative activity
  - Publish summary and proceedings as EPRI Technical Report

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**Together…Shaping the Future of Electricity**
6
RADIATION EFFECTS RESEARCH FOUNDATION
CURRENT TOPICS AND FUTURE RESEARCH
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)

**Epidemiological studies**
Life Span Study (120,000), in utero exposed (3,600), F1 (76,000)

**Clinical studies**
Adult Health Study (24,000), in utero (1,000), F1 (12,000)

Vital status and population-based cancer registries
Death and cause of death (all Japan since 1950)
Cancer incidence (in Hiroshima and Nagasaki since 1957/58)

Health examination at ABCC-RERF
Questionnaire survey, physical exam, blood exam,
X-rays/echogram, etc since 1958
Donation of research bio-samples
1. Old (but new) studies on hereditary effects

<table>
<thead>
<tr>
<th>indicator</th>
<th>number</th>
<th>duration</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPO</td>
<td>77,000</td>
<td>1948-1954</td>
<td>no effect</td>
</tr>
<tr>
<td>Sex ratio</td>
<td>140,000</td>
<td>1948-1966</td>
<td>no effect</td>
</tr>
<tr>
<td>Chromosome mutation</td>
<td>16,000</td>
<td>1967-1985</td>
<td>no effect</td>
</tr>
<tr>
<td>Biochemical changes</td>
<td>23,000</td>
<td>1975-1984</td>
<td>no effect</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>80,000</td>
<td>1946 – now</td>
<td>no effect</td>
</tr>
<tr>
<td>Cancer</td>
<td>76,000</td>
<td>1950 – now</td>
<td>no effect</td>
</tr>
</tbody>
</table>

Until now, no discernable effect was found.
Effect of radiation is small enough not to be detected in a population of ≈ 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.

2. Somatic effects: cancer epidemiology

LNT for solid cancer from LSS, 1950-2003

- The linear (L) model (ERR = βd) 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.

- The lowest dose range with a statistically significant trend is 0-0.20Gy with ERR/Gy of 0.56.
- Estimated threshold dose is 0.00Gy and upper 95% confidence limit is 0.15Gy.

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

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

<table>
<thead>
<tr>
<th>Non-cancer outcome</th>
<th>ERR/Gy (95% CI)</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circulatory diseases</td>
<td>0.11 (0.05, 0.17)</td>
<td>19,054</td>
</tr>
<tr>
<td>Respiratory diseases</td>
<td>0.21 (0.10, 0.33)</td>
<td>5,119</td>
</tr>
<tr>
<td>Digestive diseases</td>
<td>0.11 (-0.01, 0.24)</td>
<td>3,394</td>
</tr>
<tr>
<td>Genitourinary diseases</td>
<td>0.14 (-0.06, 0.38)</td>
<td>1,309</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>-0.02 (-0.15, 0.13)</td>
<td>1,962</td>
</tr>
<tr>
<td>Other diseases</td>
<td>0.01 (-0.1, 0.12)</td>
<td>4,847</td>
</tr>
<tr>
<td>External causes</td>
<td>-0.11 (-0.21, 0.02)</td>
<td>2,432</td>
</tr>
</tbody>
</table>

Ozasa, Simizu et al. 2012

---

Somatic effects: non-cancer

<table>
<thead>
<tr>
<th>Disease category (ICD-9 code)</th>
<th>No of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circulatory disease (390-459)</td>
<td>19,054</td>
</tr>
<tr>
<td>Heart disease (390-398, 402, 404, 410-429)</td>
<td>8,463</td>
</tr>
<tr>
<td>Ischemic heart disease (410-414)</td>
<td>3,252</td>
</tr>
<tr>
<td>Myocardial infarction (410)</td>
<td>1,735</td>
</tr>
<tr>
<td>Hypertensive heart disease (402, 404)</td>
<td>922</td>
</tr>
<tr>
<td>Rheumatic heart disease (393-398)</td>
<td>242</td>
</tr>
<tr>
<td>Heart failure (428)</td>
<td>2,983</td>
</tr>
<tr>
<td>Other heart diseases</td>
<td>1,064</td>
</tr>
<tr>
<td>Hypertensive disease without heart diseases (401, 403, 405)</td>
<td>411</td>
</tr>
<tr>
<td>Stroke (430-438)</td>
<td>9,622</td>
</tr>
<tr>
<td>Cerebral infarction (433, 434)</td>
<td>2,659</td>
</tr>
<tr>
<td>Cerebral hemorrhage (431)</td>
<td>4,060</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage (430)</td>
<td>461</td>
</tr>
<tr>
<td>Others or unspecified</td>
<td>2,442</td>
</tr>
<tr>
<td>Other circulatory disease</td>
<td>558</td>
</tr>
</tbody>
</table>

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 artherosclerosis
Increased risk of rheumatic heart disease may be a secondary association, among proximal survivors
Experimental approaches to elucidate the mechanism is based on the artherosclerosis 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


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

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 pubic
7
LOW DOSE-RATE RESEARCH IN CRIEPI
IDEA Workshop 2016
9th 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

http://criepi.denken.or.jp/en/index.html
## History of low dose/low dose-rate radiation research activities in CRIEPI

<table>
<thead>
<tr>
<th>Year</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987~</td>
<td>Pilot study on radiation hormesis</td>
</tr>
<tr>
<td>1988~</td>
<td>Research project on radiation hormesis</td>
</tr>
<tr>
<td>1998</td>
<td>Long-term low dose rate irradiation facility</td>
</tr>
<tr>
<td>2000</td>
<td>Low Dose Radiation Research Center</td>
</tr>
<tr>
<td>2003~</td>
<td>Research project on biological effects of low dose radiation</td>
</tr>
<tr>
<td>2007</td>
<td>Radiation Safety Research Center</td>
</tr>
<tr>
<td></td>
<td>(biology + health physics)</td>
</tr>
<tr>
<td></td>
<td>Low dose microbeam X-ray irradiation facility</td>
</tr>
<tr>
<td>2009~</td>
<td>Research projects on “mechanisms of low dose-RATE radiation effects”</td>
</tr>
<tr>
<td></td>
<td>and “rationalization of radiation protection methods”</td>
</tr>
</tbody>
</table>

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 $\mu$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

- HBR Aria
- Control Aria
- Beach with black sand containing monazite

Kerala
Epidemiological data at low dose-rate

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

![Graph showing excess relative risk vs. dose rate (mGy/year)](From Nair et al. Health Phys 96: 55- (2009))
Dose/dose-rate of interest and studied for biological experiments

- Animal experiments
- Cellular experiments containing conditions less than 6mGy/hr and more than 2-week (and TG91 animal study)

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

- Sufficient data (>1mGy/hr, >a few 10-mGy)
- Limited/ negative data 

Range of interest for public or workers
Current status of extrapolation

- Animal experiments
- Cellular experiments containing conditions less than 6 mGy/hr and more than 2-week (and TG91 animal study)

Limited/negative data

Range of interest for public or workers

Good for animal/cellular/molecular experiments

- To establish mechanistic and numerical model based on stem cell biology and radiation biology at high dose-rate
- To test and modify models by simulation and high dose-rate experiments
- To verify the model at low dose-rate experiments

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
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

High dose rate
- All TSCs are Irradiated at the same time
- Dead cells are replenished by damaged quiescent stem cells

Low dose rate
- The frequency of irradiated TSCs is low
- Competition between TSCs during turnover could cause elimination of damaged TSCs and replacement with intact TSCs

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.

