

Summary of National Council on Radiation Protection and Measurements NCRP Forty-Fourth Annual Meeting (14-15 April 2008 in Bethesda, Maryland, USA): “Low Dose and Low Dose-Rate Radiation Effects and Models”

Subtitle: Low Dose and Low Dose-Rate Radiation Effects

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Abstract. This paper summarizes the highlights of presentations at the 44th Annual National Council on Radiation Protection and Measurements (NCRP) Annual Meeting, primary conclusions drawn by the speakers, and future activities of NCRP in analyzing the biological and potential human health effects of exposure to low doses of ionizing radiation. A related subject that was discussed by speakers at the meeting was the effect of the rate of delivery of radiation doses (*i.e.*, dose rate). The goal of the 2008 NCRP Annual Meeting was to bring these subjects into the perspective of currently available data and models of the biological responses and human health impacts of exposure to low doses of radiation. Views of the public and the role of growing knowledge of low-dose radiation effects on regulatory decision making were also discussed. Future plans of NCRP to continue its analysis of biological and human health effects of low dose and low dose-rate ionizing radiation are described.

KEYWORDS: Low-dose radiation biological effects and models, epidemiological studies, linear nonthreshold (LNT) response model, mechanisms of radiation interaction, modifiers of radiation response, radiation susceptibility factors, public views, regulatory implications

1. Introduction

One of the most highly debated subjects in life sciences research is the response of living systems to low doses of radiation, especially when the doses are delivered at the low rates characteristic of most human exposures. The 2008 NCRP Annual Meeting addressed many of the primary issues related to low-dose radiation effects and models, and the advances in knowledge from recent laboratory research results, human epidemiology studies, and theoretical modeling of radiation interactions at the molecular, cellular and tissue levels. The Annual Meeting was attended by nearly 500 research scientists, government regulators, and others interested in the biological effects and human health and regulatory implications of studies on low-dose radiation. Presentations from the 2008 NCRP Annual Meeting can be obtained at <http://NCRPpublications.org>, and the proceedings will be published in *Health Physics* in 2009.

2. Meeting Highlights

Highlights of the meeting included the following.

2.1 Keynote Lecture

Dr. Dudley Goodhead¹ presented the 5th annual Warren K. Sinclair Keynote Lecture on “Issues in Quantifying the Effects of Low-Level Radiation,” in which he reviewed the rapidly expanding knowledge on physical interactions of ionizing radiation with DNA and other cellular structures. Dr. Goodhead emphasized the importance of complex DNA base damage and strand-break events in producing nonrepairable or slowly repairable cellular damage.

2.2 Lauriston Taylor Lecture on Yucca Mountain Nuclear Waste Repository

Dr. Dade Moeller² presented in the 32nd Lauriston Taylor Lecture a historically interesting and insightful evaluation of the potential value and public debate over the use of Yucca Mountain as a repository for spent nuclear fuel from U.S. reactor facilities. He discussed the radionuclides to be stored in the facility in terms of potential health effects to those living and working near the facility, and the issues to be given consideration over a period of many millennia in terms of release of radionuclides from the facility and their health impacts. He reviewed the proposed regulatory restrictions on doses to the public from the facility, and made a strong argument that the prediction of health risks over tens of thousands of years resulting from releases of radionuclides from the Yucca Mountain facility cannot be done accurately at the present time, nor should these potential risks be the subject of long-term regulations by federal agencies.

2.3 Debate on LNT Model of Radiation Response

A stimulating debate was held between Dietrich Averbeck³ and David Brenner⁴ on the topic of “Does Scientific Evidence Support a Change from the Linear Nonthreshold (LNT) Model for Low-Dose Radiation Risk Extrapolation.” Dr. Averbeck represented the position of the 2005 French Academy of Sciences Report which argued that current evidence from laboratory studies supports the existence of a threshold dose-response to radiation, whereas Dr. Brenner supported the conclusion of the 2006 National Academy of Sciences BEIR VII report that the existing evidence is consistent with a nonthreshold linear dose-response model. Neither debater scored a clear victory, but the results provided strong support for the need to conduct additional research to resolve the issue of whether the LNT model is appropriate for evaluating human health effects at low radiation doses.

2.4 Summary of Presentations on Laboratory and Epidemiological Studies

Two major sessions of the 2008 Annual Meeting led to valuable insights into the potential biological and human health effects of low radiation doses. These sessions included presentations in the following areas:

2.4.2 Life Sciences Research on Low-Dose Radiobiology.

Dr. William Morgan⁵ presented evidence that nontargeted effects of radiation such as genomic instability and bystander effects must be considered in evaluating the responses of cells and

