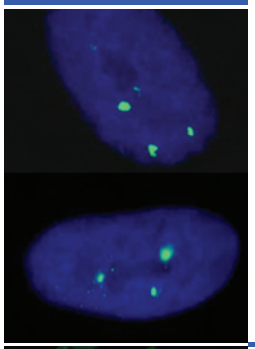
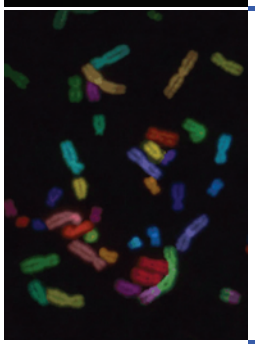
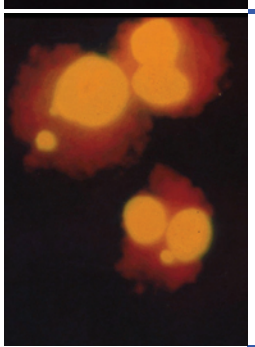






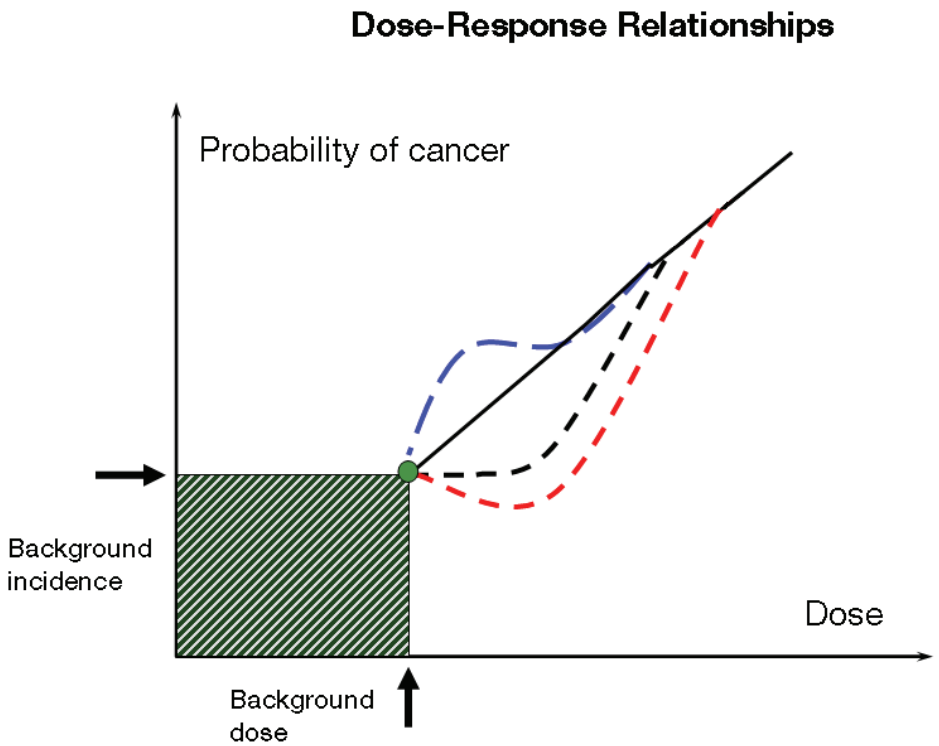
Forty-Fourth
Annual Meeting Program

Low Dose and Low Dose-Rate Radiation Effects and Models

April 14–15, 2008

Bethesda North Marriott Hotel
& Conference Center
5701 Marinelli Road
North Bethesda, MD 20852

NCRP
National Council on Radiation Protection & Measurements



See NCRP Report No. 136 (2001) for a detailed description of the contrasting types of dose-response relationships.

On the cover:

- *top*: Two nuclei have each been "hit" by three alpha particles from a microbeam and show activated γH2AX foci at the site of the traversal.
- *center*: Chromosome painting technology makes it possible to identify each human chromosome and characterize the number, location and types of aberrations produced by ionizing radiation.
- *bottom*: Measuring the frequency of micronuclei provides a rapid measure of cytogenetic damage, which increases as a function of radiation dose.

Introduction

Low Dose and Low Dose-Rate Radiation Effects and Models

Forty-Fourth Annual Meeting of the National Council on Radiation Protection and Measurements (NCRP)

Potential human health effects of low doses of ionizing radiation such as those experienced in occupational and medical exposures are of great contemporary interest. Considerable debate exists over the applicability of a linear-nonthreshold model for characterizing the biological responses and health effects of exposure to low radiation doses, and alternative models have been proposed. A related subject of interest and debate is the effect of the rate of delivery of radiation doses on the biological and health outcomes of exposure. The primary goal of the 2008 NCRP Annual Meeting will be to bring these issues into the perspective of currently available data and models of the biological responses and human health impacts of exposure to low doses of radiation. The meeting will feature presentations by international experts on the topics of (1) molecular, cellular, tissue, and laboratory animal studies on the effects of exposure to low dose and low dose-rate radiation, (2) results of epidemiological studies on human health effects of low radiation doses in occupational, medical and other exposure scenarios, (3) potential impacts of these findings on future regulatory guidance and public health policy. The perspectives of research scientists, public health officials, and regulatory agencies will be presented.

Program Summary

Monday, April 14, 2008

Opening Session

8:00 am **Welcome**
Thomas S. Tenforde
President
National Council on Radiation Protection and Measurements

8:15 am **Fifth Annual Warren K. Sinclair Keynote Address**
Issues in Quantifying the Effects of Low-Level Radiation
Dudley T. Goodhead
Medical Research Council, United Kingdom

9:15 am **Overview of Goals of the Meeting**
Antone L. Brooks
Washington State University at Tri-Cities

9:35 am **Low-Dose Extrapolation of Radiation-Related Health Risks: Status of Human Studies and State of the Art**
Charles E. Land
National Cancer Institute

10:05 am **Break**

Molecular, Cellular, Tissue and Animal Radiation Responses of Relevance to Radiation Protection

Gayle E. Woloschak and Amy Kronenberg, *Session Co-Chairs*

10:25 am **Molecular Responses: Introductory Remarks**
Amy Kronenberg
Lawrence Berkeley National Laboratory

10:30 am **DNA Damage and Repair as a Factor Contributing to Risk from Radiation**
Penny A. Jeggo
University of Sussex, United Kingdom

11:00 am **Low-Dose Gene Expression Phenotyping – Molecular Pathways for Radioprotection Against DNA Damage and Chromosomal Abnormalities in Tissues**
Andrew J. Wyrobek
Lawrence Berkeley National Laboratory

11:30 am **Radiation Protection and Nontargeted Cellular and Tissue Responses at Low Radiation Doses**
William F. Morgan
University of Maryland School of Medicine

12:00 pm **Lunch**

1:15 pm **Low-Dose Radiation Responses in Cells, Tissues and Animals: Introductory Remarks**
Gayle E. Woloschak
Northwestern University

1:20 pm **Chromosome Aberrations as a Function of Dose, Dose Rate, and Linear Energy Transfer: Implications for Radiation Risk**
Michael N. Cornforth
University of Texas Medical Branch

1:50 pm **Factors that Modify Radiation-Induced Carcinogenesis**
Ann R. Kennedy
University of Pennsylvania School of Medicine

Program Summary

2:20 pm **Role of Tissue Responses in Modification of Radiation Effects**
Mary Helen Barcellos-Hoff
Lawrence Berkeley National Laboratory

2:50 pm Break

3:10 pm **Influence of Low Linear Energy Transfer Radiation Dose and Dose Rate on Radiation Risk: Life-Span Dog Studies**
Antone L. Brooks
Washington State University at Tri-Cities

3:40 pm **Variations in Radiation Sensitivity Among Individuals—The Potential Impact on Risk Assessment**
Joel S. Bedford
Colorado State University

4:10 pm **Biophysical Modelling and Systems Biology Approaches to Understanding Low-Dose Radiation Effects**
Herwig G. Paretzke
GSF-Institut fur Strahlenschutz, Germany

4:40 pm **Break**

Thirty-Second Lauriston S. Taylor Lecture on Radiation Protection and Measurements

5:00 pm **Introduction of the Lecturer**
Michael T. Ryan

Radiation Standards, Dose/Risk Assessments, Public Interactions, and Yucca Mountain: Thinking Outside the Box
Dade W. Moeller
Dade Moeller & Associates, Inc.

6:00 pm **Reception in Honor of the Lecturer**

Tuesday, April 15

8:10 am **NCRP Annual Business Meeting**

9:10 am **Break**

Human Epidemiology Studies

John D. Boice, Jr., *Session Chair*

9:30 am **Human Epidemiology Studies as a Basis for Current Radiation Risk Estimates: Introductory Remarks**
John D. Boice, Jr.
International Epidemiology Institute

9:35 am **Low-Dose Radiation Epidemiology Studies: Status and Issues**
Roy E. Shore
Radiation Effects Research Foundation, Japan

10:05 am **Impact of Dosimetry Uncertainties on Dose-Response Analyses**
Ethel S. Gilbert
National Cancer Institute

10:35 am **Break**

10:55 am **Debate on the Topic "Does Scientific Evidence Support a Change from the LNT Model for Low-Dose Radiation Risk Extrapolation?": Moderator's Introductory Remarks**
Eric J. Hall
Columbia University

11:00 am **Affirmative Response**
Dietrich Averbeck
Institut Curie, France

11:15 am **Negative Response**
David J. Brenner
Columbia University

Program Summary

11:30 am **Reply to Dietrich Averbeck**
David J. Brenner

11:35 am **Reply to David J. Brenner**
Dietrich Averbeck

11:40 am **Questions and Discussion**

12:00 pm **Lunch**

Low-Dose Radiation Effects, Regulatory Policy and Impacts on the Public

Susan D. Wiltshire, *Session Chair*

1:00 pm **What Would It Take to Promote or Require a Change in Regulations?: Introductory Remarks**
Jill A. Lipoti
New Jersey Department of Environmental Protection

1:05 pm **Low-Dose Effects and Modeling in Public Health Decision Making: Examining the Past, Explaining the Present, and Exploring the Future**
Paul A. Locke
Johns Hopkins Bloomberg School of Public Health

1:35 pm **Low-Dose Radiation Effects, Regulatory Policy, and Impact on the Public: U.S. Nuclear Regulatory Commission Perspective**
Martin J. Virgilio

1:45 pm **U.S. Department of Energy Perspective: Supporting Research to Inform Regulatory Policy**
Noelle F. Metting

1:55 pm **U.S. Environmental Protection Agency's Perspective on What it Would Take to Promote or Require a Change in Radiation Protection Regulations**
Juan Reyes

2:05 pm **Questions and Discussion**
Paul A. Locke, *Moderator*

2:20 pm **Break**

2:40 pm **Public Perception and Policy: Introductory Remarks**
Susan D. Wiltshire
JK Research Associates

2:45 pm **Beliefs About Radiation: Scientists, the Public, and Public Policy**
Hank C. Jenkins-Smith
University of Oklahoma

3:15 pm **Federal Programs to Reimburse the Public for Environmental and Occupational Exposures**
Paul L. Ziemer
Purdue University

3:45 pm **How Do We Combine Science and Regulations for Decision Making Following Radiological Accidents and Incidents?**
John W. Poston, Sr.
Texas A&M University

4:15 pm **Closing Remarks**
Thomas S. Tenforde
President, NCRP

4:25 pm **Adjourn**

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Monday, April 14, 2008

Opening Session

8:00 am

Welcome
Thomas S. Tenforde
President, National Council on Radiation Protection and Measurements

8:15 am

Fifth Annual Warren K. Sinclair Keynote Address

Issues in Quantifying the Effects of Low-Level Radiation
Dudley T. Goodhead
Medical Research Council, United Kingdom

Much is known about health risks of ionizing radiation. Quantification of risks is far more advanced than for many other toxins. Acute tissue effects, and then cancers, became apparent remarkably soon after the discovery of x rays and radioactivity, more than 110 y ago. Experimental systems soon showed that heritable genetic risks were also possible, but these have remained elusive in humans. Studies on the survivors of the atomic bombs in Japan shifted the emphasis back to carcinogenic risk; successive follow-ups have tended to yield increased risk factors and reveal direct risks at successively lower doses. Given the inevitable statistical limitations of epidemiology, direct estimates are unobtainable at the low doses of primary relevance in radiation protection. These low-dose estimates must be obtained by purely mathematical extrapolation or with additional guidance. Commonly, the epidemiological data are fitted by applying functions containing only the simple dose dependencies that are statistically justified. Thus crucial assumptions are introduced, such as linear nonthreshold responses. Others are introduced to extend the risk factors to other exposure scenarios.

These approaches have had considerable success in protecting humans. But do they go far enough? Or, conversely, are they overprotective, thereby distorting the allocation of resources and impeding medical and industrial progress? There is a continuing need for quantification, with improved accuracy and confidence. Epidemiology is the essential starting point, but is fundamentally limited in what it can achieve. Support for the current approaches may be sought from basic studies of the critical molecules, cells, tissues, animals and humans. Historical paradigms of radiation carcinogenesis have arisen from such studies and driven the thinking of those who develop protection policy. Notions of single-hit kinetics at low doses, quadratic responses at higher doses due to interacting events, reduction at low dose rates, and increasing effectiveness with increasing ionization density, all stem from basic studies in simpler biological systems. But how robust are they as key features of radiation carcinogenesis in humans, to guide accurate quantification of risk? Advancing studies in biology should lead the way to improved quantification, including replacement of current paradigms if required, and with scope for

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extrapolations based on quantitative modelling of key steps in the carcinogenic process.

DNA damage produced by low-level radiation occurs against an extensive background of ongoing damage from natural processes. But the radiation does have special features, enabling the ubiquitous low-energy electrons to act effectively. Are the guiding messages that have been drawn from animal carcinogenesis studies sufficiently consistent for the purpose? How well justified is the reliance that has been placed on analyses of chromosome aberrations? Over the past 15 y or so, a variety of novel features have emerged in radiation biology, including induced genomic instability, bystander effects, adaptive responses, thresholds, complex and inter-related DNA repair, and signalling pathways in tissues and fundamental differences in responses between low and moderate doses. Yet, to date, these seem not to have altered basic approaches to radiation protection, nor to quantification of risk in most situations. Is this because the historical approaches are so robust and well founded, or is it because available data on the new phenomena are not sufficiently clear or relevant?

9:15 am

Overview of Goals of the Meeting

Antone L. Brooks
Washington State University at Tri-Cities

9:35 am

Low-Dose Extrapolation of Radiation-Related Health Risks: Status of Human Studies and State of the Art

Charles E. Land
National Cancer Institute

Ionizing radiation is a known and well-quantified human cancer risk factor, based on a remarkably consistent body of information from epidemiological studies of exposed populations. Typical examples of risk estimation include use of Japanese atomic-bomb survivor data to estimate future risk from radiation-related cancer among American patients receiving multiple computed tomography scans, persons affected by radioactive fallout, or persons whose livelihoods involve some radiation exposure, such as x-ray technicians, interventional radiologists, or shipyard workers. Our estimates of radiation-related risk are uncertain, reflecting statistical variation and our imperfect understanding of crucial assumptions that must be made if we are to apply existing epidemiological data to particular situations. Fortunately, that uncertainty is also highly quantifiable, and can be presented concisely and transparently.

Radiation protection is ultimately a political process that involves consent by stakeholders, a diverse group that includes people who might be expected to be risk-averse and concerned with plausible upper limits on risk (how bad could it be?), cost-averse and concerned with lower limits on risk (can you prove there is a nontrivial risk at current dose levels?), or combining both points of view. How radiation-related risk is viewed by individuals and population subgroups also depends very much on perception of related benefit, which might be (for example) medical, economic, altruistic or nonexistent.

Discussion will focus on implications of quantification and expression of radiation-related cancer risk and its uncertainty, and will draw heavily on NCRP Commentary No. 14 (*A Guide for Uncertainty Analysis in Dose and Risk Assessments Related to*

Environmental Contamination, 1996), NCRP Report No. 126 (*Uncertainties in Fatal Cancer Risk Estimates Used in Radiation Protection*, 1997), the report of the NCI-CDC Working Group to Revise the *1985 NIH Radioepidemiological Tables* (2003), and ICRP Publication 99 (*Low-Dose Extrapolation of Radiation-Related Risk*, 2006).