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).
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$^{ERT2}$

By using this method, we can evaluate long-term cumulative effects of low dose-rate radiation.
Radiosensitivity of intestinal stem cells

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

Real time RT-PCR

Quantitative evaluation of Lgr5+ replenishment

Lgr5+ stem cell pool (LacZ+)

Loss of Lgr5+ pool

Replenishment by QSCs

High dose radiation

LacZ+ crypt

LacZ- crypt
Dose-rate effects on Lgr5+ replenishment


Low dose rate irradiation facility @ CRIEPI

Dose-rate effects on Lgr5+ replenishment

Otsuka et al. (manuscript in preparation)
Summary of biological approach

1. Some parameters extracted from modeling approach can be confirmed by biological approach.
2. Colonic Lgr5+ stem cells 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+ 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’

**Organoid model**

- Intact stem cells
- Irradiated stem cells
- Mixed organoid

**Maths model**

- Damage accumulation
- Input biological data

- Which stem cells can be a winner?

Fujimichi et al. (in preparation)

Kondo et al. (in preparation)

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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

- Acute
- Fractionated
- Chronic
- Heart
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
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
LOW DOSE RADIATION RESEARCH IN EUROPE
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
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• 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.

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


Slope: should be commensurate with a proportion of ERR of 15% per Gy

Individual variation of environmental exposure
Radiation risk as perceived by the French public

Mean exposure of the public in France 2013
TOTAL DOSE = 3.7 mSv/year

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

Risk management: decisions, actions and communication to reduce contamination (Bq), reduce doses (msv) and optimize risk impact (not only radiological)

Problem: in absence of scientific consensus different risk perceptions by Experts, People Decision makers
### 4 key EU policy objectives

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

- Enhance multidisciplinarity (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

<table>
<thead>
<tr>
<th>Platforms Projects</th>
<th>MELODI</th>
<th>Alliance</th>
<th>Neris</th>
<th>Eurados</th>
<th>EURAMED</th>
</tr>
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<tbody>
<tr>
<td>DoReMi</td>
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<tr>
<td>EURATOM Call 2016</td>
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<td>✔️</td>
<td>✔️</td>
</tr>
</tbody>
</table>
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))

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 structure**

- **GA/Board**
- **Scientific Committee**
- **Working Groups**
- **50 Member Institutions**
- **Integrative actions**

**Self-governed**
- Open membership
- Perennial

**R&D operational activities**

**WG 0HPEHU LQVWLWXWLRQV, QWHJUDWLYH DFWLRQV**

**WG 0HGLFDO SDUWQHUV 2WKHUORZGRVH 5'SURJUDPPHV -DSDQ86$« (& *$%RDUG, QWHUQDWLRQDO RUJDQLVDWLRQV +(5&$816&($5 &53 0(/2',VWUXFWXUH J'SODWIRUPV ZLWK RWKHU 5'SODWIRUPV JXWXUHMRLQWUHVHDUFK SURMHFWV 5'

**Future joint research projects**

**International organisations:** HERCA, UNSCEAR, ICRP

**Other low-dose R&D programmes (Japan, USA,...)**

**WG:** E&T, SRA Infrastructures...

**50 Member Institutions**

**MELODI: an example of a European R&D associative platform**

**Concert EJP**

European Concerted Programme on Radiation Protection Research - a European Joint Programme

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

**Scientific Advisory Evaluation of CONCERT Activities**

**WP 1 Integration and SRA Development in Radiation Protection Research**

**WP 2 Priority research and joint programming needs in the perspectives of European integration**

**WP 3 Management and of the open R&D calls**

**WP 4**

- WP 5 Scientific and technical development and coordination of scientific, evidence-based and Radiation Protection research
- WP 6 Access to infrastructure
- WP 7 Education and Training

Management and Decision-Making

**WP 6**

- WP 5 Management of CONCERT Programmes and Activities
- WP 6**

**14**
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

CONCERT: an innovative two way street to integration

Spreading excellence, multidisciplinarity, and state of the art knowledge through cooperation, competitive open calls processes, communication

Listening to needs, expression of priorities and innovative ideas, through appropriate mechanisms
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

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
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-oxodGua)
  - 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

Contents

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

Conclusion
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

Potential benefits from increasing R&D cooperation upstream
- Optimisation of use of rare resources,
- Propagation of excellence and multidisciplinarity,
- Acceleration of downstream processes towards radiation protection doctrine establishment (ex: medical care, long distance space travel, rad-waste management, post-accident situations)
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 conference secretariat (need to identify potential signatories!)

Paris, October 10/12 2017: an opportunity to finalise an international low dose R&D cooperation arrangement
Thank you for your attention

R&D modelling objectives:
- Effectiveness and saturation of response mechanisms, *biomarker signatures* function of: dose rate, dose, time (fractionation), energy levels, local/whole body exp, individual factors??

Response mechanisms:
- Immune system
- Stem cell resource
- Intercellular exchange (incl inflammatory response)
- ....

- Apoptosis
- Defective cell
- Cell replacement

- Non cancer pathologies
- Systemic changes (Senescence, ecosystem evolutions, ...)
- Other effects (inc beneficial)
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).

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
9
CERTITUDE ATTITUDE: UNCERTAINTIES AND QUALITY IN RISK ESTIMATES FOR RADIATION-INDUCED DETRIMENT
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

In this world nothing can be said to be certain, except death and taxes.

-- Benjamin Franklin
Death?
Purpose Statements

• Risks of exposure to ionizing radiation are much better known than other agents.
• However, at lower doses (e.g. <100 mGy) 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.

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.
Objectives

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

Paracelsus Quandary

Dose-Response Relationships

Probability of cancer

Background incidence

Background dose

Dose

DDREF?
ICRP Publication 103
Nominal Risk Coefficients for Stochastic Effects after Exposure to Radiation at Low Dose or Low Dose Rate

<table>
<thead>
<tr>
<th>Exposed Population</th>
<th>Cancer (%/Sv)</th>
<th>Heritable (%/Sv)</th>
<th>Total (%/Sv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole</td>
<td>5.5</td>
<td>0.2</td>
<td>5.7</td>
</tr>
<tr>
<td>Adult</td>
<td>4.1</td>
<td>0.1</td>
<td>4.2</td>
</tr>
</tbody>
</table>

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.

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.
Inference and Uncertainty Propagation

- **Statistical Inference** – based on data and models used to analyze it.
- **Probability Density Functions** (likelihood).
- Frequentist (A-Bomb).
- Baysian – use prior to estimate posterior. Good for limited data or doses using Monte Carlo modeling.

- **Propagation** – combined statement of overall uncertainty.
- **Sensitivity analyses** on model inputs can help ID largest influencers.

Statistical Power – Data Needed are Large at Low Doses

- Required sample size vs dose (mGy) for different cancer categories:
  - All cancers
  - Leukemia
  - Respiratory
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.

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.
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’.

- 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.
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...

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

George E.P. Box, 1987


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.
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?

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)
Systematic Literature Review

Search and Identify
Assess Quality
Meta-Analysis

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,1 Daniel Reyner,1 and Cheryl Siegel Scott2
1Environmental and Occupational Health Sciences Institute, UMDNJ—Robert Wood Johnson Medical School, Piscataway, New Jersey USA;
2U.S. Environmental Protection Agency, Washington, DC USA

Environmental Health Perspectives • Vol 108, Supplement 2 • May 2000
Quality Scoring of Literature

- Assess for methodological strengths and weaknesses/limitations.
- Transparent Criteria
  - $0 = \text{expected design}$
  - $+1 = \text{strength}$
  - $-1 = \text{shortcoming}$
- Sum Score
- Classify Studies by Quality Tiers

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.
Cataract Risks – ICRP-118

- Absorbed Dose Eye (Gy)
  - Cataract Threshold: 5 Gy
  - Lens Opacity Threshold: 5 Gy
  - Yearly Limit: 0.15 Gy/year

- Old Limit: ~4.5 Gy Career
- New Limit: ~0.5 Gy Career

EPRI – Cataract Risk Epi Evaluation

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

EPRI Cataracts Review 2014 – REF.

  - http://www.epri.com/abstracts/Pages/ProductAbstract.aspx?productId=00000003002003162
EPRI – CVD Risk Epi Evaluation
DRAFT – Work in Progress

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

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.
- 2nd Cancer studies.
- Non-cancer studies (CVD).
- How to incorporate radiobiologics?
  - Markers of low dose?