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tissues to low-dose radiation. Dr. Michael Cornforth⁶ and Dr. Andrew Wyrobek⁷ presented evidence that chromosomal aberrations and resulting changes in gene expression are important factors in determining cellular responses to radiation. Dr. Peggy Jeggo⁸ discussed DNA damage and repair in the context of evaluating the risk from radiation exposure. Dr. Mary Helen Barcelos-Hoff⁹ presented strong arguments based on laboratory studies that the response to low-dose radiation should be viewed from the perspective of integrated tissue responses rather than from effects measured only on single cells. Dr. Ann Kennedy¹⁰ discussed a variety of factors that can influence radiation response both *in vitro* and *in vivo*, including dietary factors, drugs, hormones, vitamins, oxidative stress, anti-oxidants, and exposure to cancer promoting and suppressing agents. Evidence for sensitivity to radiation carcinogenesis associated with genetic susceptibility was summarized by Dr. Joel Bedford¹¹. Based on research involving life-span studies with dogs exposed acutely or chronically to external ⁶⁰Co radiation or internal beta-gamma emitting radionuclides, Dr. Antone Brooks¹² summarized data on cancer risk estimates in relation to radiation dose, dose rate and dose distribution in the body. A broad biophysical approach to combining experimental data and theoretical models in the development of systems biology concepts for describing the response of living systems to low radiation doses was presented by Dr. Herwig Paretzke¹³.

2.4.2 *Epidemiological Studies on Human Health Effects.*

Dr. Charles Land¹⁴ presented an informative overview of human health risks of exposure to radiation in occupational, medical, accidental and A-bomb settings, and discussed the uncertainties associated with the prediction of health effects of low-dose radiation exposures based on the results of epidemiological studies on these exposed populations. He also described the views of individuals and population subgroups on the beneficial and adverse outcomes of exposure from medical and other exposures.

Dr. Roy Shore¹⁵ summarized the radiation risk information gained from radiation workers involved in cleanup after the Chernobyl nuclear accident, workers at nuclear facilities in Russia, the U.S. and elsewhere, and individuals exposed to low doses of radiation from medical procedures. He compared the estimates of cancer risk obtained from studies on these populations to those obtained for Japanese survivors that were exposed acutely to radiation from the atomic bombs detonated in Japan in 1945. He concluded that studies on humans exposed to low radiation doses have so many dosimetric uncertainties and limitations in statistical power that clear conclusions on cancer risk from these exposures cannot be drawn using the available data. Dr. Shore also discussed the influence of individuals who are particularly susceptible to radiation cancer induction on the estimation of the aggregate human risk of exposure to low radiation doses.

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¹³ Institut für Strahlenschutz, Neuherberg, Germany

¹⁴ National Cancer Institute, Bethesda, Maryland, USA

¹⁵ Radiation Effects Research Foundation, Hiroshima, Japan

Dr. Ethel Gilbert¹⁶ concluded the discussion of human health effects with an insightful discussion of complications in determining radiation dose-response relationships for cancer induction that result from uncertainties in dosimetry for exposed populations.

2.5 Regulatory Implications of Low-Dose Radiation Exposure Effects and Models

2.5.1 Regulatory Implications of Studies on Effects of Low Radiation Exposures.

An important long-range outcome of the results of studies on low-dose and low dose-rate radiation biological effects and human health implications is the possibility of future changes in regulatory controls on human exposures in occupational, medical and public scenarios. The final session of the 2008 NCRP Annual Meeting was focused on this topic, and was initiated with a discussion by Dr. Paul Locke¹⁷ on public perceptions of radiation risk and the evolution of radiation regulations over the past century. His introductory presentation was followed by talks of representatives of the Nuclear Regulatory Commission¹⁸, the Department of Energy¹⁹ and the U.S. Environmental Protection Agency²⁰ on the views of their agencies on the potential changes in regulatory radiation exposure limits that may be introduced as a result of well-documented scientific information on dose-response relationships for exposure to low radiation doses.

2.5.2 Public Views of Radiation Risk and Combining Scientific Knowledge with Decision Making

Dr. Hank Jenkins-Smith²¹ presented informative comparisons of the views of scientists and members of the public in the United States and European nations on radiation risks and the potential benefits of nuclear energy. In general, surveys conducted in the 2002 – 2007 period found little or no difference in beliefs of scientists in the U.S. and Europe about radiation dose-response relationships, with about 20 % and 70 % supporting the linear and sublinear threshold models, respectively. Perceived risks of nuclear power accidents were higher among members of the U.S. public than among scientists surveyed in both the U.S. and European nations. However, support for nuclear power as an energy resource was as high among members of the U.S. public as among scientists. In general, the support for use of nuclear power was significantly higher among scientists from France, where nuclear power is a major source of energy, than in the U.S., England, Germany and other nations in the European Union.

Dr. Paul Ziemer²² summarized the U.S. federal programs that are in progress to reimburse public and occupational claims for radiation exposure-related health effects that have been filed by former energy workers involved in the production of nuclear weapons, military veterans involved in atmospheric nuclear testing and the occupation of Japan after the A-bomb detonations in 1945, and members of the public living downwind of atmospheric nuclear test locations.