10:05 am **Break**

Molecular, Cellular, Tissue and Animal Radiation Responses of Relevance to Radiation Protection

Gayle E. Woloschak and Amy Kronenberg, *Session Co-Chairs*

10:25 am **Molecular Responses: Introductory Remarks**

Amy Kronenberg
Lawrence Berkeley National Laboratory

10:30 am **DNA Damage and Repair as a Factor Contributing to Risk from Radiation**

Penny A. Jeggo
University of Sussex, United Kingdom

DNA damage responses encompass pathways of DNA repair and signal transduction processes that serve to effect cell cycle checkpoint arrest and apoptosis. For DNA double strand breaks (DSB), the most biologically significant lesion induced by ionizing radiation, the major DSB rejoining process is DNA nonhomologous end-joining and the most significant signaling pathway is dependent upon the kinase, ataxia telangiectasia and Rad3 related ATM. Mammalian DNA is wrapped within chromatin; regions of DNA that are frequently transcribed lie with euchromatic DNA whilst heterochromatin regions, which are likely not transcribed, are more tightly packaged. This packaging makes DNA difficult to repair and hence the repair of even low levels of DSBs can take place over many hours. The DSB signal transduction pathway regulates a process called cell-cycle checkpoint arrest, which arrests cells at critical places in the cell cycle, to allow additional time for repair before processes such as replication or mitosis. Whilst DSB repair is important for survival postirradiation and cell-cycle checkpoint arrest is important for the maintenance of genomic stability, it is the cooperation between the two processes that is really critical to avoid genomic instability. Surprisingly, however, recent studies have suggested that the cell-cycle checkpoint that regulates entry into mitosis from G2 is not sensitive to a single DSB but rather allows progression of cells with 10 to 20 DSBs to progress into mitosis. Moreover, it does not appear to be activated by very low doses of radiation inducing less than this number of DSBs. This aspect of the damage response exposes a potential window allowing genomic instability to arise even after low doses of radiation. This will be discussed in the context of evaluating the risk from radiation exposure.

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11:00 am

Low-Dose Gene Expression Phenotyping – Molecular Pathways for Radioprotection Against DNA Damage and Chromosomal Abnormalities in Tissues

Andrew J. Wyrobek

Lawrence Berkeley National Laboratory

Our research objectives are to characterize the variations in gene expression phenotypes among radiation-sensitive tissues after exposure to low-dose radiation (<100 mGy), to distinguish between pathways that are broadly conserved among tissues and species versus those that are cell-type unique, and to develop molecular models of predicting susceptibility for persistent genetic damage and risks for tissue-specific cancers from low-dose radiation. Using transcriptional profiling of human lymphoblastoid cells from unrelated individuals, we identified low-dose unique genes that were associated with cellular homeostasis, specific signal transduction pathways, and specific subcellular locations. Some genes showed transcriptional modulation at <10 mGy with flat dose-response curves indicative of nonlinearity in the underlying mechanisms. Comparative bioinformatics analyses identified substantial similarities in gene networks and pathways between irradiated human and mouse tissues, suggesting that there are broadly conserved mechanisms of low-dose radiation response. On the other hand, there was also evidence for low-dose responses that were tissue-specific (*e.g.*, low-dose exposure of brain tissue affected pathways that were associated with memory and other neural functions). Furthermore, low-dose exposures are also known to induce radioadaptation in human cells and rodent tissues, but the underlying molecular mechanisms for radioprotection remain poorly understood. We identified a set of genes associated with protection for chromosomal aberrations in human lymphoblastoid cells, suggesting that the radioadaptive response in these cells is controlled by a multi-gene switch related to TP53 function. We have also shown that whole-body radiation of mice also induced radio-adaptive protection against DNA damage and chromosomal abnormalities in various tissues, including brain and blood. In summary, there is growing evidence that: (1) the response of cells and tissues to low-dose radiation is molecularly complex with nonlinear components, (2) certain pathways appear to be conserved across tissues and species whether irradiated *in vitro* or *in vivo*, and (3) the genomic damage consequences after low-dose radiation depend on the physiological status of cells at the time of radiation as well as on the details of the exposure regimen. Gene-expression phenotyping promises to increase our understanding of how low dose and low dose-rate exposures modulate the molecular susceptibility of cells within tissue microenvironments, and to identify the molecular pathways that control the radioadaptive response and persistence of genomic damage in tissues. Understanding the molecular basis of cellular and tissue responses to low-dose radiation has important implications for assessing long-term tissue injury and cancer risks from environmental exposures to ionizing radiation and from the rapidly increasing usage of low-dose radiation for medical diagnostics.

Monday, April 14

11:30 am

Radiation Protection and Nontargeted Cellular and Tissue Responses at Low Radiation Doses

William F. Morgan
University of Maryland School of Medicine

Nontargeted responses to ionizing radiation are those cellular and tissue effects observed in cells that were not subject to energy deposition events induced by radiation. These responses can occur in cells that were the progeny of an irradiated cell (radiation-induced genomic instability), and/or they can occur in the nonirradiated neighbors of an irradiated cell (bystander effects) after receiving signals from irradiated cells. Both genomic instability and bystander effects describe responses in nonirradiated, or nontargeted cells and tissues, and the phenotype of these responses is similar to those observed in irradiated (targeted) cells. These responses include changes in gene and protein expression, induction of mutations, chromosomal rearrangements, micronuclei, transformation, and/or apoptosis. Nontargeted effects can be observed at very low radiation doses where the shape of the dose response curve is the matter of considerable debate. Furthermore, nontargeted effects indicate that responses can be observed outside the radiation field and therefore suggest that the risk for potential radiation effects may well be greater than the volume actually irradiated.

In this presentation the evidence for nontargeted effects will be presented and the experimental systems used to characterize these responses will be described. Subsequent discussion will then debate whether irradiated cells respond differently than naïve nontargeted bystander cells and whether nontargeted effects are beneficial or detrimental to the tissue or organism. The final part of the presentation will focus on whether nontargeted effects are limited to the specific organ irradiated and thus are accounted for under current risk policies, or whether they might be insidious throughout the organism and thus significantly impact current radiation protection standards.

12:00 pm

Lunch

1:15 pm

Low-Dose Radiation Responses in Cells, Tissues and Animals: Introductory Remarks

Gayle E. Woloschak
Northwestern University

1:20 pm

Chromosome Aberrations as a Function of Dose, Dose Rate, and Linear Energy Transfer: Implications for Radiation Risk

Michael N. Cornforth
University of Texas Medical Branch

Most, if not all, important radiobiological phenomena were either discovered, or subsequently verified, using chromosome damage as the experimental endpoint. These include, but are not limited to:

- ionization density (linear energy transfer) and its relationship to relative biological effectiveness;
- aberrations as a principle cause of radiation induced cell killing; and

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- the basic shape of dose response relationships following changes in dose and dose rate.

Chromosome aberrations are an exquisitely sensitive indicator of radiation damage, and provide quantitative information on a cell-by-cell basis. For these reasons, cytogenetic data has long been favored by modelers that seek to define through extrapolation, on the basis of biophysical and molecular principles the shape of the dose response following very low doses.

In cases where physical dosimetry is not a feasible option, chromosome damage has become the "gold standard" for use in dose reconstructions. It could be argued that they hold special status among other biodosimetric approaches, because the end result of processes governing their formation are known, in several instances, to be the cause of certain cancers. That is to say, chromosome aberrations are a sensitive biodosimeter of radiation damage that can be viewed as a surrogate for carcinogenic potential.

Here we discuss briefly the contribution of radiation cytogenetics in establishing and explaining various radiobiological phenomena in connection with radiation risk, particularly that associated with very low doses.

1:50 pm

Factors that Modify Radiation-Induced Carcinogenesis

Ann R. Kennedy
University of Pennsylvania School of Medicine

It is known that numerous factors influence the yields of radiation-induced malignancies in animals; these factors include the specific characteristics of the radiation (radiation type and dose, dose rate, dose fractionation, dose distribution, etc.) as well as many factors that are not specific to the radiation exposure, such as animal genetic characteristics, the environment of the animal, dietary factors, and whether specific modifying factors for radiation carcinogenesis have been utilized in the studies. This overview will focus on the modifying factors for radiation carcinogenesis, in both *in vivo* and *in vitro* systems, and will include a discussion of the factors which can increase or decrease radiation carcinogenesis.

2:20 pm

Role of Tissue Responses in Modification of Radiation Effects

Mary Helen Barcellos-Hoff
Lawrence Berkeley National Laboratory

The cell biology of irradiated tissues reveals a coordinated multicellular damage response program in which individual cell contributions are primarily directed towards suppression of carcinogenesis and reestablishment of homeostasis. Previous studies characterized the composition of irradiated mouse tissues, identified transforming growth factor β1 (TGFβ) as a key growth factor induced by radiation, and developed novel radiation models in both mouse and cultured human cells. The ability of human mammary epithelial cells to undergo tissue-specific morphogenesis in cell culture shows that radiation disrupts epithelial cell interactions with the microenvironment. A persistently dysfunctional cell-cell and cell-extracellular matrix interaction of irradiated epithelial cells is induced in irradiated tissues. This heritable phenotype is consistent with epithelial to mesenchymal transition. The underlying mechanism of this phenotypic switch is radiation-induced extracellularly regulated kinase activation that is sustained in

the presence of TGFβ. As a result, radiation exposure of individual cells leads to the generation of daughter cells with a persistently altered phenotype accompanied by increased invasion and motility that could contribute to malignant progression.

The contribution of irradiated phenotypes in the mouse mammary radiation chimera has been tested. The mammary chimera model takes advantage of the fact that the mammary epithelium can be removed from prepubertal mammary glands and the parenchyma-free stroma can then serve as the recipient of transplanted mammary tissue. To examine the dose dependence of host irradiation on mammary cancer progression, *p53* null mouse mammary fragments were transplanted to wildtype mice irradiated whole body with 100, 500 and 1,000 mGy. Tumor frequency significantly increased and median latency for cancer incidence was decreased in irradiated hosts. To assess the contribution of TGFβ, *Tgfβ1* heterozygote hosts were subjected to a similar protocol. The effect of irradiation on *p53* null tumor frequency was absent in *Tgfβ1* heterozygote hosts. Thus, single acute radiation exposure can act through the host to drive breast cancer progression, which is in large part mediated by TGFβ abundance. These data show that high-dose radiation disrupts the interactions of multiple cell types in normal tissues that effectively suppress neoplastic potential.

Together, these studies support the global hypothesis that multicellular responses and extracellular signaling following radiation exposure are integral, rather than secondary in evaluating radiation risks. A systems biology model is needed that emphasizes the irradiated tissue/organ/organism as a system rather than a collection of noninteracting or minimally interacting cells. A key property of a system is that some phenomena emerge as a property of the system rather than the parts. Cancer can thus be considered as an emergent phenomenon of a perturbed system. Given the current research goal to determine the consequences of high versus low radiation exposures, then broadening the scope of radiation studies to include systems biology concepts should benefit risk modeling of radiation carcinogenesis.

2:50 pm **Break**

3:10 pm **Influence of Low Linear Energy Transfer Radiation Dose and Dose Rate on Radiation Risk: Life-Span Dog Studies**

Antone L. Brooks
Washington State University at Tri-Cities

There is very little human data on the risk from high doses of low linear energy transfer radiation delivered at low dose rates. To help understand this risk, extensive studies were conducted on Beagle dogs exposed to ionizing radiation both from external whole-body ^{60}Co gamma rays and internally deposited beta-gamma emitting radioactive material. This presentation will evaluate this very large data set. The internal emitter studies included different routes of exposure (ingestion, injection, inhalation), a range of radionuclides with different half-lives (^{90}Y, ^{91}Y, ^{144}Ce, ^{90}Sr, ^{137}Cs) and target organs (lung, liver, bone, whole body). The isotopes were also delivered in different chemical and physical forms which influenced their retention, deposition and distribution. The data defined a high dose rate and total dose for each target organ above which acute deaths occur. Most of the animals

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that survived these early acute effects lived for long periods of time and were at increased risk for cancer. When the total data for the internally deposited radioactive material was evaluated at doses to the target organ <10 Gy there was no detectable increase in the cancer frequency. This presentation will compare the dose-response relationships from internally-deposited radioactive materials to that from chronic and acute whole-body exposure and help put dose, dose rate, and dose distribution into a useful framework for risk estimates. For the same total dose, both cancer frequency and early deaths were markedly decreased when the radiation was delivered at a low dose rate. Nonuniform dose distribution also decreased the effectiveness of the radiation in producing cancers. Such data provide a strong scientific base for predicting the outcome of low dose-rate exposures to large total doses, estimating risk from these exposures, and defining a realistic dose-rate effectiveness factor.

3:40 pm

Variations in Radiation Sensitivity Among Individuals: The Potential Impact on Risk Assessment

Joel S. Bedford
Colorado State University

The possible impact of genetic variation in susceptibility to radiation carcinogenesis has been considered and discussed for many years, especially following the discovery some 40 y ago that certain heritable defects, such as that associated with the autosomal recessive disorder, ataxia telangiectasia, could lead to extreme hypersensitivity to effects of ionizing radiation exposure. For several reasons, including the very low incidence, the limited number of genetic disorders known with hyper-radiosensitive phenotypes, and even the projected numbers of individuals who may be of intermediate radiosensitivities due to heterozygosity for such known genes was sufficiently low that their proportion in the population was not expected to significantly influence risk estimates. Reports of several studies over the past two decades have increasingly suggested that there may be a much higher proportion of individuals whose cells indicate hypersensitivity phenotypes than previously expected. The levels of hypersensitivity do not reach the extremes seen for cells from *ATM* -/- individuals, or from well known mutants in rodent cell systems, but to the extent that the cellular radiosensitivity phenotypes reflect the proportions of individuals who may be similarly hypersensitive for carcinogenesis this would clearly warrant reevaluation of the possible implications for radiation protection. The data suggesting this conclusion will be presented.

4:10 pm

Biophysical Modeling and Systems Biology Approaches to Understanding Low-Dose Radiation Effects

Herwig G. Paretzke
GSF-Institut fur Strahlenschutz, Germany

Radiation affects all three aspects of health as a status of complete physical, mental and social well-being. This is particularly true for real and perceived low-dose radiation effects on human health. Mathematical quantifications of likelihoods of such health effects in individuals is still not possible. This will never be possible based on epidemiological investigations alone because of statistical reasons

and lack of homogeneity in larger populations. The only promising approach is by close cooperation of theorists and experimentalists from various relevant disciplines, and by carefully selected experiments based on well defined, quantitative working hypotheses for important steps of maintaining regular homeostasis and for disturbances (*e.g.*, by irradiation). Studying such processes at different levels of a complex living system with adaptive responses of its various regulation networks poses high demands on life scientists as well as on mathematicians. This contribution will outline some present approaches to draw general, quantitative conclusions from many types of experimental observations.

4:40 pm **Break**

Thirty-Second Lauriston S. Taylor Lecture on Radiation Protection and Measurements

5:00 pm **Introduction of the Lecturer**
Michael T. Ryan

Radiation Standards, Dose/Risk Assessments, Public Interactions, and Yucca Mountain: Thinking Outside the Box

Dade W. Moeller
Dade Moeller & Associates, Inc.

The information in this presentation is based on studies performed during the past 5 y on various facets of the proposed Yucca Mountain high-level radioactive waste repository. The initial topic pertains to the standards promulgated for this facility by the U.S. Environmental Protection Agency under the restrictions and limitations imposed by the U.S. Congress and the Circuit Courts. This documents that the standards are neither integrated, nor consistent, one example being that the estimated release of a specific radionuclide can comply with one portion of the standards and not another. The second topic includes a summary of the evaluations of the associated dosimetry. These findings revealed that five of the eight so-called primary radionuclides that will be present in the waste, are of little or no health concern. Equally important is that it was determined that, even if the dose rates could be accurately projected hundreds or thousands of years into the future, it will not be possible to estimate their associated health risks. This, in essence, rules out the application of a risk-based approach to the long-term assessment of the performance of the repository. The third topic pertains to the anticipated events accompanying the processing of the license application. This will involve hearings before the Senate, as well as multiple public hearings in major population centers throughout the United States. If the U.S. Department of Energy

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(DOE) is to effectively and successfully complete these hearings, it will be necessary to prepare a set of statements that can be used to respond to the full range of questions that may be raised. One example of such statements would be a review of, and rebuttal to, the multiple myths about radiation that are held by members of the public. In a closing segment, the restrictions in the standards that prohibit DOE from projecting or applying estimates of "changes in … human biology, or increases or decreases in human knowledge or technology" are evaluated in the light of the fact that a poll of cancer experts showed that the vast majority projected that methods for the prevention and/or cure of most of the cancers affecting humankind today will become a reality within the next 50 to 100 y. Supporting these projections are the development and current application of a vaccine for cervical cancer, and the report of a federal expert cancer group that the annual rate of deaths from colorectal cancer, the second highest contributor to such deaths in the United States, is being reduced at an annual rate of almost 5 % for men, and 4.5 % for women. It was in anticipation of such developments that the National Council on Radiation Protection and Measurements stated that if "an increased proportion of the adverse health effects of radiation prove to be either preventable or curable by advances in medical science, the estimates of the long-term detriments may need to be revised as the consequences (risks) of doses to future populations …" are reduced. This confirms the fact that it is time that the radiation protection profession and the regulatory agencies that promulgate the applicable regulations begin "thinking outside the box," as contrasted with adherence to a requirement that DOE must estimate changes "related to the geology, hydrology, and climate" that "could affect the Yucca Mountain disposal system over the next 10,000 years." The latter approach appears neither reasonable nor appropriate in light of the fact that a decrease in the risk of fatal cancer as a disease that threatens the U.S. population will occur within the next 50 to 100 y.