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.
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?

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.
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.

Additional Information on Uncertainties in Radiation Risks

- UNSCEAR-2012; UNSCEAR-2013.
- NCRP-158, NCRP-163, NCRP-164, NCRP-171
- Dauer, Health Physics, 2011.
- Preston et al, JRP, 2013.
- Walsh, Shore, Auvinen, Jung, Wakeford, CT Epidemiology, JRP, 2014.
- EPRI – Cataracts, 2014.
- Bouville et al, 2015, Health Physics.
Certitude Attitude: Uncertainties in Risk Estimates for Radiation-Induced Detriment

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

dauerl@mskcc.org
10
THE ONE MILLION U.S. PERSONS STUDY OF LOW-DOSE RADIATION EFFECTS (MPS): DOSIMETRY ASPECTS
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

- 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?

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

- 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.

Sub-cohorts of the MPS

<table>
<thead>
<tr>
<th>Sub-Cohort</th>
<th>Number of Subjects</th>
<th>Status of analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOE - Manhattan Project</td>
<td>360,000</td>
<td>Partially completed</td>
</tr>
<tr>
<td>DOD - Atomic Veterans</td>
<td>115,000</td>
<td>Completed?</td>
</tr>
<tr>
<td>Industrial Radiographers</td>
<td>126,000</td>
<td>Dose records collected</td>
</tr>
<tr>
<td>Medical &amp; Related</td>
<td>255,000</td>
<td>Dose records collected</td>
</tr>
<tr>
<td>Nuclear Utility Workers</td>
<td>145,000</td>
<td>Dose records collected</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1,001,000</td>
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</tr>
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</table>
Sponsors – A National Effort

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

A Bouville
R Toohey
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: 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.
Radiation-weighted career lung doses (mGy) of the Rocketdyne workers

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

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

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

Available data and results: ATOMIC VETERANS
Atomic Veterans

<table>
<thead>
<tr>
<th>Whole-body dose (mGy)</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>63,193</td>
<td>55.6</td>
</tr>
<tr>
<td>5 - &lt;10</td>
<td>19,969</td>
<td>17.6</td>
</tr>
<tr>
<td>10 - &lt;25</td>
<td>18,791</td>
<td>16.6</td>
</tr>
<tr>
<td>25 - &lt;50</td>
<td>9,658</td>
<td>8.5</td>
</tr>
<tr>
<td>50 - &lt;100</td>
<td>1,700</td>
<td>1.5</td>
</tr>
<tr>
<td>100 - &lt;250</td>
<td>227</td>
<td>0.2</td>
</tr>
<tr>
<td>250 - &lt;500</td>
<td>40</td>
<td>0.04</td>
</tr>
<tr>
<td>500 - &lt;1,000</td>
<td>2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>All</td>
<td>113,580</td>
<td>100</td>
</tr>
</tbody>
</table>

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

Available data and results:
INDUSTRIAL RADIOGRAPHERS
Industrial Radiographers: $H_p(10)$ Dose Distribution

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

Available data and results: MEDICAL WORKERS
## Medical Workers - Landauer Data

**Hp(10) Cumulative Dose Distribution (mSv)**

<table>
<thead>
<tr>
<th>Recorded dose (mSv)</th>
<th>Number of workers</th>
<th>% of workers</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 - &lt;25</td>
<td>122,324</td>
<td>50.3</td>
</tr>
<tr>
<td>25 - &lt;50</td>
<td>60,470</td>
<td>24.8</td>
</tr>
<tr>
<td>50 - &lt;100</td>
<td>36,403</td>
<td>15.0</td>
</tr>
<tr>
<td>100 - &lt;250</td>
<td>19,230</td>
<td>7.9</td>
</tr>
<tr>
<td>250 - &lt;500</td>
<td>3,811</td>
<td>1.6</td>
</tr>
<tr>
<td>500 - &lt;1,000</td>
<td>910</td>
<td>0.4</td>
</tr>
<tr>
<td>1,000+</td>
<td>300</td>
<td>0.1</td>
</tr>
<tr>
<td>All</td>
<td>243,448</td>
<td>100</td>
</tr>
</tbody>
</table>

*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

---

### 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

<table>
<thead>
<tr>
<th>Work Function</th>
<th>% Collective Dose (1975-1985)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactor Operations and Surveillance</td>
<td>9-13%</td>
</tr>
<tr>
<td>Routine Maintenance</td>
<td>27-53%</td>
</tr>
<tr>
<td>Inservice Inspection</td>
<td>3-9%</td>
</tr>
<tr>
<td>Special Maintenance</td>
<td>19-47%</td>
</tr>
<tr>
<td>Waste Processing</td>
<td>3-7%</td>
</tr>
<tr>
<td>Refueling</td>
<td>4-8%</td>
</tr>
</tbody>
</table>
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 μCi, radionuclide
- Name, SSN, DOB

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

<table>
<thead>
<tr>
<th>Recorded Dose (mSv)</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>26,330</td>
<td>18.1</td>
</tr>
<tr>
<td>5 - &lt;10</td>
<td>3,620</td>
<td>2.5</td>
</tr>
<tr>
<td>10 - &lt;25</td>
<td>44,269</td>
<td>30.5</td>
</tr>
<tr>
<td>25 - &lt;50</td>
<td>29,635</td>
<td>20.4</td>
</tr>
<tr>
<td>50 - &lt;100</td>
<td>21,734</td>
<td>15.0</td>
</tr>
<tr>
<td>100 - &lt;250</td>
<td>15,947</td>
<td>11.0</td>
</tr>
<tr>
<td>250 - &lt;500</td>
<td>3,379</td>
<td>2.33</td>
</tr>
<tr>
<td>500 - &lt;1000</td>
<td>306</td>
<td>0.21</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>All</td>
<td>145,227</td>
<td>100</td>
</tr>
</tbody>
</table>
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 $D_T$
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

Multiple Dosimetry...

ORNGL Study for Cranial or Caudal Geometries

Then: Highest Reading = DDE
Now: ANSI/HPS N13.41
EPRI Task Reports, Xu HPJ 2006.
NRC Reg Guide 8.40 (EDEX)
D/Hp(10): AP geometry, male workers

D/Hₚ(10): Caudal-cranial geometry, male workers
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 \(1.02 \pm 0.09\)

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
- 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, Atwell@ncrponline.org, or abouville@aol.com

List of publications (dosimetry)


List of publications (epidemiology)


Thank you for your attention
OVERVIEW OF THE UNITED STATES DEPARTMENT OF ENERGY RADIATION HEALTH STUDIES PROGRAMS
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
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.

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
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.

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.
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

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
History of Health Studies at the Department of Energy

AEC $\rightarrow$ Energy Research and Development Administration 1974 $\rightarrow$
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

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
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

Epidemiologic Studies of DOE Workers

N ~ 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)
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.

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.orau.gov/CEDR/default.aspx
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.orau.gov/CEDR/default.aspx

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.
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.

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**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.
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.

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
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.

- 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.
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

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.
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.
(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.

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

Isaf.Al-Nabulsi@hq.doe.gov
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APPROACHES TO STUDYING THE BIOLOGICAL BASIS OF DOSE-RESPONSE
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?

Organism
Tissue
Cellular
Molecular

Early Intermediate Late
It’s the biology...

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
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.

Witse 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. Hornung, Rodney D. Johnson, David R. Mount, John W. Nichols, Christine L. Russom, Patricia K. Schmieder, Jose A. Serrano, 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 condom Boulevard, Duluth, Minnesota 55810

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 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

Molecular initiating event: Aromatase inhibition

Testosterone

17β-estradiol (E2)
Structure of the AOP

- Aromatase Inhibition
- Granulosa: Reduced E2 synthesis
- Circulation: Reduced E2 concentration
- Hepatocyte: Reduced VTG production
- Circulation: Reduced VTG concentration
- Ovary: Impaired Oocyte Dev.
- Female: Decreased ovulation/spawning
- Population: Declining Trajectory

Data supporting the AOP

- Aromatase inhibition
- Reduced E2, Vtg synthesis
- Impaired vitellogenesis/oocyte dev.
- Reduced fecundity

Temporal concordance of key events

QJPO +RXU +RXU +RXU

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

Qualitative: Defines association between a molecular initiating event and an adverse outcome.