¹⁶ National Cancer Institute, Bethesda, Maryland, USA

¹⁷ Johns Hopkins School of Public Health, Baltimore, Maryland, USA

¹⁸ Presented by Mr. Martin Virgilio, NRC, Rockville, Maryland, USA

¹⁹ Presented by Dr. Noelle Metting, U.S. DOE, Washington, DC, USA

²⁰ Presented by Dr. Juan Reyes, U.S. EPA, Washington, DC, USA

²¹ University of Oklahoma, Jenkins, Oklahoma, USA

²² Purdue University (retired), West Lafayette, Indiana, USA

The final presentation of the meeting was given by Dr. John Poston, Sr.²³, on combining scientific knowledge with decision-making in the aftermath of nuclear and radiological accidents and incidents, including acts of terrorism involving radioactive materials.

3. Primary Insights into Biological and Health Effects of Low-Dose Radiation Exposures

Overall, the 2008 NCRP Annual Meeting provided an up-to-date view of contemporary knowledge on radiation effects and models of radiation dose-response relationships, as well as pointing to the implications of this knowledge as a framework for evaluating potential human health effects. Information presented at the meeting also provided clear insights into future research needs for obtaining an improved understanding of the biological interactions and health effects of low doses of ionizing radiation, including exposures at the low dose rates typical of many occupational and public environments. The following is a concise summary of the highlights of new findings and areas of continuing research related to low dose and low dose-rate biological and human health effects.

3.1 Epidemiology Studies

Several factors limit the precision of epidemiological data in defining cancer risk and other health effects at low radiation doses. These factors include (a) a much larger sample size is required at low dose levels to attain adequate statistical power to define dose-response characteristics; (b) confidence levels on estimates of excess relative risk per Gy become much wider at low dose levels; (c) studies at low dose levels have a greater percentage of “false positive” and “false negative” results; (d) many sources of errors in measured and calculated external, internal and organ doses influence dose-response modeling; (e) national origin, age at exposure, gender, inherent genetic susceptibility, exposure to cancer promoters and other environmental risk factors, and lifestyle factors (diet, drugs, tobacco use, intake of antioxidants, etc.) all influence individual risks of cancer and other diseases.

3.2 Experimental Studies

Significant advances have been made during the past decade in gaining increased knowledge of biological effects of low doses of radiation. These include:

3.2.1 Molecular pathways of low-dose radiation damage and repair to DNA and chromosomes

Significant knowledge gained from studies in recent years include: (a) low-energy secondary electrons from photon irradiation (~ 30% of dose) can produce complex clustered double-strand break (DSB) damage, which is the least repairable type of damage and can lead to DNA losses and rearrangements; (b) nonhomologous end joining (NHEJ) at site of DSB is a more important repair pathway than homologous recombination events; (c) signaling factors such as ATM kinase play a key role in initiating DNA repair processes that depend on Artemis nuclease and other factors; (d) DSB introduce both S/G2 and G2/M cell-cycle checkpoints that provide time and signals for initiating repair pathways, but cells can have as many as 10 unrepaired DSB and enter mitosis, which is a possible mechanism for later expression of genetic damage in progeny cells; (e) low and high doses of radiation have similar effects on gene expression in mouse and human cells, and low doses (≤ 100 mGy) have some notably different transcriptional effects than higher doses on genes involved in cell-cycle regulation, cell-cell interactions, oxidative stress responses, and protein and fatty acid metabolism; (f) low and high radiation doses affect expression of the

²³ Texas A&M University (retired), College Station, Texas, USA

same genes in human and mouse cells, but results of studies on mice irradiated *in vivo* show significant tissue-specific variations in effects on gene expression; (g) dicentrics, complex translocations, inversions and deletions all provide indications of radiation damage, but dicentrics remain the usual assay for low-dose radiation effects; (h) not only chromosome dicentrics and translocations are indicators of mutation and potential neoplastic transformation, but inversions and interstitial deletions on chromosomes can serve as predictive markers.

3.2.2 Factors modifying response to low radiation doses

Several biological factors have been demonstrated to modify the response to low radiation doses. These include:

- *Bystander effects.* Adverse responses, including cytogenetic effects and cell death, in cells not directly “hit” by radiation are known as bystander effects. These effects have been successfully demonstrated by α -particle microbeam experiments and other radiation modalities. Mechanism(s) for transmission of signals from hit cells to neighboring cells remain under study, but could include cell-to-cell transmission of molecular factors (*e.g.*, cytokines) via gap junctions or release of these factors into blood or tissue fluids.
- *Genomic instability.* Many experimental studies have demonstrated that delayed genomic effects in the progeny of “hit” cells can be manifested by effects such as chromosome alterations, mutation, changes in gene expression, and cell death.
- *Radioadaptive responses.* Small priming doses (≤ 50 mGy) have been demonstrated to lead to reduced adverse effects of larger challenge doses (*e.g.*, less cytogenetic damage, cell death, and carcinogenic risk). Upregulation of *TP53* and *MYC* genes by low doses may be a “switch” increasing transcription of a broad array of other genes involved in protective responses to larger challenge doses. Low-dose radiation produces adaptive responses that have been found in experimental systems to reduce the frequency of chromosomal alterations and cell mutation and transformation below the spontaneous level.
- *Integrated tissue responses.* Studies with epithelial tissue models *in vitro* have demonstrated that low radiation doses (≤ 100 mGy) can induce dysfunctional cell-cell and cell-extracellular matrix interactions that lead to heritable phenotypic changes characteristic of malignancy; the “trigger” is a radiation-induced elevation in transforming growth factor, which serves to sustain extracellularly-regulated activation of kinases at the integrated tissue level. These effects are well characterized by a “systems biology” modeling approach.
- *Genetic susceptibility.* Although relatively small groups of people have well-documented diseases associated with susceptibility to radiation-induced cancer (*e.g.*, ataxia-telangiectasia and retinoblastoma), it is expected that the fraction of humans with uncharacterized sensitivity to radiation may be much larger (perhaps 20% or more). Many laboratory animal-based studies have clearly demonstrated the effects of defined genetic mutations on susceptibility to radiation carcinogenesis. Some candidate genotypic markers of sensitivity have been identified in humans (*e.g.*, BRCA genes in breast tissue), but progress is at an early stage.
- *Individual factors.* Many factors related to lifestyle are known to influence cancer risk, including age at exposure, gender, genetic background, exposure to cancer promoting agents and other environmental risk factors, and lifestyle factors such as diet, drugs, tobacco use, intake of antioxidants, etc.