6:00 pm **Reception in Honor of the Lecturer**

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Tuesday, April 15

8:10 am **NCRP Annual Business Meeting**

9:10 am **Break**

Human Epidemiology Studies

John D. Boice, Jr., *Session Chair*

9:30 am **Human Epidemiology Studies as a Basis for Current Radiation Risk Estimates: Introductory Remarks**
John D. Boice, Jr.
International Epidemiology Institute

9:35 am **Low-Dose Radiation Epidemiology Studies: Status and Issues**
Roy E. Shore
Radiation Effects Research Foundation, Japan

Although the Japanese atomic-bomb study and radiotherapy studies have clearly documented cancer risks from high-dose radiation exposures, the National Council on Radiation Protection and Measurements and other radiation risk assessment groups have long recognized that protracted or low exposures to low linear energy transfer radiations are key radiation protection concerns, because these are far more common than high-exposure scenarios. Epidemiologic studies of human populations with low dose or low dose-rate exposures are one approach to addressing those concerns. A number of large studies of radiation workers (Chernobyl cleanup workers, Mayak workers, United States and Chinese radiologic technologists, and the 15-country worker study) or those exposed to environmental radiation at moderate to low levels (residents near Techa River, Semipalatinsk, Chernobyl, or nuclear facilities) have been conducted. A variety of studies of medical radiation exposures (multiple fluoroscopy, diagnostic ^{131}I, scatter radiation doses from radiotherapy, etc.) also are of interest. Key results from these studies will be summarized and compared with risk estimates from the Japanese atomic-bomb study.

Ideally, one would like the low dose and low dose-rate studies to guide radiation risk estimation regarding the shape of the dose-response curve, dose and dose-rate effectiveness factor, and risk at low doses. However, the degree to which low-dose studies can do so is subject to various limitations, especially those pertaining to dosimetric uncertainties and limited statistical power.

The identification of individuals who are particularly susceptible to radiation cancer induction is of high interest in terms of occupational and medical radiation protection. Questions also have been raised as to how susceptible individuals in the population may influence the aggregate risk at low doses. Issues pertaining to radiation-related cancer susceptibility studies will be outlined, and several examples of such studies will be discussed.

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10:05 am

Impact of Dosimetry Uncertainties on Dose-Response Analyses

Ethel S. Gilbert
National Cancer Institute

Radiation dose estimates used in epidemiological studies are subject to many sources of uncertainty, and the error structure may be a complicated mixture of different types of error. Increasingly, efforts are being made to evaluate dosimetry uncertainties and to take account of them in statistical analyses. The impact of these uncertainties on dose-response analyses depends on the magnitude and type of error as discussed below.

Errors that are independent from subject to subject (random errors) reduce statistical power for detecting a dose-response relationship and increase uncertainties in estimated risk coefficients. However, statistical tests based on uncertain dose estimates are generally valid even without using special statistical methods that account for dose uncertainties. Without improving dose estimates, it is not possible to avoid this loss of power.

Other effects of random errors depend on whether the errors are "classical" or "Berkson." A measurement error is classical if the error is independent of the true dose, that is, the measured doses vary about the true doses. Classical error can be thought of as error that arises from an imprecise measuring device such as a film badge dosimeter. If data are analyzed without attention to dose uncertainties, the presence of classical error attenuates the dose-response toward the null and may distort the shape of the dose-response.

A measurement error is Berkson if the error is independent of the observed dose. Berkson error occurs when a single dose is used to represent a group so that the true doses of individuals vary about the assigned group dose. An example is the application of a single factor to convert recorded doses to organ doses for nuclear workers in a given facility and time period even though the correct factor varies among the workers to whom it is applied. In contrast to classical error, the presence of Berkson error does not result in bias in linear risk coefficients. However, non-Berkson error may also be present if the assigned group doses differ from true mean doses for the groups to whom they are assigned.

Uncertainties in quantities that are common to some or all subjects are "shared" uncertainties. For example, in the Japanese atomic-bomb study, uncertainty in the yields of the bombs is a shared uncertainty since it affects doses of all subjects in a given city in a similar manner. Such uncertainties increase the possibility of bias, and accounting for this possibility increases the length of confidence intervals.

The impact of dose uncertainty on the direct evaluation of risks at low doses and dose rates is, in general, as noted above. First, if a significant dose-response relationship is found in a low-dose study, it is unlikely to result from dose uncertainties. Second, the low power inherent in studying small risks may be further reduced by random dosimetry uncertainties. Thus, dosimetry errors are much are more likely to mask a true effect than to create a spurious one. In addition, classical errors and shared dosimetry uncertainties increase the potential for bias in estimated risks coefficients, but this potential may already be large due to the extreme vulnerability to confounding in studies involving very small relative risk.

10:35 am **Break**

10:55 am **Debate on the Topic "Does Scientific Evidence Support a Change from the LNT Model for Low-Dose Radiation Risk Extrapolation?": Moderator's Introductory Remarks**
Eric J. Hall
Columbia University

11:00 am **Affirmative Response**
Dietrich Averbeck
Institut Curie, France

Low dose effects of ionizing radiation are usually less evident than high dose effects on living matter. The latter effects are more easily quantifiable and experimentally accessible. Epidemiological studies do not easily detect biological risks at low doses and low dose rates. Thus, knowledge of fundamental mechanisms involved are essential to understand and assess low dose radiation risks. The linear nonthreshold (LNT) model is based on the notion that the physical energy deposition of ionizing radiation lets the carcinogenic risk increase linearly with increasing dose (*i.e.*, the carcinogenic effectiveness remains constant irrespective of dose and dose rate). The model has been taken as a useful basis for regulatory measures in radiation protection. However, recent developments and new findings in radiation and molecular biology strongly challenge the LNT concept. Indeed, as pointed out by the report of the French Academies recent biological results (also quoted in BEIR VII and ICRP reports) are in contradiction with the use of the LNT model for evaluating radiation risks at low and very low-dose exposure levels. In fact, there is evidence against its validity. Several lines of evidence demonstrate that living cells and tissues react differently (quantitatively and qualitatively) to radiation insults from high and low dose exposures. At the cellular level, some protection mechanisms are especially active at low doses. These include protection against reactive oxygen species (induced by ionizing radiation), cellular signaling activation of DNA repair, and elimination of damaged cells by cell death. In line with this, at very low doses (1 mGy) and dose rates (1.5 mGy min^{-1}) repair of DNA double strand breaks has been shown to be absent due to absence of proper signaling, and damaged cells disappear by cell death. Following the somatic cell mutation theory of carcinogenesis this implies that at those very low exposures there is no initiation of cancer cells. At slightly higher doses and dose rates, DNA repair is fully activated, and at doses >200 mGy repair is increased, probably in order to maintain sufficient cell viability and tissue functions. This repair can be in part error-prone giving rise to chromosomal damage and mutations. If cellular damage is too high, some cells will undergo apoptosis or even necrosis. In accord with this, very low doses induce or repress different types of genes than higher doses. Data from transcriptome and proteome analysis (phosphoproteome) demonstrate that different gene and protein families are induced (or repressed) or activated (or not) at low (20 mGy) and high doses (gray). Thus, different signaling and processing after ionizing irradiation determine the final outcome in terms of mutagenesis and carcinogenesis, and it is illegitimate to extrapolate from high to low doses.

Also, we observed that enzymes involved in DNA damage signaling at low dose-rate

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exposures differ from those operating at high dose rate. Cell death, mutation induction, induction of cell transformation *in vitro* and carcinogenicity have been demonstrated to be lower at low than at high dose rate, probably due to more efficient DNA repair at low dose-rate exposures.

In addition, phenomena like low dose hypersensitivity and radioadaptive responses confirm that cellular responses are highly dependent on initial exposure levels. The activation of the nick sensor, poly (ADP-ribosyl) polymerase and induction of apoptosis depend on the dose levels. Bystander effects are known to induce nonlinear responses at low levels due to intercellular communication and signaling, and dose thresholds and protective effects have been reported. Although a low-dose bystander effect giving rise to enhanced mutagenesis has been observed with alpha rays on human cells *in vitro*, epidemiological data on dial painters contaminated with radium or patients contaminated with thorotrast revealed no excess of cancer cases at cumulative doses <1 Gy from alpha ray emitters. Recent work shows that low-dose exposures (alpha and gamma rays) of normal cells, co-cultured with unirradiated preneoplastic cells, exert signaling (including factors such as TGFβ) from irradiated normal cells which effectively induce apoptosis in the unirradiated preneoplastic cells (threshold at >2 mGy for gamma rays, and 0.29 mGy for alpha rays). This eliminates premalignant cells at low doses but not at high doses. Effective immunosurveillance is also likely to play an important role in protecting against cancer development after low doses. Indeed, high doses can affect immunological defenses.

Altogether, the above arguments are in favor of lower than expected biological effects (threshold responses) at low doses and low dose rates. Thus, the hithero plausible biophysical rationale for using LNT for extrapolation from high doses to low doses is overcome by new biological facts concerning low-dose exposures. We are facing higher complexity of the biological response at low dose and low dose rates. This is also true for epidemiological data where the number of possible confounding factors involved appears to be greater at low than at high radiation doses. Thus, risk evaluations at low exposure levels have to take more parameters into account and ask for a different type of modeling. Obviously, the LNT model cannot fulfill this role.

Up to now, radioprotection regulatory measures were conceived as being regularly adjustable to increasing scientific knowledge. Thus, it is scientifically sound, and wise from the practical and economical point of view, to decrease existing uncertainties for low-dose risk evaluation by taking into account the new findings.

11:15 am

Negative Response

David J. Brenner
Columbia University

There is convincing epidemiological evidence that doses of ionizing radiation above about a few tens of milligray cause a small but significant increase in cancer risk. At lower doses, however, even the largest epidemiological studies have insufficient power, and so we have to rely on “expert opinion” guided, where appropriate, by the best available biology.

Two expert reports have been published recently which give diametrically opposing expert opinions. The BEIR-VII report, from the U.S. National Academy of Sciences, concludes that, at low doses, as the dose

is lowered, the cancer risk simply decreases proportionately—a "linear no threshold" model down to arbitrarily low doses. By contrast, the French Academy of Sciences (FAS) suggested that, at very low doses, the risk per unit dose for ionizing radiation-induced cancer is lower than that established at higher doses, and may well be effectively zero, or even negative.

FAS arguments essentially revolve around the claim that different biological processes dominate radiation damage responses at very low doses (below ~10 mGy), compared with higher doses. For example, the claim is made by FAS that, at these very low doses, essentially all radiation-damaged cells will be eliminated through apoptosis or other mechanisms, while at somewhat higher doses, radiation damage and subsequent misrepair can ultimate result in cancer. It will be argued that (1) there is no plausible evidence for different damage response pathways at very low doses, and (2) even if there were such evidence, which would by necessity come from *in vitro* studies, we would not be able to predict the consequences in terms of low dose cancer risks in humans.

There is no doubt that the linear (nonthreshold) approach for extrapolating risks to low doses (which has been adopted by most national and international organizations) can and should be critically examined. The arguments for a linear nonthreshold model at very low doses are plausible, but rely on assumptions about single cells acting autonomously, which are unlikely to be completely correct. However, at this time we don't know if deviations from the predictions of this linear approach will be large or small, nor even whether they will increase or decrease low-dose cancer risk estimates. We are only just beginning to scratch the surface of our understanding of the impact of intercellular interactions on very low-dose cancer risks, so it is more than premature to be advocating changes in policy or practice.

11:30 am **Reply to Dietrich Averbeck**
David J. Brenner

11:35 am **Reply to David J. Brenner**
Dietrich Averbeck

11:40 am **Questions and Discussion**

12:00 pm **Lunch**

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Low-Dose Radiation Effects, Regulatory Policy and Impacts on the Public

Susan D. Wiltshire, *Session Chair*

1:00 pm

What Would It Take to Promote or Require a Change in Regulations?: Introductory Remarks

Jill A. Lipoti
New Jersey Department of Environmental Protection

1:05 pm

Low-Dose Effects and Modeling in Public Health Decision Making: Examining the Past, Explaining the Present, and Exploring the Future

Paul A. Locke
Johns Hopkins Bloomberg School of Public Health

The majority of our public health and environmental protection laws, and the federal agencies that administer them, are less than a century old. Public health policy and regulatory decision making at these agencies and in Congress has been transformed substantially, especially during the last 50 y. Scientific methods and understanding about biological processes has evolved during this same time period, particularly in the area of low-dose radiation effects. Policies and practice at federal agencies have sought to keep up with these advancements and Congress has passed laws to respond to this shifting scientific landscape.

During this same period, the scope and character of radiation exposures to the public has changed and public perception about radiation risk has evolved. In setting public policies and promulgating regulations, scientific information about low-dose effects is one of several factors that decision makers weigh. This presentation will examine how issues associated with low-dose radiation exposure were addressed in the past and how they are treated in policy making today. It will also explore the emerging public health protection and policy challenges that are likely to arise as our scientific knowledge expands.

1:35 pm

Low-Dose Radiation Effects, Regulatory Policy, and Impact on the Public: U.S. Nuclear Regulatory Commission Perspective

Martin J. Virgilio

The system of radiological protection implemented by the U.S. Nuclear Regulatory Commission (NRC) aims primarily to provide adequate protection of public health and safety, and to protect the environment. Its health objectives are relatively straightforward: to manage and control exposures to ionizing radiation, so that deterministic effects are prevented, and the risk of stochastic effects is reduced to the extent reasonably achievable.

Analysis of literature reviews by the National Academy of Sciences and the United Nations Scientific Committee on the Effects of Atomic Radiation and the 2007 radiation protection recommendations published by the International Commission on Radiological Protection do not suggest that any significant change to our system of regulatory protection is warranted. However, several issues have been raised that may prompt the NRC to reexamine its radiation protection

standards. These issues include: potential gender and age differences in radiation sensitivity, evidence suggesting that the threshold for cataracts formation may be less than several gray, the ability to identify genetic markers in people who may be abnormally sensitive to radiation exposure, and the possible existence of a real or practical threshold in radiation dose response.

The current system of radiological protection is considered to be adequately protective of both sexes and all ages, especially in view of the considerable uncertainty regarding the induction of adverse biological effects following very low radiation exposures (<10 mSv). Use of the linear nonthreshold (LNT) model is considered to be the best practical approach to managing risk from radiation exposure and remains a prudent basis for radiological protection at low doses and low dose rates. However, additional information is needed, particularly as it pertains to deoxyribonucleic acid (DNA) damage repair, the identification and characterization of radiation sensitive populations, obtaining evidence that supports or refutes the LNT assumption at low dose and low dose-rate exposures, and data to support the beneficial, or adverse, effects of low-dose radiation exposure.

NRC will continue to monitor basic research programs such as the U.S. Department of Energy's low-dose radiation research program and the European Commission's radiosensitivity and cancer susceptibility research program, and will work with our stakeholders to ensure that our regulations are effective, efficient and realistic, and based on sound scientific information. NRC endorses radiological protection recommendations that (1) provide tangible improvements in the adequate protection of public health and safety and (2) can be implemented by practitioners and regulatory authorities in a practical, timely, and cost effective manner. NRC will continue to review the scientific literature, encourage the scientific community to develop new techniques for better elucidating the biological effects attributable to very low radiation doses, and will work with other federal agencies to develop documents that relate such effects to the needs of radiological protection. NRC supports the development of realistic models that best predict stochastic health effects without incorporating excess conservatism into prediction models.

1:45 pm

U.S. Department of Energy Perspective: Supporting Research to Inform Regulatory Policy
Noelle F. Metting

The U.S. Department of Energy (DOE) is responsible for regulating and managing both the use of radioactive material and the exposure to radiation by its contractors and operations. DOE is committed to ensuring that radiation exposures to its workers and the public and releases of radioactivity to the environment are maintained below regulatory limits, and takes deliberate efforts to further reduce dose where practicable. To meet this objective, DOE establishes and maintains a system of regulatory policy and guidance reflective of national and international radiation protection standards and recommendations. The incorporation of these recommendations is consistent with federal policies established through interagency coordination that include all of the agencies having radiation protection responsibilities. Coordination is accomplished through such groups as the Interagency Steering Committee on Radiation Standards.

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DOE is the primary agency supporting low dose radiation effects research. DOE's Low Dose Radiation Research Program is supporting research to determine health risks from exposures to low levels of radiation. The new scientific information generated by this research is critical input for regulatory agencies who seek to adequately and appropriately protect people from radiation while making the most effective use of our country's national resources.

The Low Dose Program has emphasized research on a number of critical biological phenomena induced by radiation exposure, including adaptive responses, bystander effects, and genomic instability. The research is focusing greater attention on use of more normal tissue systems, moving away from use of artificially isolated cell culture systems and/or tumor cell lines. DOE also partners with the National Aeronautics and Space Administration to fund some of these research projects. To date, the Program has resulted in publication of over 480 peer-reviewed papers. Future research will be directed towards developing models that incorporate both biological and epidemiological data.

Radiation protection standards are viewed by some as based on overly conservative assumptions that may exaggerate health risks, while others hold equally strong views that the standards should not be changed or may not be conservative enough. Results of this research may help resolve some of the differences between these strongly held views. While our understanding of the biological effects of and responses to low doses of ionizing radiation has increased dramatically as a result of this research program, translating this information into radiation risk models and radiation protection standards remains a significant challenge. This presentation will give a brief review of the status of current low-dose research and our thoughts on how it could impact future regulatory policy.