Quantitative: Dose-response and time-course predictions

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
The computational model reflects current understanding

Model draft

Experimental data
Biological knowledge

Comparison with experimental data

In silico analysis

Hypotheses formulation

Model refinement

Validated model


The qAOP:
A combination of linked quantitative models

HPG axis model

Aromatase Inhibition → Granulosa Reduced E2 synthesis → Circulation Reduced E2 concentration → Hepatocyte Reduced VTG production → Circulation Reduced VTG concentration

Oocyte growth dynamics model

Ovary Impaired Oocyte Dev. → Female Decreased ovulation/spawning

Population dynamics model

Population Declining Trajectory
Fathead minnow HPG axis model

Homeostasis:
Adaptation/Compensation
Adaptation: Plasma estradiol in fathead minnows exposed to fadrazole

![Graph showing plasma estradiol levels in control (CON), FAD-3, and FAD-30 groups over time.

Villeneuve et al. (2010) EHP

HPG axis model: Effect of aromatase inhibition on venous estradiol

![Graph showing venous estradiol levels over time, comparing simulated and measured FAD 30 ug/L.

Simulate FAD 30 ug/L
Measured FAD 30 ug/L

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HPG axis model:
Effect of aromatase inhibition on venous VTG

A. Simulated control
  Lab control

B. Simulated FAD 0.5 µg/L
  Lab FAD 0.5 µg/L

C. Simulated FAD 3 µg/L
  Lab FAD 3 µg/L

D. Simulated FAD 30 µg/L
  Lab FAD 30 µg/L

Oocyte growth dynamics model:
Predicts fecundity based on VTG levels

A. Model prediction
  Laboratory data

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

B. Effects of fadrozole on predicted fecundity vs lab results
Population dynamics model:
Prediction of population dynamics

The aromatase inhibition QAOP

HPG axis model
- Aromatase Inhibition
- Granulosa Reduced E2 synthesis
- Circulation Reduced E2 concentration
- Hepatocyte Reduced VTG production
- Circulation Reduced VTG concentration

Oocyte growth dynamics model
- Ovary Impaired Oocyte Dev
- Female Decreased ovulation/spawning

Population dynamics model
- Population Declining Trajectory
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

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.
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

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.
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**
- **USEPA-RTP, NC**
  - R. Conolly, W. Cheng (STD)

End
Extrapolation
Extrapolation

Extrapolation
**Oocyte growth dynamics model**
*(Egg development in the fathead minnow ovary)*
Adaptation: Plasma estradiol in fathead minnows exposed to fadrazole

Plasma E2

(ReLU - Relative to control; log 2)

0 2 6 8 12 14 16

direct effect compensation recovery

CON

FAD-3

FAD-30

Plenty of published guidance on good modeling practice
Confidence (uncertainty\textsuperscript{-1})

- 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

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
Errors in model

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

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
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:

HPG axis model
- Activation Inhibition
- Graphine Reduced E2 synthesis
- Circulation Reduced E2 Concentration
- Oocyte Reduced VTG production
- Circulation Reduced VTG concentration

Oocyte growth dynamics model
- Quick Impacted Oocyte Dev.
- Female Decreased Ovulation/suppression

Population dynamics model
- Population Declining Trajectory

Key events:
Reduced VTG in circulation

![Graph showing plasma VTG (fold-change relative to control: log2) over days for different treatments.]

○ Control  ▬ Fad 3 ug/L  ▬ Fad 30 ug/L

Computers are essential
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LOW DOSE RESEARCH AT CHALK RIVER LABORATORY
Low Dose Research at Chalk River Laboratory

EPRI IDEA Workshop

November 9, 2016
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

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
Missions
A broad mandate, serving both government and private sector

Decommissioning & Waste Management
Science and Technology for Government
Science and Technology for Industry

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
- Gammarcell 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 m² 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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**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
Gamma Beam Irradiation Facility

Two gamma irradiation devices in a 30 m long irradiation hall

GB 150C Irradiator

Irradiation Hall (Animals and Cells)

GC60-1000 Irradiator

Gamma Beam Irradiation Facility

Two gamma irradiation devices in a 30 m long irradiation hall

Gamma Beam Irradiation Facility

Two gamma irradiation devices in a 30 m long irradiation hall

Gamma Beam Irradiation Facility

Two gamma irradiation devices in a 30 m long irradiation hall

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$^2$/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)

HPNG Facility

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

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

**Objective:** examine relative effectiveness of internal beta-irradiation from 3H 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?
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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
  - Pre- and post-exposure individual risk and/or countermeasures

General populations

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

- Self-sufficiency in growth signaling
- Insensitivity to growth inhibition signaling
- Limitless replicative potential
- Evasion of programmed cell death
- Sustained angiogenesis
- Activating invasion and metastases

Conditions for Carcinogenesis

Emerging Hallmarks

- Deregulating cellular energetics
- Avoiding immune destruction
- Tumor-promoting inflammation
- Genome instability and mutation

Emerging Characteristics

Genetic diversity

Hanahan & Weinberg, Cell 2011.

Conditions for Carcinogenesis

Emerging Hallmarks

- Deregulating cellular energetics
- Avoiding immune destruction
- Tumor-promoting inflammation
- Genome instability and mutation

Emerging Characteristics

Reprogramming (energy) metabolism

cancer versus normal cells → disrupted microenvironment

Hanahan & Weinberg, Cell 2011.
Altered immune function
Aberrant molecular signaling
Chronic oxidative stress
Cell loss

Dysregulated microenvironment

Normal tissue disease/dysfunction (e.g. pneumonitis, cardiac dysfunction, sarcopenia, cognitive deficits, fracture, myelodysplastic syndrome)


Chronic oxidative stress
Altered immune function
Aberrant molecular signaling
Cell loss

Dysregulated microenvironment

Chromosomal mutation

Normal tissue disease/dysfunction (e.g. pneumonitis, cardiac dysfunction, sarcopenia, cognitive deficits, fracture, myelodysplastic syndrome)

Primary and secondary tumors

Cell Signals as Biomarkers of Microenvironmental Disruption

1. Cell loss/death

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. NFκB, 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
deadth (e.g. NFκB, 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, TNFα, IFNγ, TGFα, PDGF, TGFβ, bFGF,
     IL6 – some found in circulation/urine/saliva

IL6 – Some found in circulation/urine/saliva
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. NFκB, 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

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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
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LOW DOSE RISKS – ANIMAL EXPERIMENTS
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)

- 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
Linear Non-Threshold Radiation Dose Response Model

Sparse data

Data on radiation-induced cancer

Cancer Frequency

Hypersensitive response?

Adaptive response?

Dose

Background Cancer Rate
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 1. Relationship between causes of death and daily dose rate (average absorbed dose) in adult beagles exposed continuously (22 h day⁻¹) to ⁶⁰Co γ-irradiation.


Figure 2. Relationship between dose rate, time to death and causes of death in adult beagles continuously irradiated (22 h day⁻¹) at several dose rates (rads day⁻¹; average absorbed dose).

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.


Use of Animal Archives – Evaluation of DDREF
Risk

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

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)

- 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

### ERR
- \( \alpha \text{Dose} + \beta \text{Dose}^2 \)

### DDREF
- acute / protracted
- \( \frac{\alpha D + \beta D^2}{\alpha D} \) / \( \alpha D \)

### LSS DDREF
(at 1 Gy)
- Estimated to be 1.5 (1.1 - 2.3) by the BEIR VII committee.

LSS cohort

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

- 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**
\[
1 + \frac{\beta}{\alpha} = 1 + \theta
\]

Radiobiological prior = ORNL Animal Data

---

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

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 I)

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

Analyzed
- Red boxes indicate the groups used to estimate DDREF.