- *Radiation quality and dose rate.* Ongoing studies on the relative biological effects (RBE) of radiations of differing qualities have continued to demonstrate the importance of this factor in evaluating the health risk of exposure to neutrons and charged-particle radiation. In addition, continuing research on the influence of dose level and dose-rate on biological responses to low-dose radiation have demonstrated the importance of this factor in estimating the risk of cancer and other radiation-induced diseases. Although experimental studies have shown large variations in dose-rate effects for different biological endpoints, a dose and dose-rate effectiveness factor (DDREF) of 2.0 proposed by the International Commission on Radiological Protection and NCRP is generally consistent with the existing data.

4. Public Policy and Regulatory Decisions on Low-Dose Radiation Exposures

The final session of the 44th NCRP Annual Meeting was focused on public views of radiation benefits and risks and the implications of new research on low-dose radiation effects for the development of future radiation exposure regulations for workers and the public.

4.1 Public Attitudes and Expectations

Concerns over public exposures from occupational, nuclear power, and many environmental sources are decreasing in the United States and other national worldwide. However, concerns have been expressed recently over the rapidly growing use of radiation in medical procedures such as computed tomography (CT) imaging.

Expectations remain high that exposed members of the military (atomic veterans) and energy workers who were involved in nuclear weapons production in the United States will be compensated for debilitating diseases such as cancer potentially related to their prior radiation exposures.

Concerns are also high for public safety and health protection in the event of a nuclear or radiological terrorism incident.

4.2 Views of Government Regulatory Agencies in the United States

Efforts to obtain an improved knowledge of low-dose radiation effects are considered an important activity with a potential impact on future guidelines for public and worker exposure limits. A major area of interest is the confirmation, or the development of a scientifically defensible alternative, to the LNT dose-response model as a basis for regulations. Research focused on characterizing the range of individual sensitivities to radiation health effects is considered to be an area of major importance. Changes in regulatory policies and practices will not occur rapidly, but will be given a high priority if changes are warranted on the basis of well-documented scientific evidence and predictive models of radiation health effects.

5. Future Plans of NCRP Related to Low-Dose Biological and Human Health Effects

A significant near-term initiative of NCRP is to prepare a major report on *Low Dose and Low Dose-Rate Biological Effects and Implications for Human Health Effects*. The report, to be prepared in the 2010-2014 time frame, will incorporate results of extensive research worldwide and will extend analysis of low-dose effects recently published by ICRP (Publication 99, 2004), the French Academy of Sciences (2005), and the United States National Academy of Sciences (BEIR VII, 2006). The primary report goals include: (a) integrate research results into reliable predictive models of low-dose radiation health effects; (b) analyze health protection and

regulatory implications of findings; and (c) recommend effective mechanisms of communication of projected radiation risks of low-dose radiation.

6. Publication of Proceedings of NCRP Annual Meetings

Papers for the proceedings of the 2008 NCRP Annual Meeting are in an advanced stage of preparation and peer review, and will be published in *Health Physics* in 2009.

The 45th Annual Meeting will be on the topic of “Future of Nuclear Power Worldwide: Safety, Health and Environment,” which will be held on March 2-3, 2009 at the Hyatt Hotel Convention Center in Bethesda, Maryland (USA). Information on the meeting can be obtained from the NCRP website cited above, along with information on pre-registration for the meeting and hotel accommodations. There will be no registration fee.

Proceedings of other recent NCRP Annual Meetings can be accessed in *Health Physics*. The proceedings of four other recent meetings are published in the following issues of *Health Physics*:

2004: 40th Annual Meeting on “Advances in Consequence Management for Radiological Terrorism Events,” *Health Physics* 89(5), 416-588 (2005).

2005: 41st Annual Meeting on “Managing the Disposition of Low-Activity Materials,” *Health Physics* 91(5), 413-536 (2006).