1:55 pm

U.S. Environmental Protection Agency's Perspective on What it Would Take to Promote or Require a Change in Radiation Protection Regulations
Juan Reyes

The U.S. Environmental Protection Agency (EPA) is committed to using the best available science when writing regulations and establishing policy. As science has moved forward, so have EPA's regulations. Often this means that the regulations we issue today use better science than was available when we issued older regulations. A decision to go back and update a regulation is often determined by whether the old regulation is still adequately protective or not. The rulemaking process, including seemingly minor updates to rules, can be lengthy and costly. When allocating resources to projects during annual budget planning, a decision to update a still adequate regulation may be deferred in favor of more immediate priorities. That is why EPA has regulations in place dating back to the early 1970s when the International Commission on Radiological Protection's (ICRP) Publication 2 was used to calculate maximum permissible body burdens and critical organ doses. Compared against the newer science, it is often easy to demonstrate that the regulations based on the older dosimetry methods are still protective. Therefore, the first answer to the question posed by this session is that EPA would require a change in a regulation when it can be demonstrated that it is no longer protective of public health and the environment.

A second reason for bringing a regulation in line with current science would be when

doing so would bring substantial regulatory relief, including cost savings, while still maintaining an optimal level of protection for the public and the affected work force. It is this second reason, the relaxing of overly burdensome regulations, which most people will think of when asking the above question. Many critics of current radiation protection regulations believe that the linear nonthreshold model, which serves as the basis for many standards, is itself overly burdensome and unnecessarily conservative. It is therefore worth considering how EPA would react to scientific evidence of a dose threshold for radiogenic cancer.

First, there would be a need to fully examine the validity and implications of this finding. Regulatory changes would not likely come fast. If the research was sufficiently compelling, EPA would look to the major radiation advisory bodies for advice. Among these organizations are the National Council on Radiation Protection and Measurements, the National Academy of Sciences, the United Nations Scientific Committee on the Effects of Atomic Radiation, and ICRP. Scientific consensus among these organizations would likely lead EPA to reconsider its radiation protection standards. However, implementing a set of standards based on a threshold, which may vary across members of the population, would pose challenging practical and philosophical problems.

2:05 pm **Questions and Discussion**
Paul A. Locke, *Moderator*

2:20 pm **Break**

2:40 pm **Public Perception and Policy: Introductory Remarks**
Susan D. Wiltshire
JK Research Associates

2:45 pm **Beliefs About Radiation: Scientists, the Public, and Public Policy**
Hank C. Jenkins-Smith
University of Oklahoma

Human behavioral responses to potential hazards are mediated by the beliefs people hold about those hazards. This holds whether the “behavior” under consideration is the provision of advice about the hazard, statements of support for policies that address the hazard, or personal behaviors in response to the hazard. This paper focuses on beliefs about radiation and the implications of those beliefs for views about radiation protection by both scientists and members of the U.S. public. Data are used from a large sample of scientists, collected in 2002, and a series of surveys of the U.S. public collected between 2005 and 2007. Among scientists, the paper focuses on how beliefs about radiation are related to policy prescriptions for radiation protection. Among members of the lay public the focus shifts to the relationship between beliefs about radiation risks and policy preferences for nuclear energy and nuclear waste policy options. The importance of the differences and similarities in the patterns of beliefs of scientists and the lay public are discussed.

Abstracts

3:15 pm

Federal Programs to Reimburse the Public for Environmental and Occupational Exposures

Paul L. Ziemer
Purdue University

Since the mid-1980s there has been growing public concern about possible health effects associated with radiation exposures of veterans and atomic weapons workers. These concerns have led to a series of Congressional actions that have resulted in legislation creating four compensation programs that are intended to compensate individuals whose radiation exposures may be considered a causative agent for specified health effects.

The Veterans Dioxin and Radiation Exposure Compensation Act of 1984 is administered by the U.S. Department of Veterans Affairs (VA) and is directed to veterans exposed while participating in atmospheric nuclear testing or in the occupation of Hiroshima and Nagasaki. The Defense Threat Reduction Agency (DTRA) determines the participation and dose status for some 1,000,000 potential claimants. Eligibility for compensation is based on verification that the individual was in a specified participant group, has medical proof of a qualifying disease, and has a dose estimate for which the probability of causation shows that the disease was "at least as likely as not" caused by the radiation. The program does not provide lump-sum awards, but rather makes use of a somewhat complex award formula.

The Radiation-Exposed Veterans Compensation Act of 1988 is also administered by VA. This program grew out of dissatisfaction of veterans and members of the public on the dose reconstruction processes and payout rates for the 1984 program. In this program, the claimant need only show proof of being in the specified participant group and medical proof of having the eligible disease. Compensation for the 400,000 potential claimants is also based on a complex awards formula.

The Radiation Exposure Compensation Act of 1990 grew out of political pressure by nuclear test-site worker advocates, and civilians who lived downwind from atmospheric test locations. The program is administered by the U.S. Department of Justice, with support from DTRA. Compensation for the 50,000 potential claimants is based on proof that the claimant falls into a defined participant group and medical proof that the claimant has a qualifying disease. Lump-sum compensation is provided for successful claimants in the amount of $75,000 for on-site atmospheric test participants, $50,000 for downwinders, and $100,000 for uranium workers.

The Energy Employees Occupational Illness Compensation Act of 2000 provides for $150,000 in lump-sum compensation to workers who contracted certain diseases as a result of exposure to beryllium, silica, or radiation while working for the U.S. Department of Energy (DOE), its contractors, or subcontractors in the nuclear weapons industry. The program is administered by the U.S. Department of Labor with support of the U.S. Department of Health and Human Services and DOE. Eligibility is determined by proof that the claimant worked at one of the specified weapons-related sites during an eligible time period, and proof of an eligible disease. Compensation is provided for claimants in cases where the reconstructed dose is shown to result in a probability of causation of 50 % or greater at the 99 % credibility level. In cases where claimants' doses cannot be reconstructed "with sufficient accuracy," the legislation provides a process whereby such individuals may become part of a "special exposure cohort" for which dose reconstruction is not required.

Tuesday, April 15

3:45 pm

How Do We Combine Science and Regulations for Decision Making Following Radiological Accidents and Incidents?

John W. Poston, Sr.
Texas A&M University

Approaches to safety regulations—particularly radiation safety regulations—must be founded on the very best science possible. However, radiation safety regulations always lag behind the science for a number of reasons. First, the normal scientific process of peer-review, debate, and confirmation must ensure that the conclusions are indeed correct, the implications of the research are fully understood, and a consensus has been established. Finally, in the United States, there is a well-established, all-inclusive political process that leads to changes in radiation safety regulations. This process can take a very long time, as was demonstrated when the process was initiated to change the Code of Federal Regulations more than 20 y ago in response to Publication 26 from the International Commission on Radiological Protection and other recommendations.

Currently we find ourselves in a situation where the possibility of a radiological accident or attack may occur and where the existing body of regulations provides very little guidance. Many international and national bodies, including several federal agencies, have provided recommendations on the appropriate levels of exposure for first responders and first receivers, as well as for the general public. However, some agencies provide guidelines based on very conservative dose limits which are not appropriate in situations where there is a substantial chance for the loss of lives and critical infrastructure. It is important that an emergency response is not hampered by overly cautious guidelines or regulations. In a number of exercises the impact of disparate guidelines and training in radiological situations has highlighted the need for clear reasonable limits that maximize the benefit from an emergency response and for any cleanup after the incident.

This presentation will focus first on the federal infrastructure established to respond to radiological accidents and incidents. It will review briefly the major recommendations, both international and national, for responders and will attempt, where possible, to establish the scientific foundation for these guidelines. We will also stress the need to clearly and openly communicate the recommendations to the first responders and the public so that no unnecessary anxiety or associated irrational actions on their part impedes the ability to respond to a disaster. Finally, the use of these guidelines and recommendations by decision makers at all levels will be discussed.

4:15 pm

Closing Remarks

Thomas S. Tenforde
President, NCRP

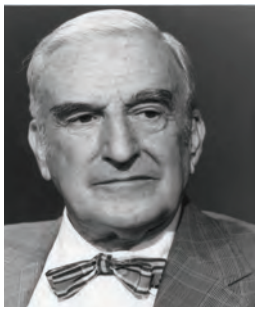
4:25 pm

Adjourn

Mission Statement

The National Council on Radiation Protection and Measurements (NCRP) seeks to formulate and widely disseminate information, guidance and recommendations on radiation protection and measurements which represent the consensus of leading scientific experts. The Council monitors areas in which the development and publication of NCRP materials can make an important contribution to the public interest.

The Council's mission also encompasses the responsibility to facilitate and stimulate cooperation among organizations concerned with the scientific and related aspects of radiation protection and measurements.



Lauriston S. Taylor
1929–1977

Warren K. Sinclair
1977–1991

Charles B. Meinhold
1991–2002

Thomas S. Tenforde
2002–

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Registration

Monday, April 14, 2008	7:00 am – 5:00 pm
Tuesday, April 15, 2008	7:00 am – 1:00 pm

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2009 Annual Meeting

Future of Nuclear Power Worldwide: Safety, Health and Environment

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NCRP Publications

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Low Dose and Low Dose-Rate Radiation Effects and Models

Publication	Title	Price
Report No. 150	Extrapolation of Radiation-Induced Cancer Risks from Nonhuman Experimental Systems to Humans	$ 65.00
Report No. 136	Evaluation of the Linear-Nonthreshold Dose-Response Model for Ionizing Radiation	50.00
Report No. 126	Uncertainties in Fatal Cancer Risk Estimates Used in Radiation Protection	25.00
Report No. 117	Research Needs for Radiation Protection	30.00
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Report No. 104	The Relative Biological Effectiveness of Radiations of Different Quality	45.00
Report No. 96	Comparative Carcinogenicity of Ionizing Radiation and Chemicals	40.00

Excerpts from reviews and correspondence related to NCRP reports:

"The report [NCRP Report No. 150] was authored by an outstanding committee of scientists who have extensive experience in radiation carcinogenesis and mutagenesis in nonhuman systems and in risk assessment."

"This report will be of considerable interest to anyone concerned with problems in risk assessment and particularly how studies of nonhuman systems can help reduce uncertainties in risks that cannot be addressed in epidemiological studies."

K.L. Mossman [published in Health Physics **91** (2006) 171]

"Although an exhaustive citation of the vast literature was outside the scope of its report [NCRP Report No. 136], the Committee made a concerted effort to evaluate all data pertinent to the LNT hypothesis, whether pro or con."

A.C. Upton [published in Health Physics **82** (2002) 256]

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Issues in Quantifying the Effects Of Low Level Radiation

Dudley T Goodhead

c/o Medical Research Council
Harwell, UK.

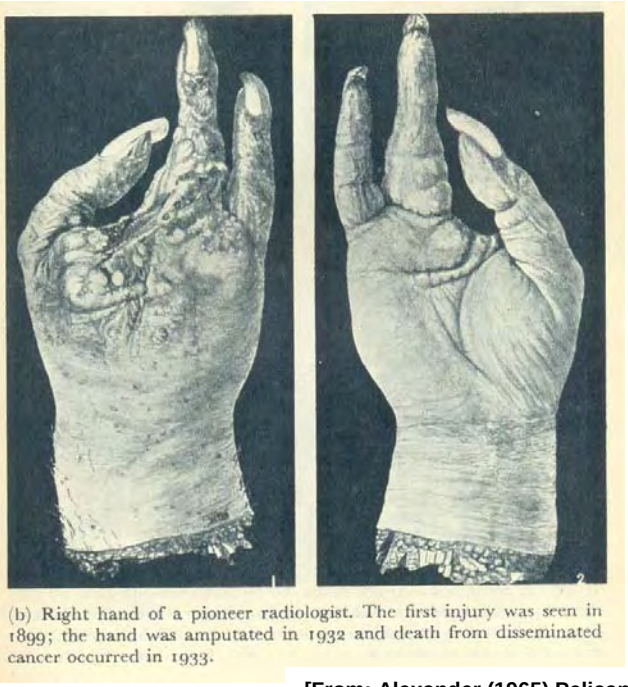
44th Annual Meeting of the NCRP
Bethesda, 14 April 2008

X-rays discovered in 1895 by Roentgen

FIG. 1.—Photograph of the bones in the fingers of a living human hand. The third finger has a ring upon it.

+ 1 year ⟶ skin burns reported
+ 7 years ⟶ skin cancer reported

(1899-1932)



(b) Right hand of a pioneer radiologist. The first injury was seen in 1899; the hand was amputated in 1932 and death from disseminated cancer occurred in 1933.

[From: Alexander (1965) Pelican]

In following years:

- Acute tissue damage
- Malignant disease
  (leukaemia excess in radiologists)
- Germ-line mutations in experimental systems

(b) Ears from different barley mutants produced by irradiation. *Left to right*: Ears of Bonus barley (control), erectoides 32, erectoides 23, giant 1, calcaroides.

1940s: Birth of the atomic age

- **Hereditable mutations as the main concern for population**
  (mouse genetics programs at Oak Ridge, Harwell)

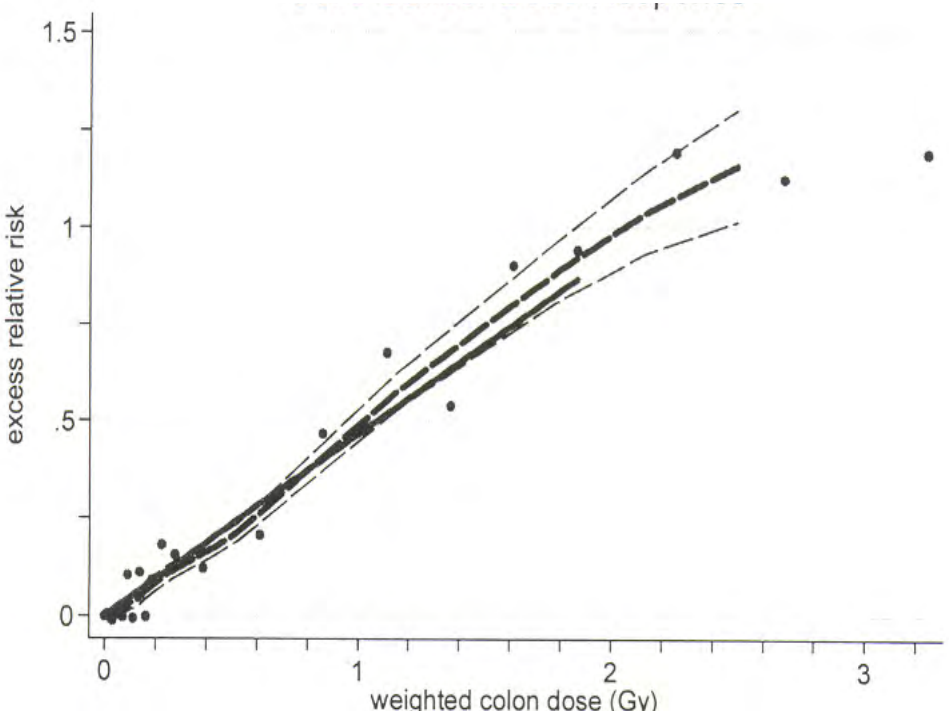
1950s onwards: Follow-up studies of A-bomb survivors

- **Main concern shifted to malignant disease**
  leukaemia, then solid cancers
- **Clear evidence of dose-dependent increases**
- **Assessed risks tended to increase with successive follow-ups**
- **Statistically significant excesses at lower doses**
- **Supporting evidence from medically exposed groups**

Cancer in Japanese survivors of the Atomic bombs

Solid Cancer Incidence

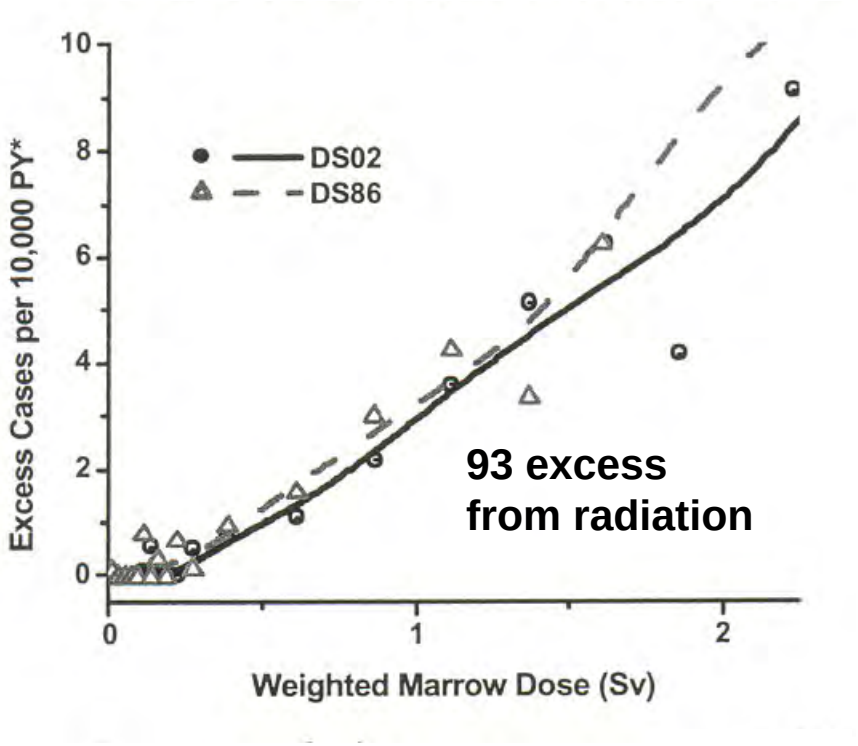
Preston et al, Radiat Res 168, 1 (2007)