### TABLE I

<table>
<thead>
<tr>
<th>Strain and sex</th>
<th>Dose (rad)</th>
<th>No. of mice exposed</th>
<th>No. lost to follow-up*</th>
<th>Mean age at death (days ± SE)</th>
<th>Life shortening (days ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFM 2</td>
<td>0</td>
<td>4014</td>
<td>457</td>
<td>633.2 ± 2.86</td>
<td>—</td>
</tr>
<tr>
<td>16</td>
<td>2627</td>
<td>48</td>
<td>28.7 ± 1.1</td>
<td>533.8 ± 3.11</td>
<td>29.9 ± 4.34</td>
</tr>
<tr>
<td>28</td>
<td>952</td>
<td>7</td>
<td>0.9 ± 1</td>
<td>610.6 ± 2.82</td>
<td>24.1 ± 6.02</td>
</tr>
<tr>
<td>58</td>
<td>1143</td>
<td>34</td>
<td>555.8 ± 3.21</td>
<td>88.4 ± 1.99</td>
<td>11.6 ± 5.9</td>
</tr>
<tr>
<td>73</td>
<td>216</td>
<td>1</td>
<td>335.3 ± 11.19</td>
<td>90.4 ± 11.81</td>
<td>11.4 ± 5.81</td>
</tr>
<tr>
<td>100</td>
<td>1100</td>
<td>16</td>
<td>336.5 ± 3.1</td>
<td>98.1 ± 6.77</td>
<td>11.6 ± 5.91</td>
</tr>
<tr>
<td>150</td>
<td>1084</td>
<td>10</td>
<td>406.4 ± 3.27</td>
<td>149.2 ± 6.45</td>
<td>11.7 ± 5.93</td>
</tr>
<tr>
<td>200</td>
<td>333</td>
<td>2</td>
<td>672.1 ± 5.55</td>
<td>162.0 ± 10.00</td>
<td></td>
</tr>
<tr>
<td>300</td>
<td>4333</td>
<td>517</td>
<td>471.7 ± 2.67</td>
<td>218.1 ± 3.98</td>
<td></td>
</tr>
<tr>
<td>400</td>
<td>396</td>
<td>1</td>
<td>303.3 ± 7.28</td>
<td>311.0 ± 7.63</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE II**

<table>
<thead>
<tr>
<th>Strain and sex</th>
<th>Dose rate (rad/min)</th>
<th>Dose (rad)</th>
<th>No. of mice exposed</th>
<th>No. lost to follow-up*</th>
<th>Mean age at death (days ± SE)</th>
<th>Life shortening (days ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFM 2</td>
<td>0</td>
<td>740</td>
<td>2</td>
<td>641.4 ± 0.96</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>50</td>
<td>775</td>
<td>17</td>
<td>573.0 ± 0.97</td>
<td>67.5 ± 8.4</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>605</td>
<td>769</td>
<td>2</td>
<td>480.5 ± 0.45</td>
<td>100.9 ± 8.78</td>
<td></td>
</tr>
<tr>
<td>0.00009</td>
<td>50</td>
<td>1469</td>
<td>11</td>
<td>614.2 ± 4.10</td>
<td>28.7 ± 7.26</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>1833</td>
<td>9</td>
<td>698.2 ± 4.36</td>
<td>42.7 ± 7.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200</td>
<td>3221</td>
<td>13</td>
<td>564.1 ± 4.70</td>
<td>77.3 ± 7.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>400</td>
<td>865</td>
<td>2</td>
<td>494.8 ± 5.60</td>
<td>166.8 ± 8.36</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Storer, 1979 (link)

---

**Other archived data**

**European Radiobiology Archives (ERA)**

<table>
<thead>
<tr>
<th>Labs</th>
<th>Studies</th>
<th>Groups</th>
<th>Animals total</th>
<th>Animals with data</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERA</td>
<td>21</td>
<td>4,623</td>
<td>232,587</td>
<td>93,445</td>
</tr>
<tr>
<td>NRA</td>
<td>11</td>
<td>1,861</td>
<td>190,471</td>
<td>115,801</td>
</tr>
<tr>
<td>JRA</td>
<td>14</td>
<td>376</td>
<td>29,537</td>
<td>3,396</td>
</tr>
<tr>
<td>Sum</td>
<td>46</td>
<td>6,851</td>
<td>452,595</td>
<td>212,642</td>
</tr>
</tbody>
</table>

**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.

**Janus Tissue Archive**

Janus Radiobiology Archives (link)
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

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)).

(Ozasa et al Radiat Res. 2012;177: 229–43.)
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 UC Davies)
  - 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/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**

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

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**

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>ERA Identifier</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1003-21-6</td>
<td>This treatment group was abandoned. Cause of death is listed as 'abandon' or 'remove to another experiment'.</td>
<td></td>
</tr>
<tr>
<td>11-2-79</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>11-2-80</td>
<td>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 Ulrich and Storer.</td>
<td></td>
</tr>
<tr>
<td>11-2-81</td>
<td>These groups are identical to those listed in study 3-2.</td>
<td></td>
</tr>
<tr>
<td>1007-3-8</td>
<td>No external data source was found to confirm the treatments and lifespans in this study.</td>
<td></td>
</tr>
<tr>
<td>1007-3-16</td>
<td>No external data source was found to confirm the treatments and lifespans in this study.</td>
<td></td>
</tr>
</tbody>
</table>

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

\[
DDREF = \frac{\text{acute risk}}{\text{protracted risk}} = \frac{\alpha \cdot \text{dose} + \beta \cdot \text{dose}^2}{\alpha \cdot \text{dose}} = 1 + \frac{\beta}{\alpha} \cdot \text{dose}
\]

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

...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

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)

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

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

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

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.

“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

---

**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:

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

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

- DNA
  - DNA modifications: histones, methylation...
- *tRNA*
- *rRNA*
- *mRNA*
  - RNA modulation by degradation...
- *proteins*
  - protein modifications: ubiquitination, phosphorylation...

* “Full” information accessible (often through heroic efforts and only from POOLED cells)

Key Biological Molecules 2016

- *DNA*
  - DNA modifications: histones (acetylation etc.), methylation...
- *tRNA*
- *rRNA*
- *mRNA*
  - RNA modulation by degradation... in dozens of ways
- *micro RNA*
- *long noncoding RNA*
- *circular RNA*
- *proteins*
  - protein modifications: ubiquitination, phosphorylation, SUMOylation, NEDylation, acetylation,...

* Full information accessible and often from individual cells
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 overprotecting the population at low doses and low-dose rates.
- International collaboration has enhanced dataset availability and conclusions that can be drawn.
16
RESEARCH NEEDS IN THE LOW-DOSE RADIATION FIELD
Research Needs in the Low-dose Radiation Field

Mohan Doss, PhD, MCCPM  
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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.

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?
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.

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?

15-Country Study of Radiation Workers

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


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.
Effect of prolonged low-dose radiation exposures on cancer

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.

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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 ~0.25 Gy, decreases with dose from ~0.25 to ~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.
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. \((\text{Doss, 2012}), (\text{Doss, 2013})\)

Since the publication of the \((\text{Ozasa, 2012})\) 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” \((\text{Doss, 2013})\)

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).
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.