2006: 42nd Annual Meeting on “Chernobyl at Twenty,” *Health Physics* 93(5), 345-595 (2007).

2007: 43rd Annual Meeting on “Advances in Radiation Protection in Medicine,” *Health Physics* 95(5), 461-657 (2008).

Acknowledgements

The author gratefully acknowledges the efforts of the Program Committee for the 44th NCRP Annual Meeting: Antone L. Brooks (Chairman), Joel S. Bedford, Bruce B. Boecker, R.J. Michael Fry, Dudley T. Goodhead, Eric J. Hall, Kenneth R. Kase, Ann R. Kennedy, Amy Kronenberg, Charles E. Land, Roy E. Shore, Julie E. Timins, Susan D. Wiltshire, and Gayle E. Woloschak.

**National Council on Radiation Protection
and Measurements (NCRP) 2008 Annual
Meeting: “Low Dose and Low Dose-Rate
Radiation Effects and Models” –
Summary, Conclusions and Plans for
Future NCRP Report**

Thomas S. Tenforde
President, NCRP

Bethesda, Maryland (USA)

Presentation at IRPA 12 Congress

Buenos Aires, Argentina

October 21, 2008



Primary Topics of Discussion



- **Status of knowledge and key scientific issues remaining to be addressed in understanding and modeling low-dose radiation interactions and biological effects**
- **Implications of increased knowledge of low-dose radiation effects for public policy and regulatory decisions on exposure limitations**
- **NCRP's future plans for a major report on low-dose radiation biological effects and implications for human health**

Primary Sessions at 2008 NCRP Annual Meeting (April 14-15 in Bethesda, Maryland)

- Human epidemiology studies
- Molecular, cellular, tissue and animal radiation responses of relevance to radiation protection
- Low-dose radiation effects, regulatory policy and impacts on the public
- Presentations at 2008 meeting available at website <http://NCRPpublications.org>
- Proceedings of meeting to be published in *Health Physics* (2009)



Special Lectures at 2008 NCRP Annual Meeting

- *Fifth Annual Warren K. Sinclair Keynote Address --*

Dr. Dudley T. Goodhead: “Issues in Quantifying the Effects of Low-Level Radiation”

- *Thirty-Second Lauriston S. Taylor Lecture --*

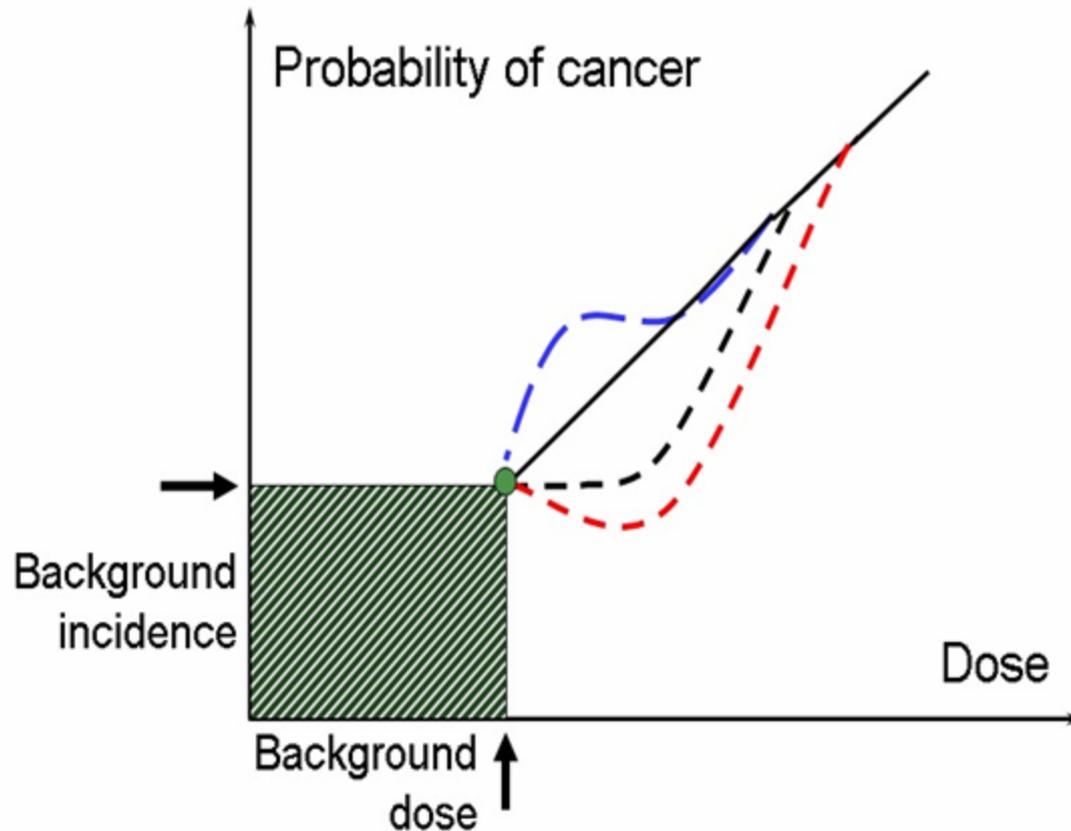
Dr. Dade W. Moeller: “Radiation Standards, Dose/Risk Assessments, Public Interactions, and Yucca Mountain: Thinking Outside the Box”