Based on a cohort of 105,427 people,
followed to 31 Dec 1998;
105,427 first primary cancers

Leukaemias Mortality

Preston et al, Radiat Res 162, 377 (2004)



Based on a cohort of 86,611 people,
followed to 31 Dec 2000;
45% still alive.
296 leukaemia deaths

- **Assessed cancer risks have tended to increase over the decades**
- **Dose limits have been successively reduced**

		‘Dose Limit’ (averaged per year)			
ICRP Report	Year	Occupational		Public (adult)	
		rem	mSv	rem	mSv
	1951	25(R)			
	1955	15	150	1.5	15
1	1959	12	120	1.5	15
9	1965	5	50	0.5	5
26	1977	5	50	0.5	5
60	1991	2	20	0.1	1
103	2008	2	20	0.1	1

- **Hence meaningful dose limits**

- **Strict regulations**

  Substantial effect on technical developments and practices -- prevented many cancers and other harm

- **Based primarily on epidemiological studies of disease mortality and incidence at higher doses and dose rates**

BUT **major limitation of epi studies:**

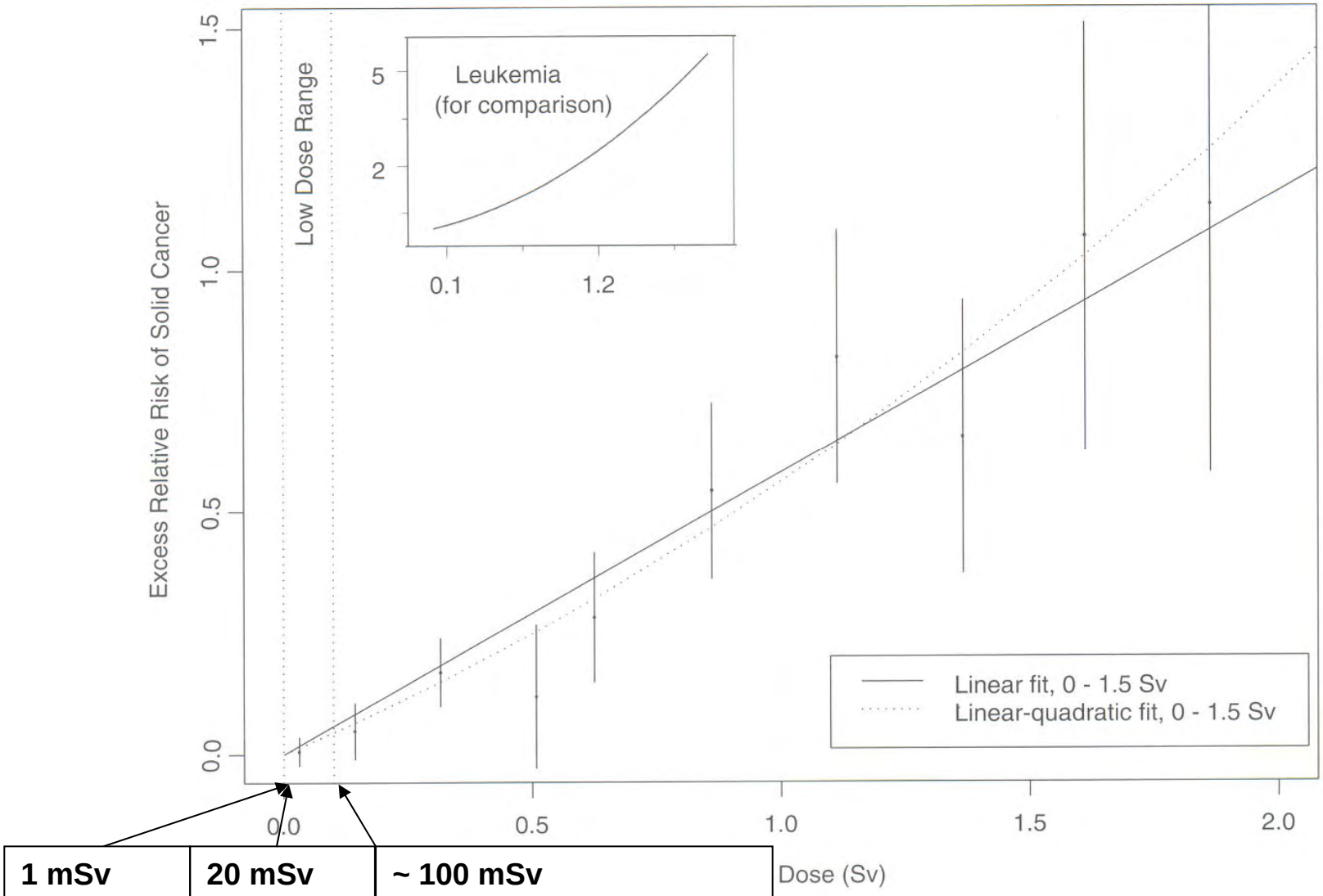
- **lack of statistical power at lower doses**

  (no clear distinction between radiation-induced disease and background disease)

- **extrapolation of data is essential**
- **only simple extrapolation curves can be justified statistically**

Solid cancer risk in A-bomb survivors

BEIR VII (2006)

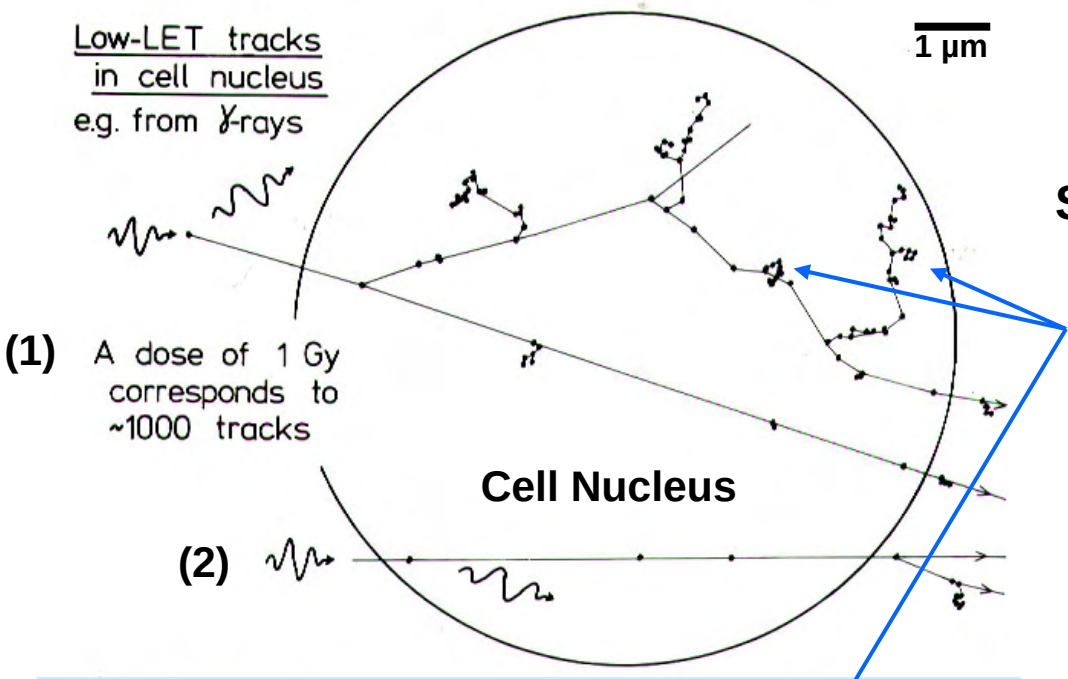


1 mSv
Public limit per year

20 mSv
Worker limit per year

~ 100 mSv
Statistically significant increased risk in A-bomb survivors

Low doses ⟶ few ionizing tracks (electrons)



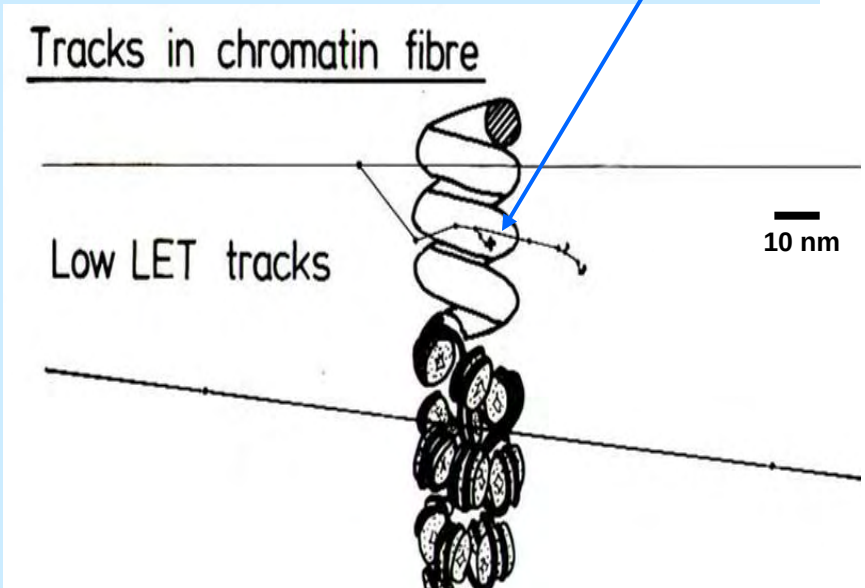
Sparsely ionizing on average, but ~ 1/4 of energy deposited via denser clusters of ionizations from low-energy secondary electrons (on scale of nanometres)

(Magnified in diagram)

Very low dose from a single track

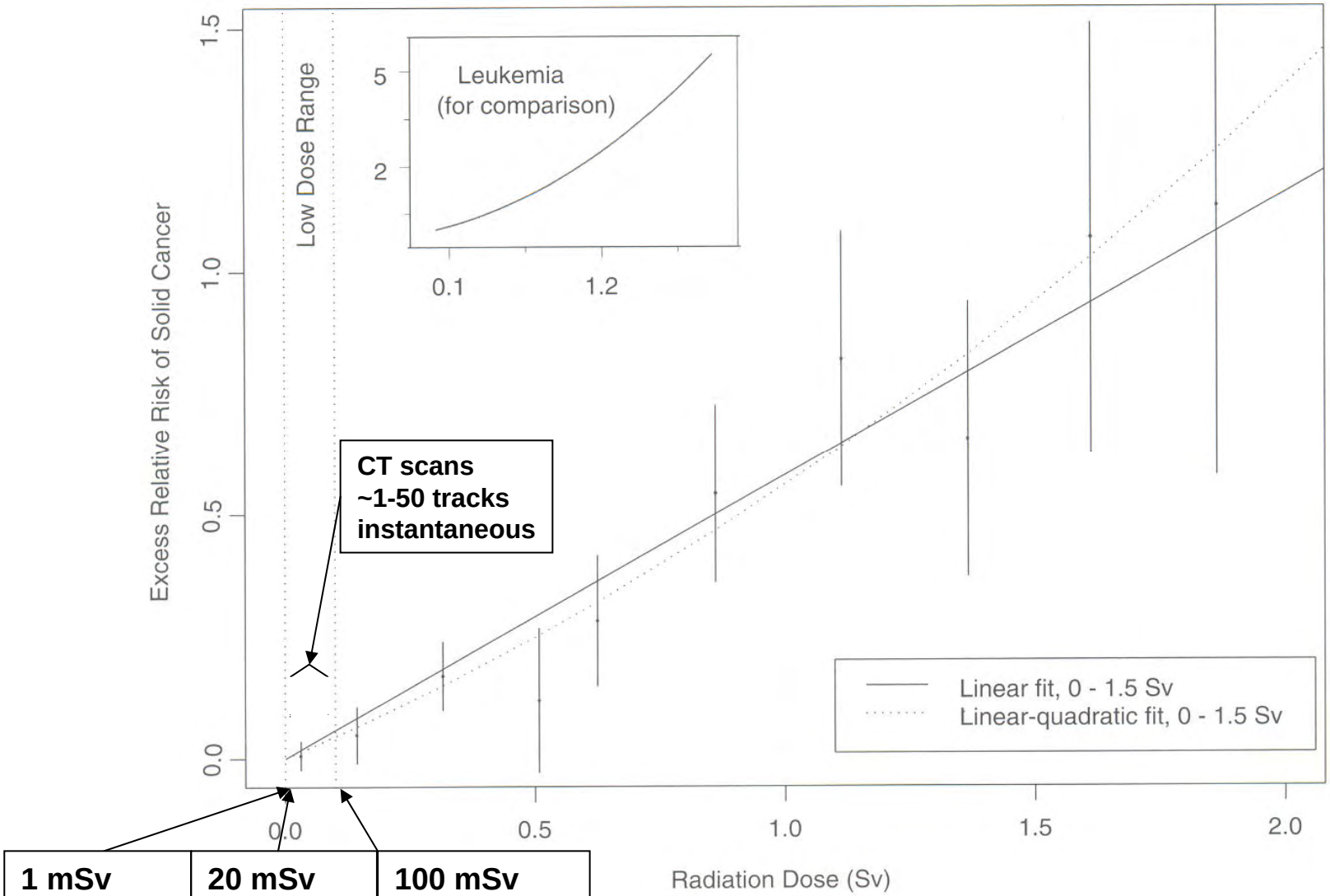
(ave ~ 0.001 Gy to cell nucleus)

(~ 1 mGy)



Solid cancer risk in A-bomb survivors

BEIR VII (2006)



CT scans
~1-50 tracks
instantaneous

1 mSv	20 mSv	100 mSv
~1 track	~20 tracks	~100 tracks
Public limit per year	Worker limit per year	A-bomb instantaneous

Numbers of tracks (electrons) per cell nucleus

Single-track regime

Dear Mr & Mrs Goodhead

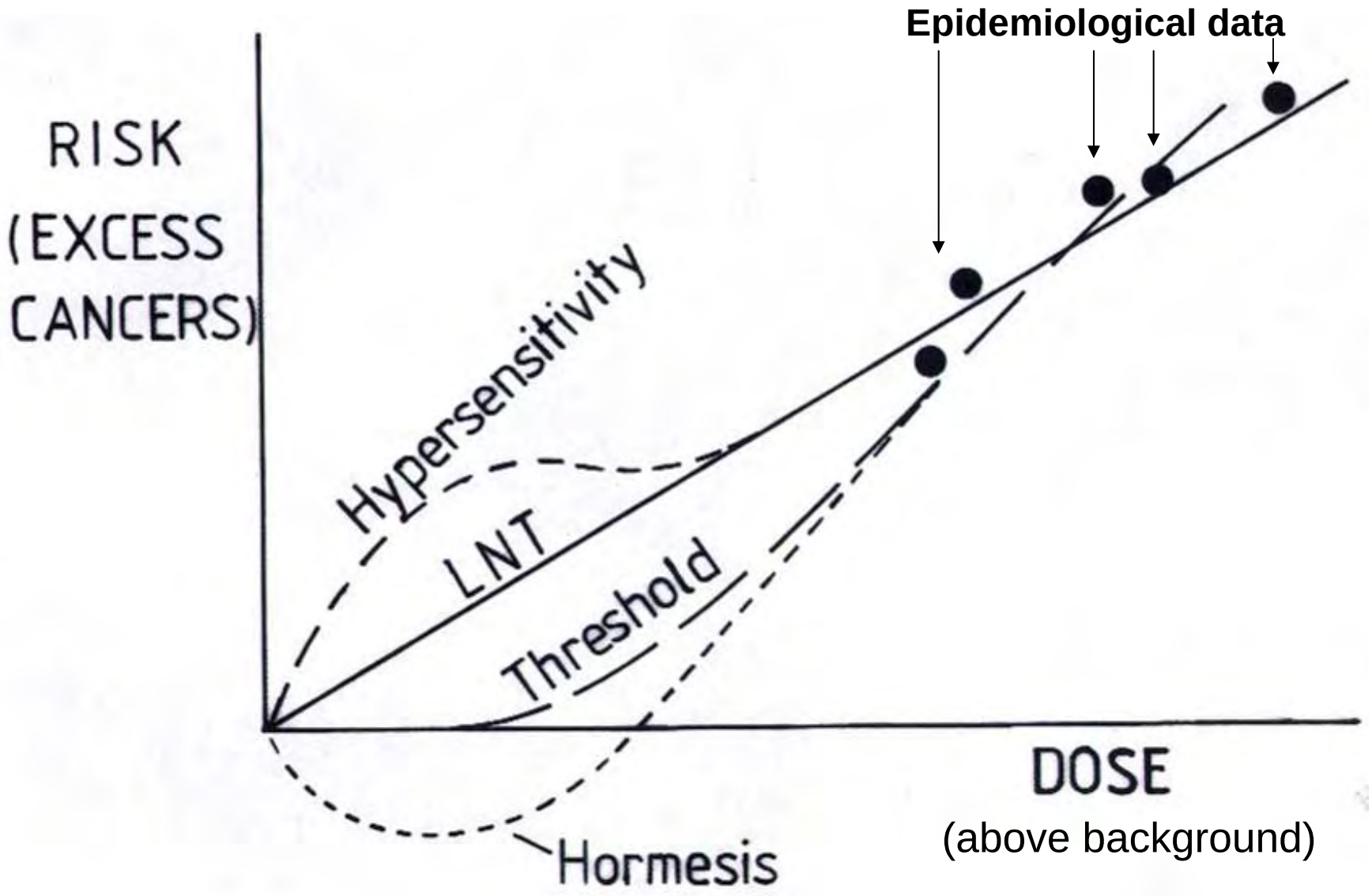
January 2008

Book a CT scan before 15 February 2008 to receive our current, lower prices

At Saga we know that health is a very important concern for people aged 50 and over, so we provide a number of health-related products and services for them. One of these is Saga Health Screening, which offers the advantages of private CT scanning at competitive rates.