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.
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


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


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

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](http://energy.lbl.gov/ie/high-radon/frac4.htm)

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

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

Publications claiming cancer risk from low-dose radiation

<table>
<thead>
<tr>
<th>Study</th>
<th>Criticism</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Leuraud, 2015], (Richardson, 2015) – INWORKS studies</td>
<td>(Doss, 2015), (Sacks, 2016): Ignored medical radiation dose, which was small compared to occupational dose in early years but was much higher in later years. Used 90% CIs.</td>
</tr>
<tr>
<td>(Kendall, 2013) Childhood Leukemias vs. Natural Background Radiation</td>
<td>(Doss, 2014), (Sacks, 2016): Data are of marginal significance. All cancers RR=1.03 (1.00-1.07 95%CI). Did not consider confounding by breastfeeding &amp; daycare attendance, which result in 20% and 30% cancer reduction respectively.</td>
</tr>
<tr>
<td>(Hwang, 2008) Taiwan apartment residents</td>
<td>One cancer type had higher incidence (90% CI), quite likely due to chance. (Doss, 2013): Reduction of all cancers (95% CI).</td>
</tr>
<tr>
<td>[Schonfeld, 2013] Techa River solid cancer mortality</td>
<td>Statistics not sufficient to determine dose-response shape; LNT model was used for analysis. (Jargin, 2014): Possible medical examination bias in higher dose population.</td>
</tr>
<tr>
<td>[Krewski, 2006], (Darby, 2005) Radon lung cancer</td>
<td>(Fornalski, 2011): Bayesian analysis of 28 studies shows no dose-dependence can be determined.</td>
</tr>
</tbody>
</table>
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.

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.
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.

Challenge to LNT Model Proponents

1. Explain the significant reduction of cancer mortality rates in atomic bomb survivors as radiation dose increases from ~0.25 Gy to ~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 ~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.
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.

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
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

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
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.

**Proposed Project: 3 (Cont’d)**

- 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.**
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

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.
Questions and Answers
LOW DOSE RESEARCH AT CANDU OWNERS GROUP
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.

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
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 $^3$H and gamma-rays. The project provided the $^3$H retention data necessary for the dosimetry needed to create equivalent gamma-irradiation schedules.

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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?
AFTER FUKUSHIMA: WHAT WE DID AND HOW WE SHOULD DO FOR THE FUTURE
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.phelaboratory.ox.ac.uk/links/2016-EPRI-conference/207-Abstracts

In collaboration with

After 3・11
Confusion after Fukushima

Distribution of opinions on the biological effects caused by low dose and low dose rate radiation exposure
People were confused under such situation.

The fundamental cause of this in science

Not only mass media and extreme views expressed by some people but also among the scientists themselves!
safe

dangerous

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。

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。

覚え方は
「1秒1発1ベクレル」

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
Interdisciplinary symposium

What we did

Multidisciplinary research meetings
We reviewed science and history of radiations

Scientists from various fields;
physics, epidemiology, biology,
animal experiment, immunology,
medical doctors, sociologists · · · ·
· · ·
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

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

Research
Whack-A-Mole

Construction of a mathematical model
Mutation Frequency

- Mutation rate is very low
  \[ N_m \text{ is almost constant} \rightarrow N_n = \text{const.} \quad N_m/N_n = F(t) \]

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

\[
A = a_0 + a_1d, \quad B = b_0 + b_1d
\]

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

- \( d \): dose rate of artificial irradiation
- \( d_{\text{eff}} \): effective dose rate
Characteristic feature

![Graph showing excess frequency vs. dose (D) for different dose rates.

A legend for the graph includes:
- 1 Gy/hr
- 0.1 Gy/hr
- 20 mGy/hr
- 5 mGy/hr
- 1 mGy/hr

An inset graph shows mutation frequency vs. time (t) for:
- 1 mGy/hr
- 100 µGy/hr
- 10 µGy/hr

DDREF depends on D

<table>
<thead>
<tr>
<th>“DDREF”</th>
<th>Total dose D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose rate $d$</td>
<td>20 mGy</td>
</tr>
<tr>
<td>0.1 Gy/hr</td>
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</tr>
<tr>
<td>20 mGy/hr</td>
<td>1.00</td>
</tr>
<tr>
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<tr>
<td>10 µGy/hr</td>
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<tr>
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</tbody>
</table>
Towards Next Step

Thyroid Cancer Survey in Fukushima
People aged 18 years or younger as of April 1, 2011, living in Fukushima underwent thyroid ultrasound screening.

First round
- 367,672
- 300,476 (81.7%)
- 115

Second round
- 381,286
- 267,769 (70.2%)
- 57

Surely physicists contribute everywhere!

Tow more collaborators have joined us!
Remind the importance of dose response relationship

Learn from Chernobyl
Without any prejudice

Dose response relationship
Combined with the dose distribution data......

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

The thyroid gland of children is especially vulnerable to the carcinogenic action of ionizing radiation. 

10 years After Chernobyl

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)
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

1st Step to our aim

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

Animal exp. data

Mutual Intensive Discussion

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).

International and Interdisciplin ery collaboration

- Fukushima Radiation 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

Multidisciplinary Low dose initiative

PLANET +IMELODI

- 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 have been 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 modeling and analyzing 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

Outcome
Radiology
Energy for our Future

Evolutionary Biology
Radiation Biology as Science
Dellbruck    Bohr
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”
Space adventure
Dyson Culture

THE END
LOW DOSE RESEARCH AT QST-NIRS
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)

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*

✓ 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
Dept. of Radiation Effects Research, QST-NIRS

✓ 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

Dept. of Radiation Effects Research, QST-NIRS

✓ 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
Low dose research

Radiation carcinogenesis animal experiments

**Fast neutron source**
- $^9\text{Be}(d,\gamma)^{10}\text{B}$
- 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
- C3H mouse
- SD rat
- WM rat

Heterozygotic cancer models

- Brain
- Intestine
- Kidney

- Ptc11/- mouse
- Apomin/+ mouse
- Mlh1/- mouse
- Tsc2ekr/+ rat

Tissue weighting factors (ICRP, 2007)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Weighting Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>0.12</td>
</tr>
<tr>
<td>Colon</td>
<td>0.12</td>
</tr>
<tr>
<td>Gonad</td>
<td>0.08</td>
</tr>
<tr>
<td>Bladder</td>
<td>0.04</td>
</tr>
<tr>
<td>Esophagus</td>
<td>0.04</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.04</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>0.12</td>
</tr>
<tr>
<td>Female breast</td>
<td>0.12</td>
</tr>
<tr>
<td>Residual tissue</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Low dose rate exposure animal experiments

Chronic exposure
1 Gy (0.0263 mGy/min x 27 days) irradiation
4 Gy (0.1052 mGy/min x 27 days) irradiation

- 1 Gy (4 weeks)
- 4 Gy (10 weeks)
- Life span shortening
- Lymphomas
- Liver tumors
- Lung tumors
- Other solid tumors

Survival rate (%) vs. Days

Acute | 1 week

Chronic | 1-4 weeks
Low dose rate exposure animal experiments

Mammary tumor

<table>
<thead>
<tr>
<th>Relative risk</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 Gy/min</td>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
</tr>
<tr>
<td>0.1 mGy/min</td>
<td><img src="image3" alt="Graph" /></td>
<td><img src="image4" alt="Graph" /></td>
</tr>
</tbody>
</table>

SD female rats
Irradiation at 7 ages of the weeks
(Imaoka et al)

Brain tumor (Medulloblastoma)

<table>
<thead>
<tr>
<th>Rate of MB free mice (%)</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-irradiation</td>
<td><img src="image5" alt="Graph" /></td>
<td><img src="image6" alt="Graph" /></td>
</tr>
<tr>
<td>Acute radiation at PN1 (0.5 Gy/min, total 0.5 Gy)</td>
<td><img src="image7" alt="Graph" /></td>
<td><img src="image8" alt="Graph" /></td>
</tr>
<tr>
<td>Continuous radiation during PN1 (0.09 mGy/min, total 0.5 Gy)</td>
<td><img src="image9" alt="Graph" /></td>
<td><img src="image10" alt="Graph" /></td>
</tr>
</tbody>
</table>

Ptch -/- mice
Irradiation at one day old
(Tsuruoka et al)

Oncogenic mutations in radiation-induced cancer

Deletion mutations in MB of Ptch1+/- mouse
(Ishida, Takabatake et al.)