Low-Dose Radiation Biological Effects



Dose-Response Relationships

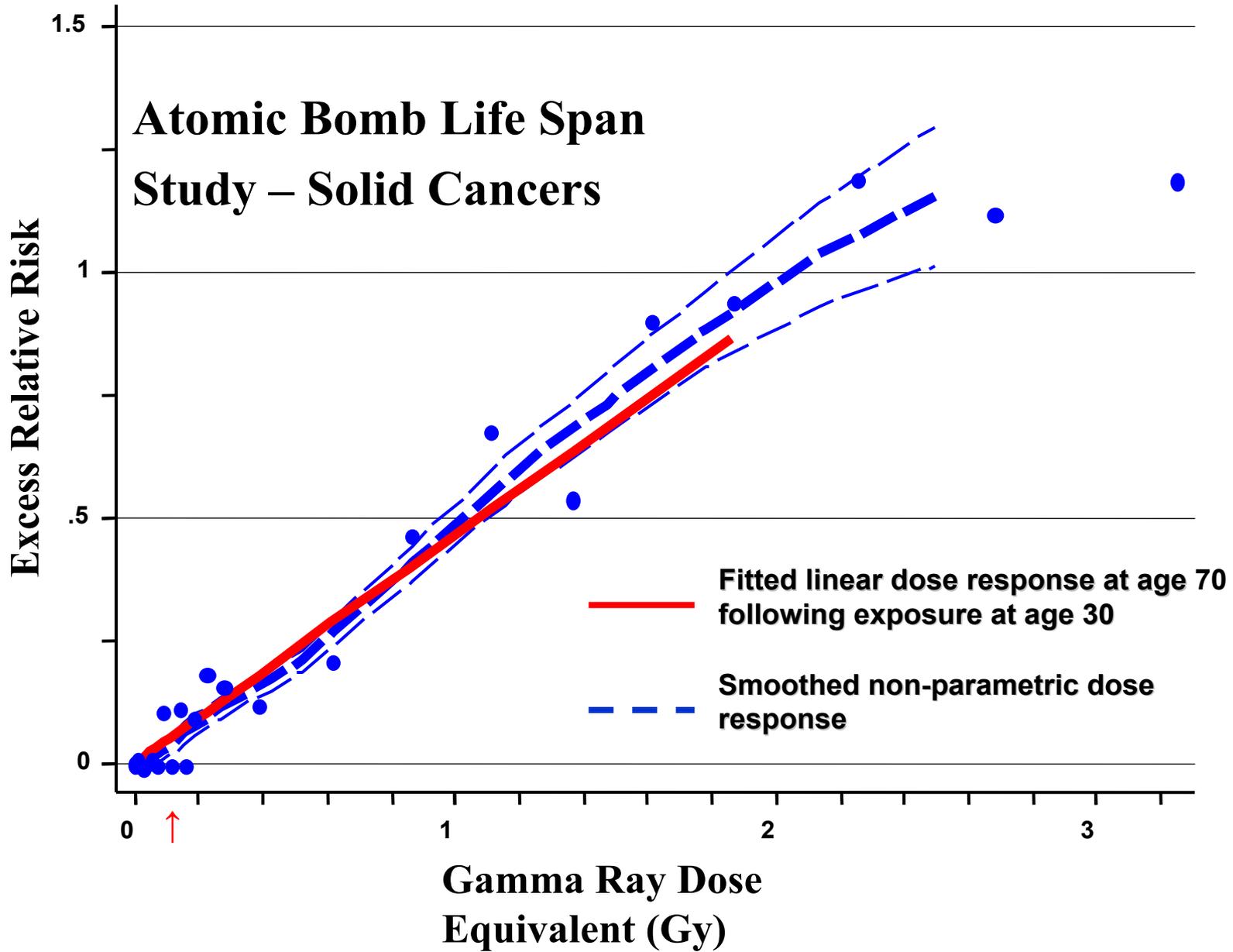


Primary Goals in Low-Dose Radiation Studies:

- Determine dose-response properties for cellular, tissue and whole-animal biological effects
- Evaluate validity of LNT (linear nonthreshold) model
- Integrate data on dose-response properties into reliable predictive model(s) of potential human health effects

Limits on Precision of Epidemiology

Data at Low Radiation Doses -- 1



Limits on Precision of Epidemiology Data at Low Radiation Doses -- 2

- *Statistical Power:*

- Studies at low dose levels require a *much larger* sample size to attain adequate statistical power to define dose-response characteristics
- confidence intervals on estimates of excess relative risk per Gy become much wider at low dose levels
- studies at low dose levels have a greater percentage of “false positive” and “false negative” results, with “false positive” results often giving significant overestimates of risk



Limits on Precision of Epidemiology Data at Low Radiation Doses -- 3

- **Dosimetry Uncertainties:**
 - Many sources of errors in measured and calculated external, internal and organ doses that influence dose-response modeling
 - *Classical errors:* influence estimates of average for exposed group; shared by all members of group
 - *Berkson errors:* lead to variations among estimates for individual members of exposed group
- **Response Modifying Factors:** National origin, age at exposure, gender, inherent genetic susceptibility, exposure to cancer promoters and other environmental risk factors, general health status, lifestyle factors (diet, drugs, tobacco use, intake of antioxidants ...)