The Saga MultiScan is a unique combination of scans and tests designed to address the most common concerns of people over 50. It searches for signs of heart disease, colon cancer and osteoporosis, with checks for diabetes and cholesterol. It is exclusive to Saga for the special price of £530. Since you are recommended to have a scan only every five years, this is equivalent to £106 a year - a price well worth paying for such a valuable insight into the state of your health.

Low-dose risk extrapolation ??



Simplifying assumptions embedded in radiation protection practice:

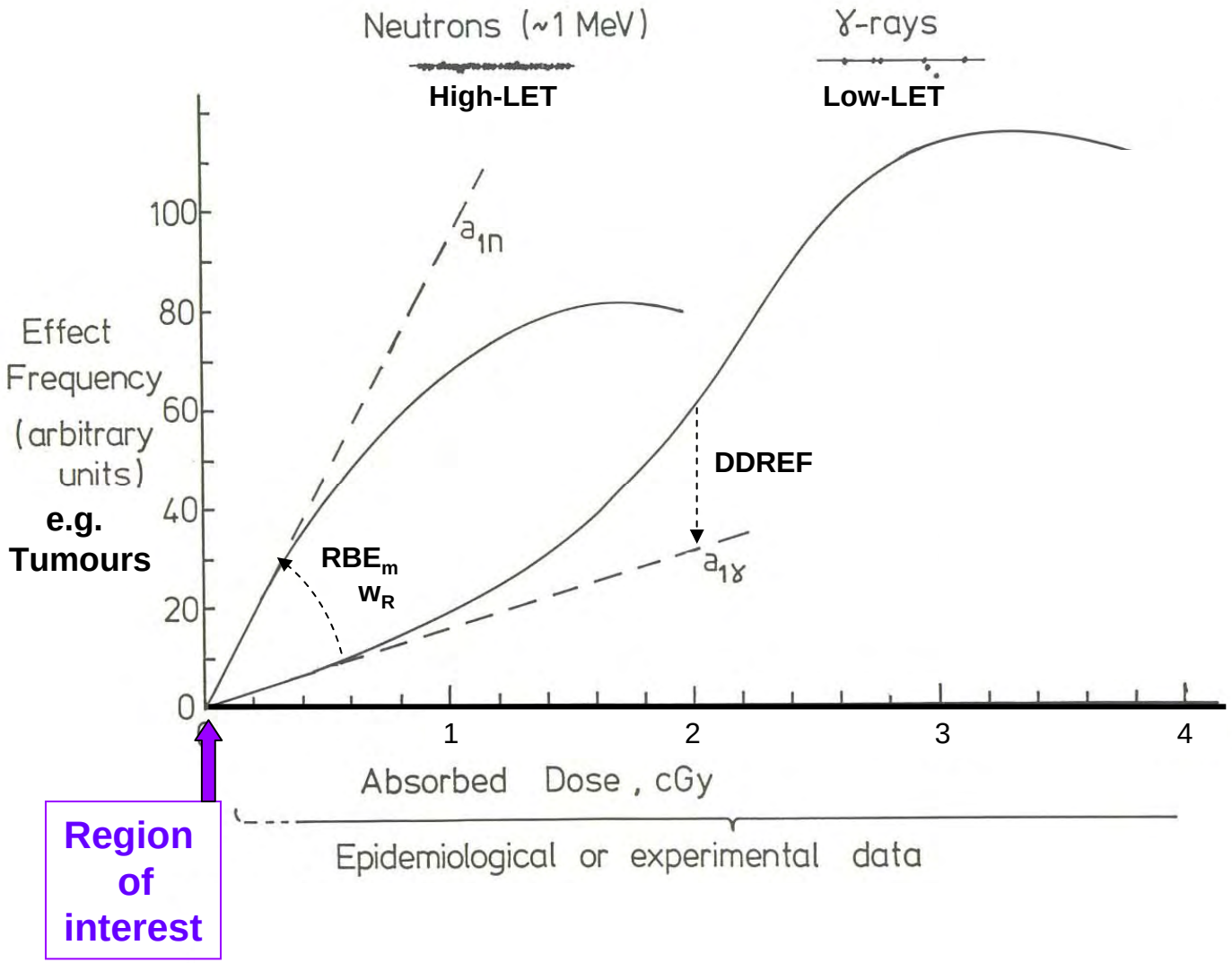
(pragmatic and based on early underpinning mechanistic rationale)

- **linear response at low doses**
- **no dose threshold**

} **LNT**

- **reduced risk at low dose rate (at higher doses) [DDREF]**
- **increased risk for densely ionizing (high LET) radiations [w_R]**
- **independent risk for each exposed organ/tissue [w_T]**

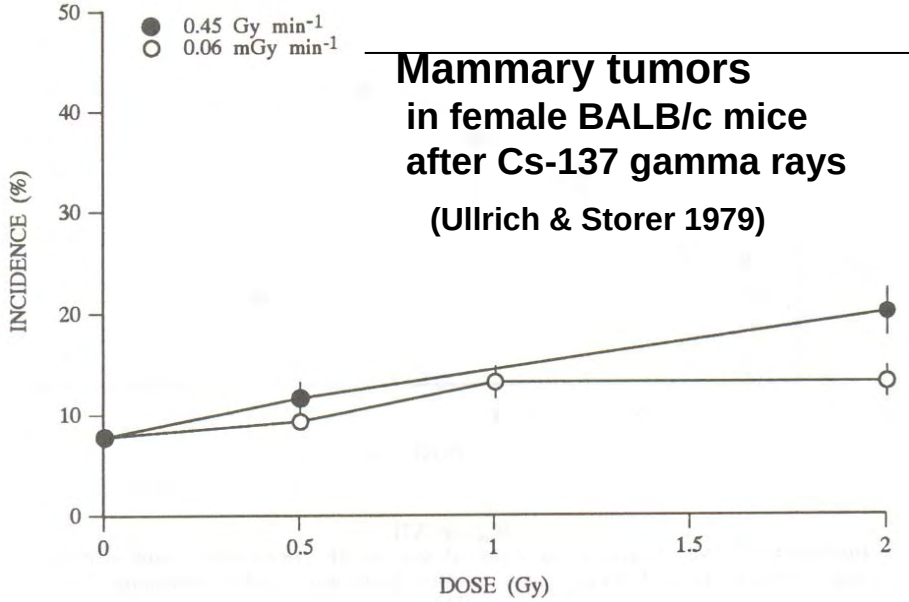
Schematic dose responses for radiation risks



LET = Linear Energy Transfer
RBE_m = Relative Biological Effectiveness (maximum)
w_R = Radiation weighting factor
DDREF = Dose and Dose-Rate effectiveness Factor

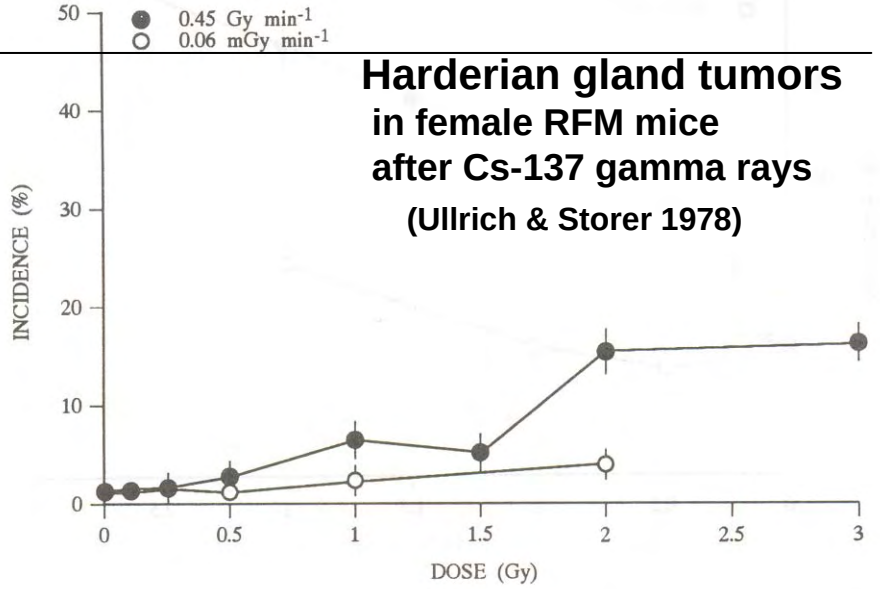
Mod from Goodhead, Adv Radiat Biol 16, 7 (1992)

Dose rate dependence of animal tumorigenesis (1) [UNSCEAR 1993]



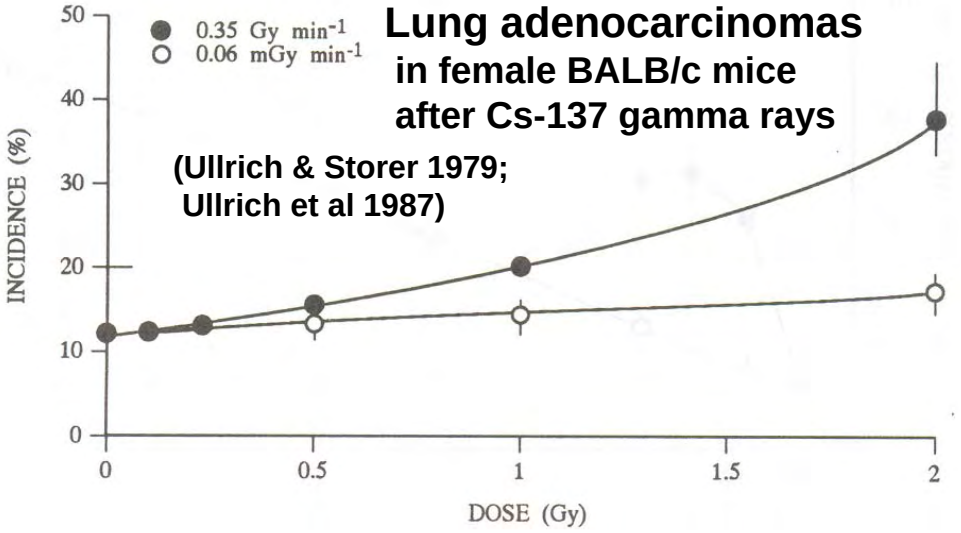
Mammary tumors
in female BALB/c mice
after Cs-137 gamma rays

(Ullrich & Storer 1979)



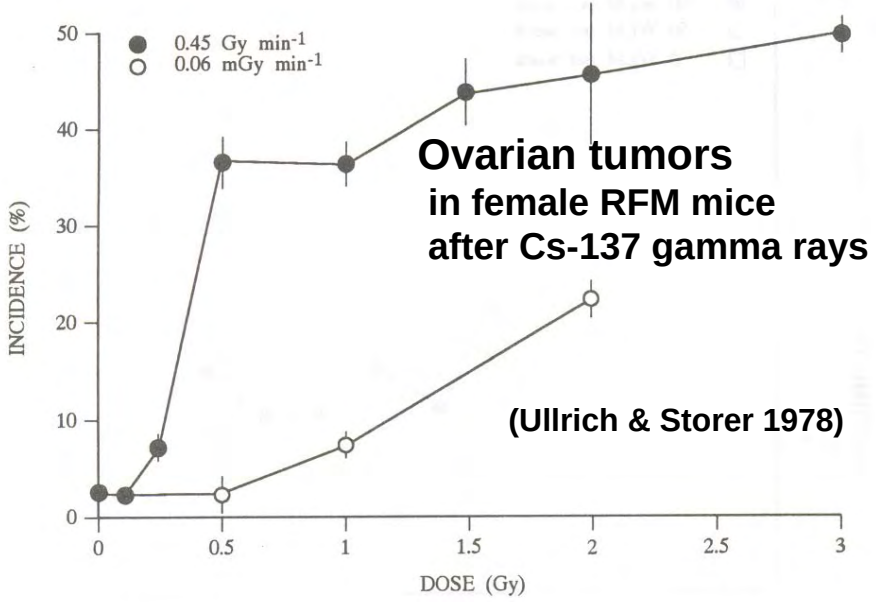
Harderian gland tumors
in female RFM mice
after Cs-137 gamma rays

(Ullrich & Storer 1978)



Lung adenocarcinomas
in female BALB/c mice
after Cs-137 gamma rays

(Ullrich & Storer 1979;
Ullrich et al 1987)

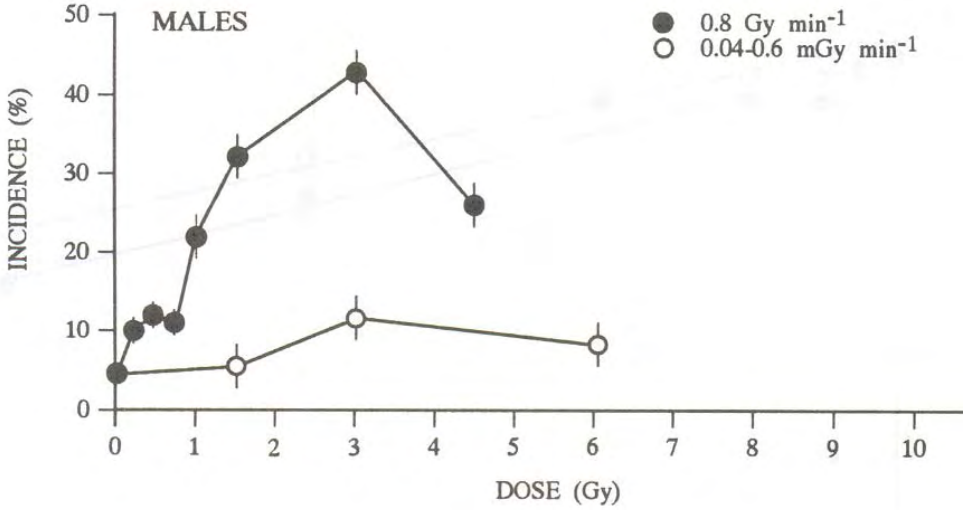


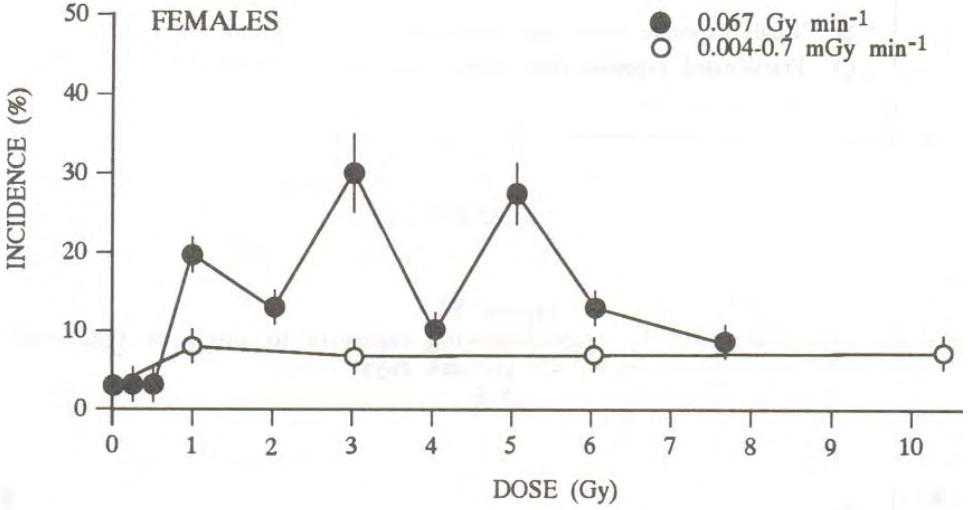
Ovarian tumors
in female RFM mice
after Cs-137 gamma rays