Spontaneous
Radiation-induced

Ptch1- (mutated)  Ptch1+
Normal cell  Tumor cells

Mutations screening in mammary tumor of SD rat
(Showler, Nishimura, Daino et al.)

Pik3ca mutation (1/14 carcinomas)

SEILSK

NGS analysis

Needs: Further identification of oncogenic mutations in radiation-induced cancer models
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
All experiment include non-irradiated animals.

Number of samples to be stored in J-SHARE

<table>
<thead>
<tr>
<th>Animals</th>
<th>Radiation</th>
<th>Number of animals</th>
<th>Age at exposure (E:Fetal days, W:Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B6C3F1 mice</strong></td>
<td>Gamma (acute)</td>
<td>2300</td>
<td>E3, E13, E17, 1W, 3W, 7W, 15W</td>
</tr>
<tr>
<td>Female, Male Life span study</td>
<td>Gamma (fractionated)</td>
<td>1460</td>
<td>1W, 7W, 15W</td>
</tr>
<tr>
<td></td>
<td>Gamma (low dose rate)</td>
<td>1400</td>
<td>1W, 7W, 15W</td>
</tr>
<tr>
<td></td>
<td>Carbon ions</td>
<td>1800</td>
<td>E3, E13, E17, 1W, 3W, 7W, 15W</td>
</tr>
<tr>
<td></td>
<td>Carbon ions (fractionated)</td>
<td>960</td>
<td>1W, 7W</td>
</tr>
<tr>
<td></td>
<td>Neutron</td>
<td>2300</td>
<td>E3, E13, E17, 1W, 3W, 7W, 15W</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>10220</strong></td>
<td></td>
</tr>
</tbody>
</table>

| Sprague Dawley rats | Gamma (acute)           | 600               | E3, E13, E17, 1W, 3W, 7W, 15W                     |
| Female Breast cancer study | Gamma (low dose rate)   | 500               | 3W, 7W                                            |
|                  | Carbon ions             | 600               | E3, E13, E17, 1W, 3W, 7W, 15W                     |
|                  | Neutrons                | 500               | 3W, 7W                                            |
| **Total**        |                         | **2200**          |                                                   |

| Wistar rats      | X-rays                  | 757               | 1W, 5W, 15W                                       |
| Female Lung cancer study | Neutrons               | 480               | 5W, 15W                                           |
|                  | Neutrons (fractionated) | 192               | 5W, 15W                                           |
| **Total**        |                         | **1429**          |                                                   |

Samples to be stored in J-SHARE

Genetically-modified animal experiments
- Brain tumors: *Ptch1*+/− mice
- Digestive tract tumors: *Apc*Min/+, *Mlh1*+/− 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*Min/+ mice
Access to J-SHARE

- User's registration (user ID, password)
- Free
- Download and utilize only the disclosed data

Data search and parameters

- Experiment Code
- MPATH Code
- Species
- Strain
- Sex
- Radiation
- Dose
- Age at exposure
  etc.
Results of data search

<table>
<thead>
<tr>
<th>Animal ID</th>
<th>Animal No</th>
<th>Type Code</th>
<th>MPATH Code</th>
<th>Radiation</th>
<th>Total Dose</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>S8498</td>
<td>8A-B</td>
<td>C-O-2-1-w</td>
<td>C-O-2-1-w</td>
<td>Carbon ion</td>
<td>0.20y</td>
<td></td>
</tr>
<tr>
<td>S9137</td>
<td>8A-B</td>
<td>C-O-2-1-w</td>
<td>C-O-2-1-w</td>
<td>Carbon ion</td>
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<tr>
<td>S9235</td>
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<td>Carbon ion</td>
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</tr>
<tr>
<td>S9356</td>
<td>8A-B</td>
<td>C-O-2-1-w</td>
<td>C-O-2-1-w</td>
<td>Carbon ion</td>
<td>0.20y</td>
<td></td>
</tr>
<tr>
<td>S9472</td>
<td>8A-B</td>
<td>C-O-2-1-w</td>
<td>C-O-2-1-w</td>
<td>Carbon ion</td>
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</tr>
<tr>
<td>S9542</td>
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<td>Carbon ion</td>
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<td></td>
</tr>
<tr>
<td>S9603</td>
<td>8A-B</td>
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<td>Carbon ion</td>
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<tr>
<td>S9844</td>
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<td>Carbon ion</td>
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<td></td>
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<tr>
<td>S10104</td>
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<td>C-O-2-1-w</td>
<td>Carbon ion</td>
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<td></td>
</tr>
<tr>
<td>S10165</td>
<td>8A-B</td>
<td>C-O-2-1-w</td>
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<td>Carbon ion</td>
<td>0.20y</td>
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</tr>
<tr>
<td>S10465</td>
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<td>C-O-2-1-w</td>
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<td></td>
</tr>
<tr>
<td>S10466</td>
<td>8A-B</td>
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<td>Carbon ion</td>
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</tr>
<tr>
<td>S10483</td>
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<td>C-O-2-1-w</td>
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<td></td>
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<tr>
<td>S10520</td>
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<td></td>
</tr>
<tr>
<td>S10526</td>
<td>8A-B</td>
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<td></td>
</tr>
<tr>
<td>S10619</td>
<td>8A-B</td>
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<td></td>
</tr>
<tr>
<td>S10629</td>
<td>8A-B</td>
<td>C-O-2-1-w</td>
<td>C-O-2-1-w</td>
<td>Carbon ion</td>
<td>0.20y</td>
<td></td>
</tr>
<tr>
<td>S10640</td>
<td>8A-B</td>
<td>C-O-2-1-w</td>
<td>C-O-2-1-w</td>
<td>Carbon ion</td>
<td>0.20y</td>
<td></td>
</tr>
<tr>
<td>S10762</td>
<td>8A-B</td>
<td>C-O-2-1-w</td>
<td>C-O-2-1-w</td>
<td>Carbon ion</td>
<td>0.20y</td>
<td></td>
</tr>
<tr>
<td>S10716</td>
<td>8A-B</td>
<td>C-O-2-1-w</td>
<td>C-O-2-1-w</td>
<td>Carbon ion</td>
<td>0.20y</td>
<td></td>
</tr>
<tr>
<td>S10785</td>
<td>8A-B</td>
<td>C-O-2-1-w</td>
<td>C-O-2-1-w</td>
<td>Carbon ion</td>
<td>0.20y</td>
<td></td>
</tr>
<tr>
<td>S11018</td>
<td>8A-B</td>
<td>C-O-2-1-w</td>
<td>C-O-2-1-w</td>
<td>Carbon ion</td>
<td>0.20y</td>
<td></td>
</tr>
<tr>
<td>S10825</td>
<td>8A-B</td>
<td>C-O-2-1-w</td>
<td>C-O-2-1-w</td>
<td>Carbon ion</td>
<td>0.20y</td>
<td></td>
</tr>
<tr>
<td>S10840</td>
<td>8A-B</td>
<td>C-O-2-1-w</td>
<td>C-O-2-1-w</td>
<td>Carbon ion</td>
<td>0.20y</td>
<td></td>
</tr>
<tr>
<td>S11055</td>
<td>8A-B</td>
<td>C-O-2-1-w</td>
<td>C-O-2-1-w</td>
<td>Carbon ion</td>
<td>0.20y</td>
<td></td>
</tr>
</tbody>
</table>

View of individual data

Autopsy sheet
**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.
International partnership

NIRS

Related projects

Collaborative Researches

Integration of data and samples

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

Current status of low dose/low dose-rate biological research
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
  - 1st meeting, 26th July
  - 2nd meeting, 26th Sep
  - Introduction in JRRS annual meeting, 26th Oct
  - Comment from high level experts (Jan, 2017)
  - Publish a report (Mar, 2017)

PLANET (tentative name)
- April, 2017?
Issues for research (tentative)

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)

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

Nuclear Regulation Authority, MEXT, METI, ME, RE, JAEC, etc.
ICRP, MELODI, IAEA
IDEA, UNSCEAR, etc.
NPO, FEPC,
CPDS, etc.