Scientific Approaches to Defining Dose-Response Characteristics for Low-Dose Radiation Effects

- **Lack of precision in epidemiological studies for characterizing responses to low radiation doses has led to a research focus on studies with controlled laboratory experimental systems**
- **Ten years of research supported by U.S. Department of Energy and other organizations worldwide has led to important insights into, and modeling of, low-dose radiation effects:**
 - **molecular and cellular effects on DNA and cytogenetic control mechanisms and damage repair pathways**
 - **direct and indirect (nontargeted) effects on cellular and tissue/organ functional properties and regulatory controls**
 - **evaluation of important factors influencing radiation response, including dose rate, radiation quality (LET), and biological modifiers of radiation response**



Molecular Pathways of Low-Dose Radiation Damage and Repair to DNA and Chromosomes –1



- Significant advances over last decade in characterizing DNA lesions, repair kinetics and pathways, and effects at chromosomal and cellular levels
- Low-energy secondary electrons from photon radiation (~ 30 % of dose) can produce complex clustered double-strand break (DSB) damage – the least repairable type of damage that can lead to DNA losses and rearrangements
- Nonhomologous end joining (NHEJ) at site of DSB is a more important repair pathway than homologous recombination events
- Signaling factors such as ATM kinase play a key role in initiating DNA repair processes that depend on Artemis nuclease and other factors

Molecular Pathways of Low-Dose Radiation

Damage and Repair to DNA and Chromosomes – 2



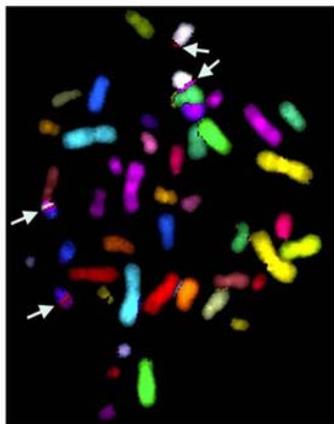
- DSB introduce both S/G2 and G2/M cell-cycle checkpoints that provide time and signals for initiating repair pathways, but cells can have as many as 10 unrepaired DSB and enter mitosis (a possible mechanism for later expression of genetic damage in progeny cells)
- Low and high doses of radiation have similar effects on gene expression in mouse and human cells, and low doses (≤ 100 mGy) have some notably different transcriptional effects than higher doses on genes involved in cell-cycle regulation, cell-cell interactions, oxidative stress responses, and protein and fatty acid metabolism
- Low and high radiation doses affect expression of the same genes in human and mouse cells, but results of studies on mice irradiated *in vivo* show significant tissue-specific variations in effects on gene expression

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Molecular Pathways of Low-Dose Radiation Damage and Repair to DNA and Chromosomes – 3



- Visualization of chromatid and chromosome damage significantly enhanced by use of multi-color fluorescence in situ hybridization (mFISH) painting, use of γ H2AX markers of DSB loci, and micronuclei assays
- Dicentrics, complex translocations, inversions and deletions all provide indications of radiation damage, but dicentrics remain the usual assay for low-dose effects



- Not only dicentrics and translocations are indicators of mutation and potential neoplastic transformation, but inversions and interstitial deletions on chromosomes can serve as markers

Factors Modifying Response to Low Radiation Doses – 1: Nontargeted Effects

- **Bystander Effects**: Adverse responses, including cytogenetic effects and cell death, in cells not directly “hit” by radiation
 - Successfully demonstrated by α -particle microbeam experiments and other radiation modalities
 - Mechanism(s) for transmission of signals from hit cells to neighboring cells remain under study, but could include cell-to-cell transmission of molecular factors (e.g., cytokines) via gap junctions or release of these factors into blood or tissue fluids
- **Genomic Instability**: Delayed genomic effects in progeny of “hit” cells, manifested by effects such as chromosome alterations, mutation, changes in gene expression, and cell death



Factors Modifying Response to Low Radiation Doses – 1: Nontargeted Effects (con't.)

- **Radioadaptive Responses:** Small priming doses (≤ 50 mGy) lead to reduced adverse effects of larger challenge doses (e.g., less cytogenetic damage, cell death, and carcinogenic risk)
 - Upregulation of *TP53* and *MYC* genes by low doses may be a “switch” increasing transcription of a broad array of other genes involved in protective responses to larger challenge doses
 - Low-dose radiation produces adaptive responses that have been found in experimental systems to reduce the frequency of chromosomal alterations, cell mutation and neoplastic transformation below the spontaneous level



Factors Modifying Response to Low Radiation Doses – 1: Nontargeted Effects (con't.)