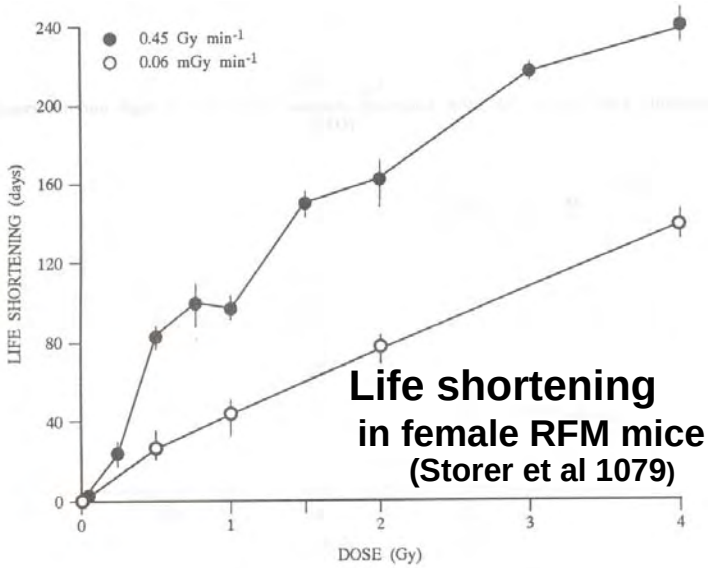
(Ullrich & Storer 1978)

Dose rate dependence of animal tumorigenesis (2) [UNSCEAR 1993]

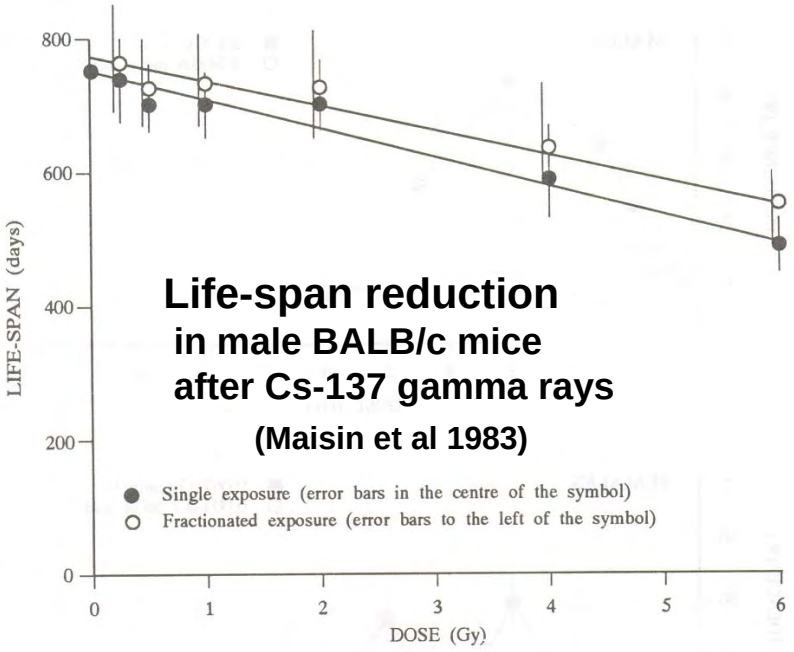
Myeloid leukaemia
in RF mice after X-rays **(Ullrich & Storer 1978)**







Life shortening
in female RFM mice
(Storer et al 1079)



Life-span reduction
in male BALB/c mice
after Cs-137 gamma rays
(Maisin et al 1983)

Acute myeloid leukaemia in mice from X-ray exposure:

and fission neutrons

(Mole and Davids, 1982)

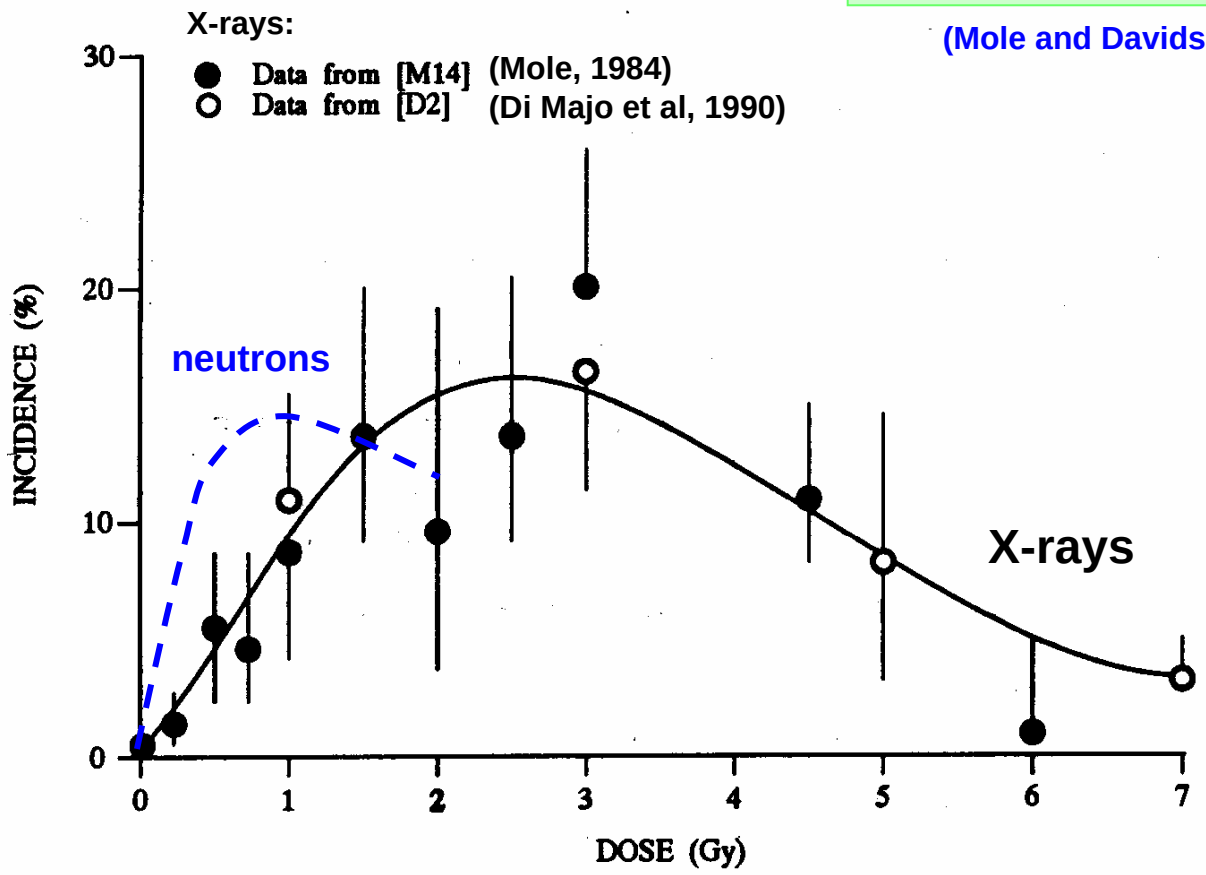
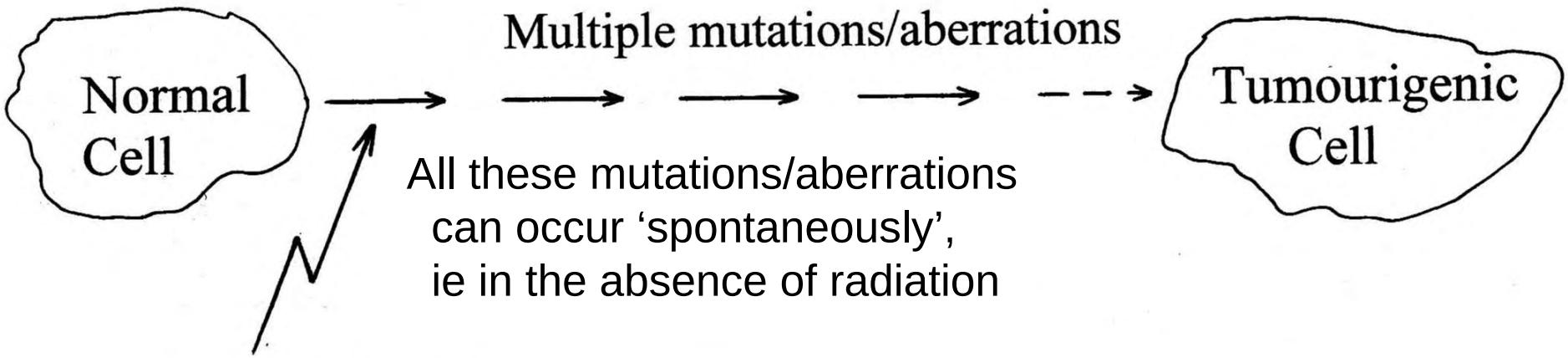


Figure II.
Incidence of myeloid leukaemia in male CBA/H mice following brief exposures to x rays. [D2, M14]

(From UNSCEAR 1993)

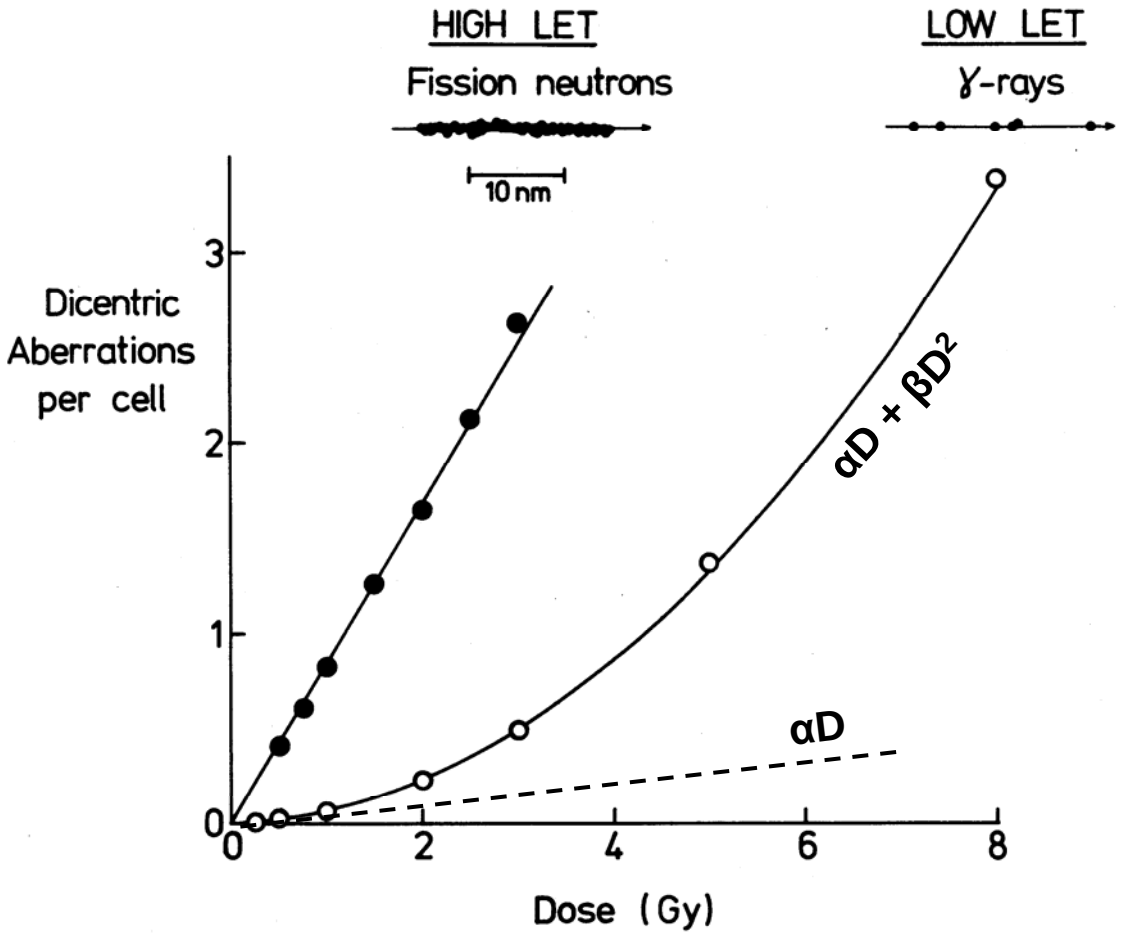
A PARADIGM FOR RADIATION TUMOURIGENESIS:
(conventional)



From damage directly to DNA ('targeted').
Very low frequency event.

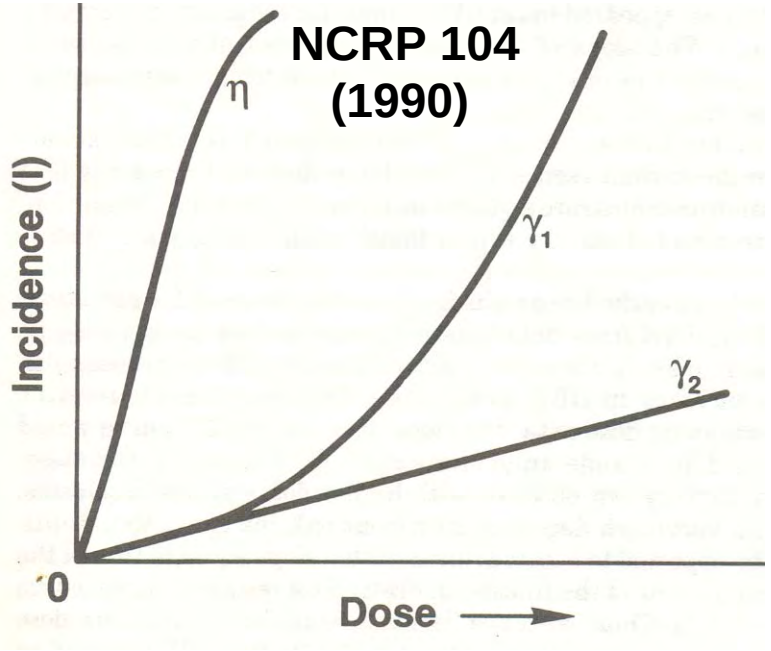
Principles for extrapolation have been strongly influenced by experimental data on chromosome aberrations *in vitro*
(implicitly assuming aberration is key rate limiting step in radiation carcinogenesis)

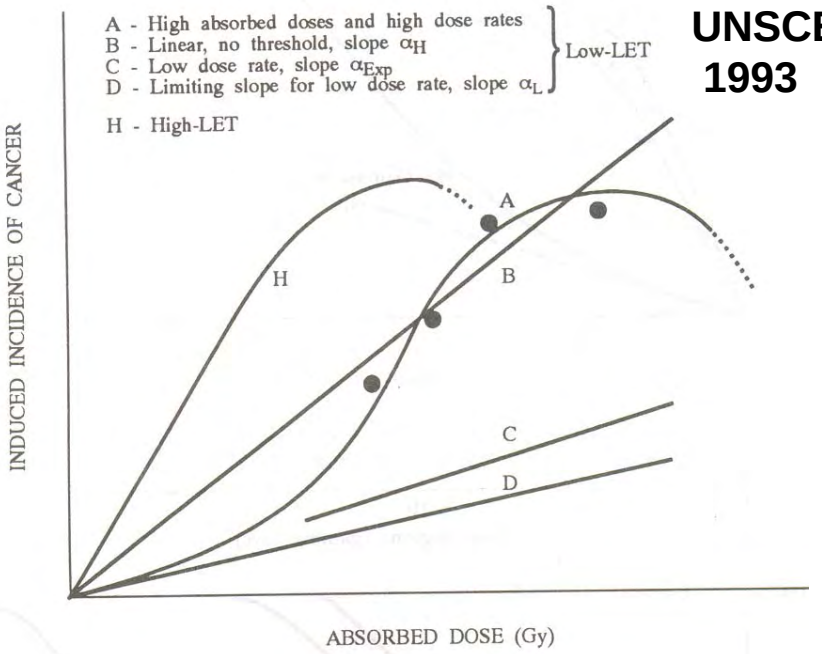
Especially, dicentric chromosome exchange aberrations in human lymphocytes