Universities and Research Institutes of Radiation Research in Japan

Hokkaido Univ.
Hiroshima Univ.
Gunma Univ.
Toyama Univ.
Fukui Univ.
Kyoto Univ., Rad. Biol. Center
Okayama Univ.
Hiroshima Univ.
RERF
Univ. Occu. Environ. Health
Nagasaki Univ.

Tohoku Univ.
Fukushima Med. Univ.
JAEA
Ibaraki Univ.
KEK
JAXA
Tokyo Univ. Sci.
QST-NIRS
Univ. Tokyo
Tokyo Inst. Tech.
CRIEPI
REA
Nara Med. Univ.
Osaka Univ.
Kindai Univ.
Osaka Pref. Univ.
Kyoto Univ. Res. Reactor Inst.
Kagoshima Univ.
Future plan of radiation network in Japan

Umbrella of radiation safety

- Radiation emergency medicine network
- Low dose research network (PLANET)
- Medical exposure network (J-RIME)
- Radiation measurement and dose assessment network

J-RIME: Japan Network for Research and Information on Medical Exposure

Acknowledgements

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Kyoko Kadono
Mari Ogawa
Masaaki Sunaoshi
Masami Ootawara
Masaru Takabatake
Mayumi Nishimura
Mayumi Okabe
Mayumi Shinagawa
Misuzu Fujita
Mutsumi Kaminishi
Rika Yamada
Seiji Kito
Shino Takeda
Shizue Sasaki
Shunsuke Yamazaki

Shusuke Tani
- Toshiaki Kokubo
Toshie Honda
Yasuko Morimoto
Yi Shang
Yoshika Kin
Yoshiko Amasaki
Yuka Ishida
Yumiko Sugawara
Thank you for your attention
and good collaboration with IDEA.
LIFELONG LOW DOES-RATE RADIATION INCREASES LIFESPAN OF AVERAGE DOGS AND EVEN MORE SO FOR SHORT-LIVED DOGS
Lifelong low dose-rate radiation increases lifespan of average dogs and even more so for short-lived dogs

Jerry M. Cuttler and Ludwig Feindendegen
Dose-Response Journal (in press)
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
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>
<thead>
<tr>
<th>Deaths from All Causes, Person-years and Death Rates¹ for high-dose nuclear workers (NW&gt;0.5 rem); low-dose nuclear workers (NW&lt;0.5 rem); and non-nuclear workers (NNW) (after Matanoski 1991 p. 333)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Workers in Subset</td>
</tr>
<tr>
<td>Person-years</td>
</tr>
<tr>
<td>Deaths</td>
</tr>
<tr>
<td>Death Rates Per 1,000²</td>
</tr>
<tr>
<td>Death Rate (SMR)³</td>
</tr>
<tr>
<td>95% C.I.⁴</td>
</tr>
</tbody>
</table>

---

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. Graesle □ 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 reviews 1) medical histories with emphasis on the hematopoietic 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 lifespan studies. The data are consistent with the hypothesis that hematopoietic 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 hematopoiesis throughout life. Further studies perhaps on separated hematopoietic 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 Techa 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

<table>
<thead>
<tr>
<th>Dose Rate (cGy/day)</th>
<th>Dose Rate (mGy/year)</th>
<th>50% mortality</th>
<th>10% mortality</th>
<th>5% mortality</th>
<th>50% mortality</th>
<th>10% mortality</th>
<th>5% mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>background</td>
<td>2.4 x 10^2</td>
<td>4300</td>
<td>2700</td>
<td>2150</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>0.3</td>
<td>1.1 x 10^2</td>
<td>4050</td>
<td>2700</td>
<td>2150</td>
<td>0.94</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>0.75</td>
<td>2.7 x 10^2</td>
<td>3300</td>
<td>2200</td>
<td>1800</td>
<td>0.77</td>
<td>0.82</td>
<td>0.84</td>
</tr>
<tr>
<td>1.88</td>
<td>6.9 x 10^2</td>
<td>3000</td>
<td>1300</td>
<td>850</td>
<td>0.70</td>
<td>0.48</td>
<td>0.386</td>
</tr>
<tr>
<td>3.75</td>
<td>1.4 x 10^4</td>
<td>1900</td>
<td>600</td>
<td>400</td>
<td>0.44</td>
<td>0.222</td>
<td>0.182</td>
</tr>
<tr>
<td>7.5</td>
<td>2.7 x 10^4</td>
<td>400</td>
<td>220</td>
<td>95</td>
<td>0.093</td>
<td>0.081</td>
<td>0.043</td>
</tr>
<tr>
<td>12.75</td>
<td>4.7 x 10^4</td>
<td>150</td>
<td>91</td>
<td>40</td>
<td>0.035</td>
<td>0.034</td>
<td>0.0182</td>
</tr>
<tr>
<td>26.25</td>
<td>9.6 x 10^4</td>
<td>51</td>
<td>40</td>
<td>30</td>
<td>0.012</td>
<td>0.0148</td>
<td>0.0136</td>
</tr>
<tr>
<td>37.5</td>
<td>1.4 x 10^6</td>
<td>32</td>
<td>23</td>
<td>15</td>
<td>0.0074</td>
<td>0.0085</td>
<td>0.0068</td>
</tr>
<tr>
<td>54</td>
<td>2.0 x 10^8</td>
<td>24</td>
<td>13</td>
<td>11</td>
<td>0.0056</td>
<td>0.0048</td>
<td>0.0050</td>
</tr>
</tbody>
</table>
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 $^{239}$PuO$_2$ in Dogs

Bruce A. Muggenburg,* Raymond A. Guilmette,* Fletcher F. Hahn,* Joseph H. Diel,* Joe L. Maderly,*
Steven K. Seilkop1 and Bruce B. Boecker1

* Lovelace Respiratory Research Institute, Albuquerque, New Mexico 87108; and 1 SKS Consulting Services, Siler City, North Carolina 27344


Beagle dogs inhaled graded exposure levels of insoluble plutonium dioxide ($^{239}$PuO$_2$) aerosols in one of three monodisperse particle sizes at the Lovelace Respiratory Research Institute (LRRI) 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

Radiotoxicity of inhaled $^{239}$PuO$_2$ in beagle dogs

![Graph showing survival rates over time](image-url)
<table>
<thead>
<tr>
<th>Group</th>
<th>Initial Lung Burden (kBq/kg)</th>
<th>Lifespan (days)</th>
<th>Lifespan (normalized)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50% mortality</td>
<td>10% mortality</td>
<td>5% mortality</td>
</tr>
<tr>
<td>Control</td>
<td>0</td>
<td>5150</td>
<td>3610</td>
</tr>
<tr>
<td>1</td>
<td>0.16</td>
<td>5316</td>
<td>4760</td>
</tr>
<tr>
<td>2</td>
<td>0.63</td>
<td>4526</td>
<td>3780</td>
</tr>
<tr>
<td>3</td>
<td>1.6</td>
<td>3482</td>
<td>2500</td>
</tr>
<tr>
<td>4</td>
<td>3.7</td>
<td>2421</td>
<td>1940</td>
</tr>
<tr>
<td>5</td>
<td>6.4</td>
<td>1842</td>
<td>1280</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>1122</td>
<td>840</td>
</tr>
<tr>
<td>7</td>
<td>29</td>
<td>807</td>
<td>625</td>
</tr>
</tbody>
</table>

**Lifespan versus $^{239}$PuO$_2$ lung burden**

![Graph showing lifespan regression against initial lung burden](image)
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

Jerry M. Cuttler¹, Eugene R. Moore², Victor D. Hosfeld³, and David L. Nadolski⁴

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 dogs.
- 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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