- **Integrated Tissue Responses:** Studies with epithelial tissue models *in vitro* have demonstrated that low radiation doses (≤ 100 mGy) can induce dysfunctional cell-cell and cell-extracellular matrix interactions that lead to heritable phenotypic changes characteristic of malignancy; the “trigger” is a radiation-induced elevation in transforming growth factor, which serves to sustain extracellularly-regulated activation of kinases at the integrated tissue level. These effects are well characterized by a “systems biology” modeling approach.



Factors Modifying Response to Low Radiation Doses – 2: Individual Factors



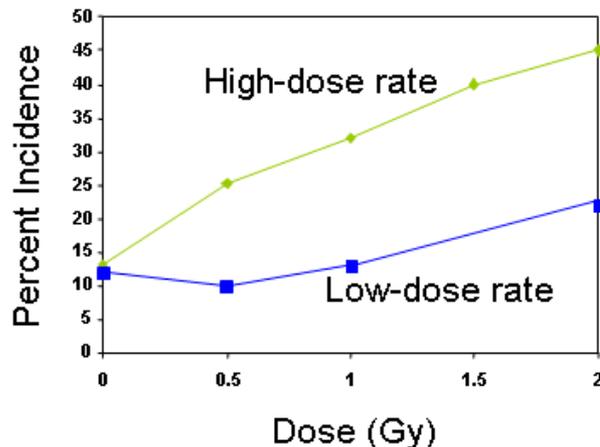
- **Genetic Susceptibility**: Although relatively small groups of people have well-documented diseases associated with susceptibility to radiation-induced cancer (*e.g.*, AT and Rb), it is expected that the fraction of humans with uncharacterized sensitivity to radiation may be much larger (perhaps 20% or more)
- Many laboratory animal-based studies have clearly demonstrated the effects of defined genetic mutations on susceptibility to radiation carcinogenesis
- Some candidate genotypic markers of susceptibility have been identified in humans (*e.g.*, BRCA genes in breast tissue), but progress is at an early stage

Factors Modifying Response to Low Radiation Doses – 3: RBE and Dose Rate

• Relative Biological Effectiveness (RBE): Different tissue, cellular, and cytogenetic endpoints often exhibit significant variations in RBE estimates for high-LET radiations – a factor of importance in evaluating health risks for persons exposed to neutrons and charged-particle radiation

• Dose and Dose-Rate Effectiveness Factor (DDREF): Large variations observed for different biological endpoints, but DDREF estimates are generally consistent with the value of 2.0 proposed by ICRP and NCRP

Dose-Rate Effects
Incidence of Thymic Lymphoma in RFM Mice



Importance of Gaining Increased Knowledge on Low-Dose Radiation Effects in Relation to Public Policy and Regulatory Decisions – 1

- *Public Attitudes and Expectations:*

- Concerns over public exposures from occupational, nuclear power, and many environmental sources are decreasing in the United States and other nations worldwide, although concerns have been expressed recently over the rapidly growing use of radiation in medical procedures such as computed tomography (CT) imaging
- Expectations remain high that exposed members of the military (atomic veterans) and energy workers involved in nuclear weapons production will be compensated for debilitating diseases such as cancer potentially related to prior exposures
- Concerns are high for public safety and health protection in the event of a nuclear or radiological terrorism incident



Importance of Gaining Increased Knowledge on Low-Dose Radiation Effects in Relation to Public Policy and Regulatory Decisions – 2



- **Regulatory Agency Views:** Efforts to obtain an improved knowledge of low-dose radiation effects are considered an important activity with a potential impact on future guidelines for public and worker exposure limits
- A major area of interest is the confirmation, or the development of a scientifically defensible alternative, to the LNT dose-response model as a basis for regulations
- Research focused on characterizing the range of individual sensitivities to radiation health effects is considered to be an area of major importance
- Changes in regulatory policies and guidance will not occur rapidly, but will be given a high priority if changes are warranted on the basis of well-documented scientific evidence and predictive models of radiation health effects

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Plans for Major New NCRP Report Activity

- Major report being planned on *Low Dose and Low Dose-Rate Biological Effects and Implications for Human Health*
 - Report will incorporate results of extensive research worldwide and extend analysis of low-dose effects recently published by ICRP (Publication 99, 2004), French Academy of Sciences (2005), and U.S. National Academy of Sciences (BEIR VII, 2006)
- Primary report goals include:
 - integrate research results into reliable predictive models of low-dose radiation health effects
 - analyze health protection and regulatory implications of findings
 - recommend effective mechanisms of communication of projected radiation risks of low-dose radiation



2009 NCRP Annual Meeting (March 2-3 at Hyatt Hotel Convention Center in Bethesda, Maryland)



- ***Future of Nuclear Power Worldwide: Safety, Health and Environment***
- **International participants will discuss all aspects of nuclear power technology, safety, and health and environmental protection goals**
- **Program description and registration information available at <http://NCRPonline.org>**
- **Preregistration available on NCRP website**
- **No registration fee will be charged**