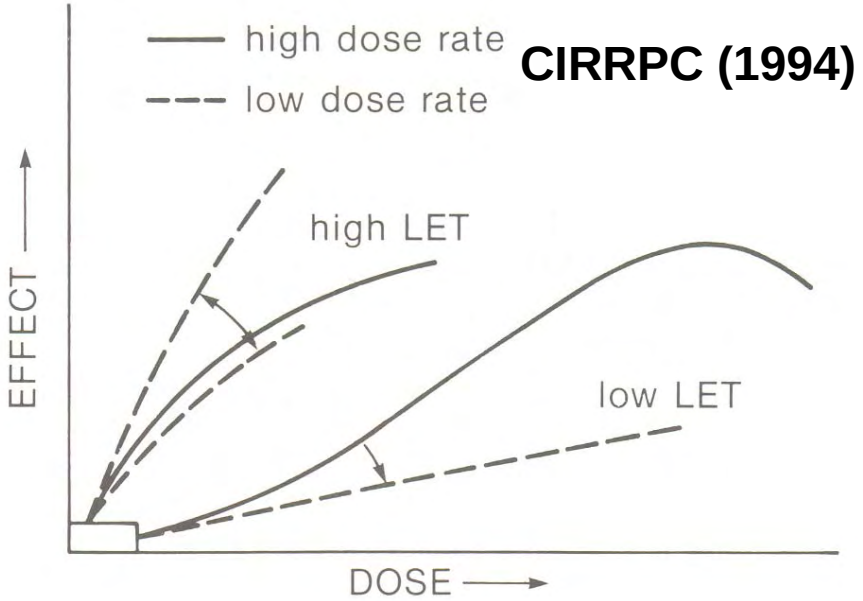


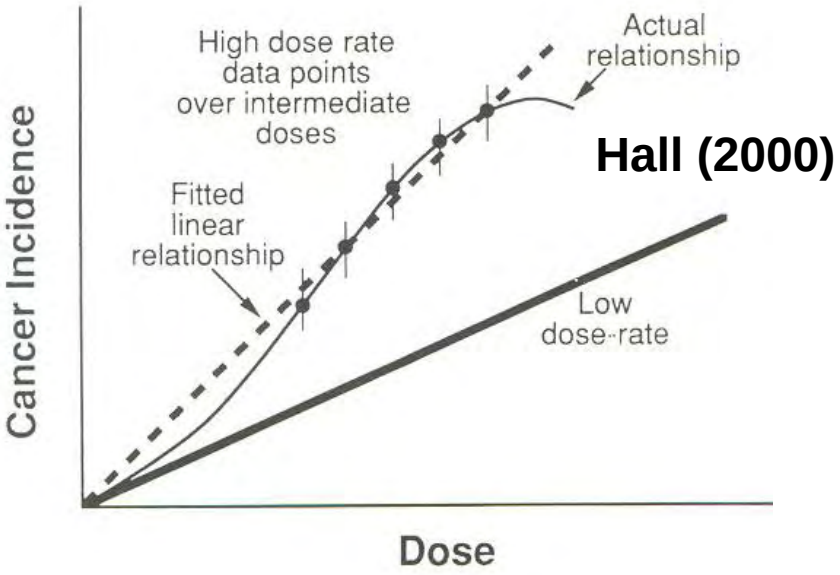
(Data replotted from Lloyd et al)

Standard committee assumptions for dose responses (1)



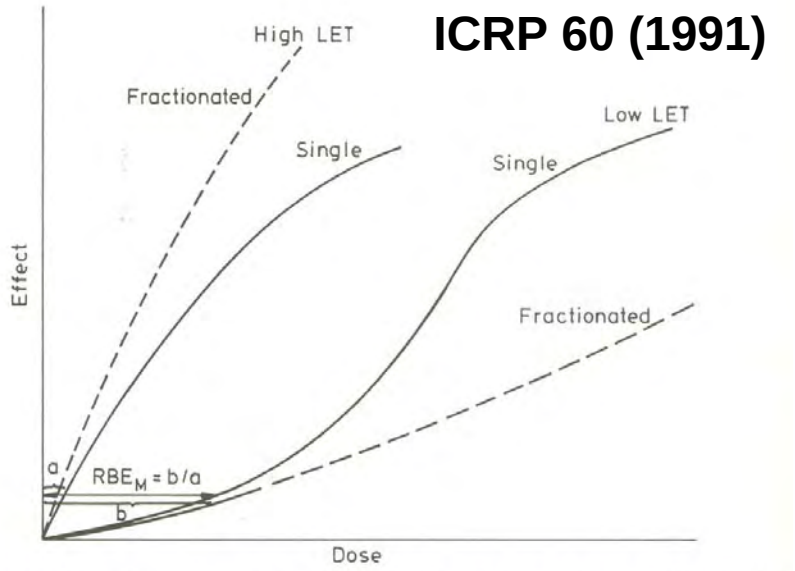




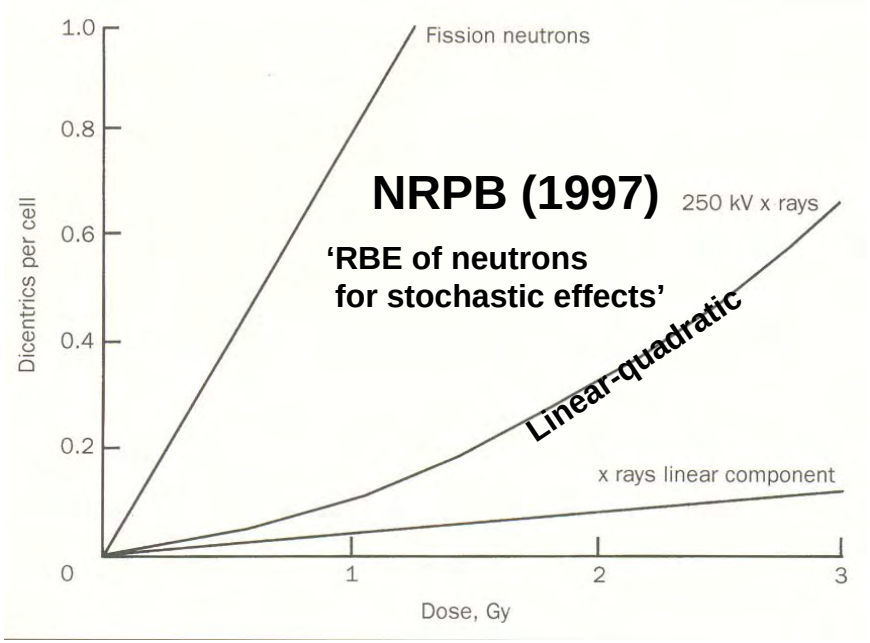


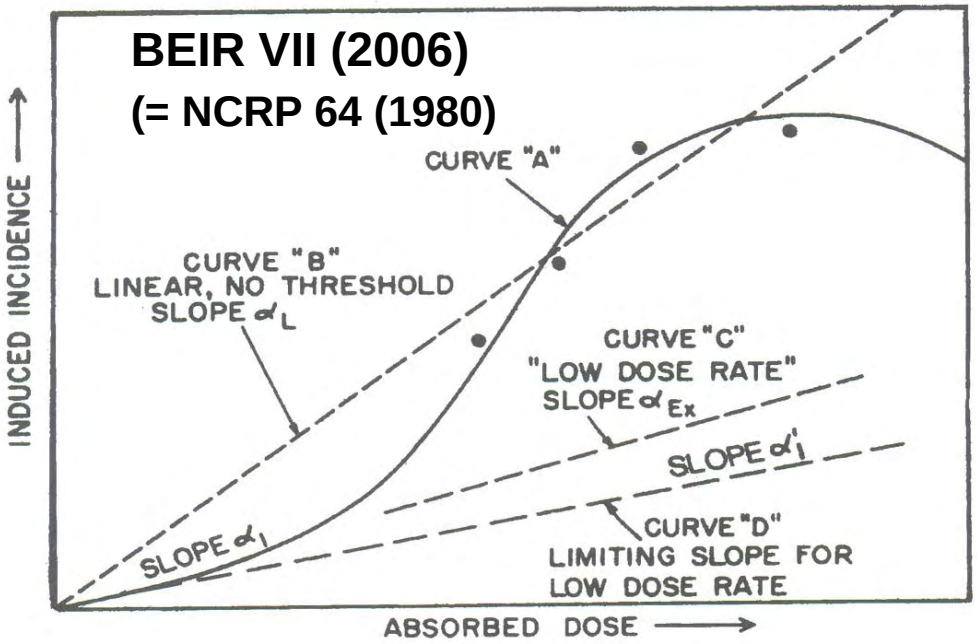
Standard committee assumptions for dose responses (1)

ICRP 60 (1991)



. B-6. Shapes of dose responses for low LET and high LET radiations plotted on linear axes (Sinclair, 1982).





How reliable are these underlying assumptions for extrapolation of epidemiological data?

Consider:

1. Can radiation produce biologically significant damage to DNA and chromosomes, even at the lowest doses (ie single electron)?

2. Is such damage not swamped by large amounts of endogenous DNA damage (oxidative processes, etc)?

3. Is a chromosome aberration the key event ('initiation') in radiation carcinogenesis?

4. Are dose responses for dicentric aberrations reliable guides for analysis of relationships between cancer dose responses?

5. ……..

1. Can radiation produce biologically significant damage to DNA and chromosomes, even at the lowest doses (ie single electron)?

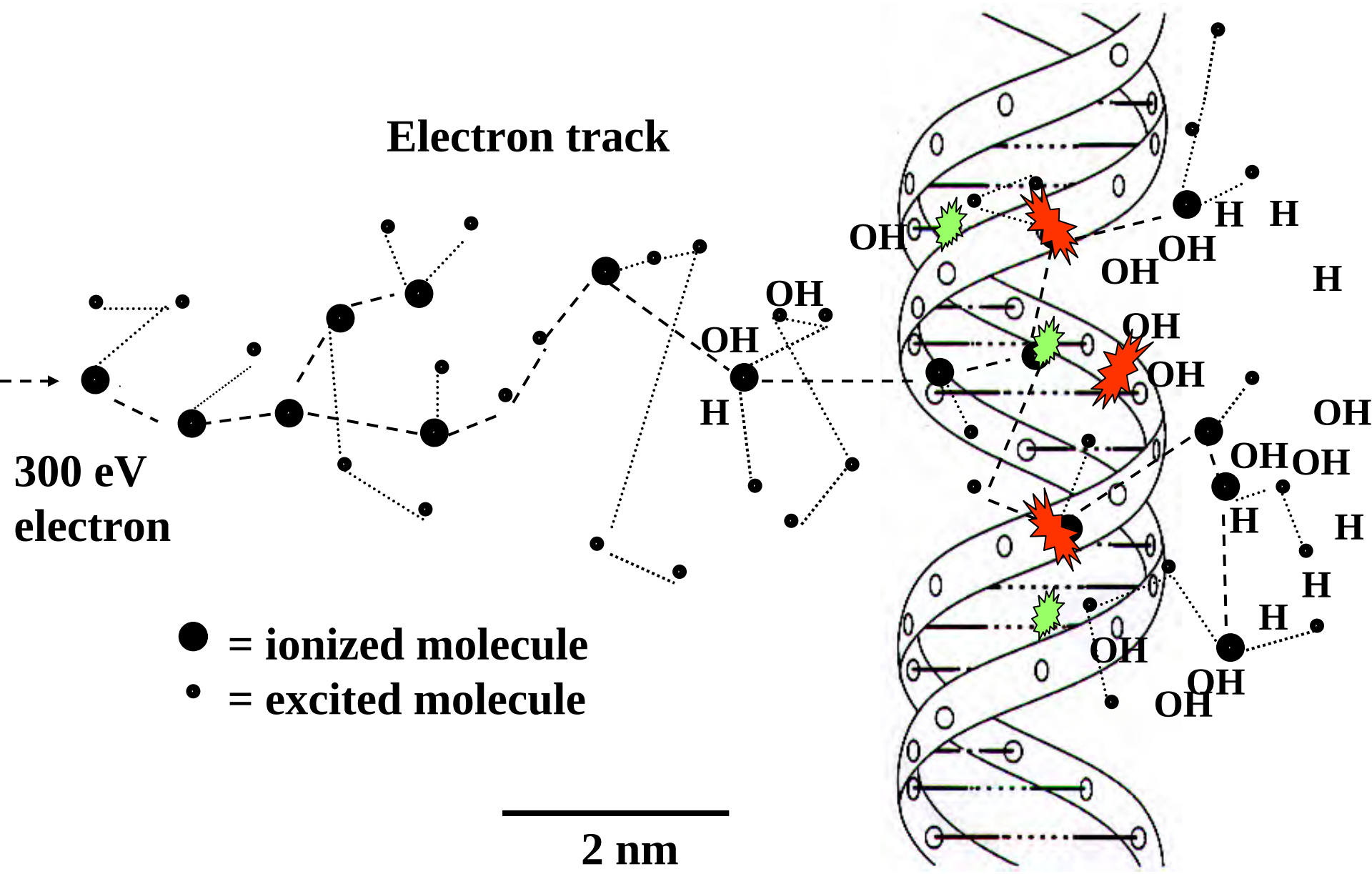
YES

- ~ All ionizing radiations produce low-energy secondary electrons, in abundance (Typically $^1/_4$ to $^1/_3$ of dose from X- or gamma-rays)

- Low-energy electrons are efficient at producing clustered DNA damage, notably -- simple double-strand breaks (DSB)
  -- base-damage clusters
  -- complex double-strand breaks

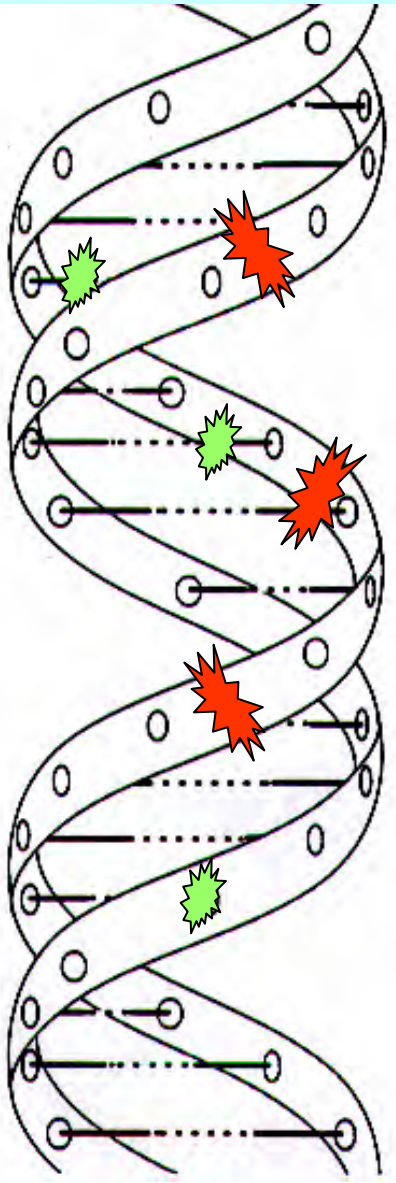
From track structure simulations

- Complex DSB are likely to be least repairable and lead to DNA losses/rearrangements


Electron track
300 eV
electron
OH
OH
H
OH
OH
OH
H
H
OH
OH
OH
OH
OH
H
H
H
H
OH
OH
OH
= ionized molecule
= excited molecule
2 nm

Complex Clustered DNA Damage

Example of complex Clustered Damage in DNA resulting from a single electron track from low-LET radiation

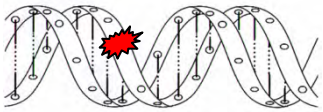


2 nm

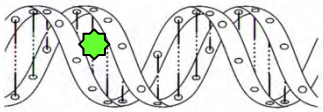
Clustered Damage in DNA

Simple damage (1 component):

Single strand break (SSB)

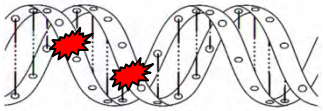


Damaged base (BD)

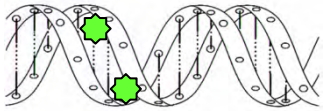


Simple Clustered Damage (2 components):

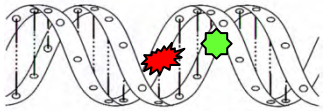
Double strand break (DSB)



Double base damage



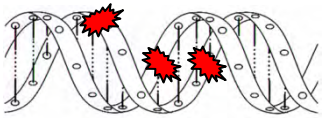
SSB + BD

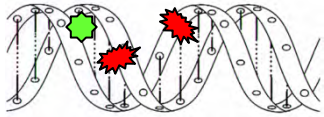


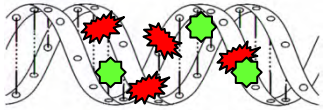
Also pairs on same strand

Complex Clustered Damage (3 or more components):

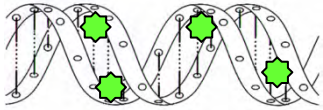
eg Complex DSB

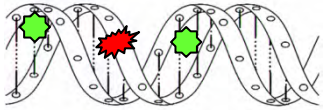






eg Other combinations





Low-LET X, γ: ~ 20% of dsb are complex via 1 or more additional strand break(s)*

~ 50% " " " " " additional break(s) and/or base damage(s)*

High-LET α: ~ 70% " " " " " 1 or more additional strand break(s)*

~ 90% " " " " " additional break(s) and/or base damage(s)*

All radiations produce a substantial proportion of complex DSB

* Nikjoo et al, Radiat Res 148, 485 ('97); 156, 577 ('02); IJRB 71, 467 ('97) 156, 577 ('02); Rad Prot Dosim 99, 77 ('02)

* Goodhead, Rad Prot Dosim 122, 3-15 (2006)

Ionization clustering has been known for a long time

But the full biological significance was not appreciated

From: Goodhead, In 'Genes, Cancer & Radiation Protection' Proc 27th Ann Meeting of NCRP, 1991

Biological importance of ionization clusters - partial history

FROM RADIATION PHYSICS:

Micro-organisms		Critical feature	
1958 Howard-Flanders 1962 Brustad	1D (LET + energy-loss fluctuations)	≳1-10 ions in 3-10nm	
Mammalian cells			
1964 Barendsen	"	≳10-15 ions in 7-10 nm	
		Low-LET	High-LET
1980 Goodhead	"	≳3 ions in 3nm	≳10 ions in 3nm
1983 Goodhead and Brenner	3D (Monte-Carlo track structure)	≳4 ions in 3nm (≳100eV)	------
1985 Goodhead, Charlton, Nikjoo ↓	"	≳4 ions in 2-3nm (≳100eV)	≳16 ions in 5-10nm (≳400eV)

FROM RADIATION CHEMISTRY

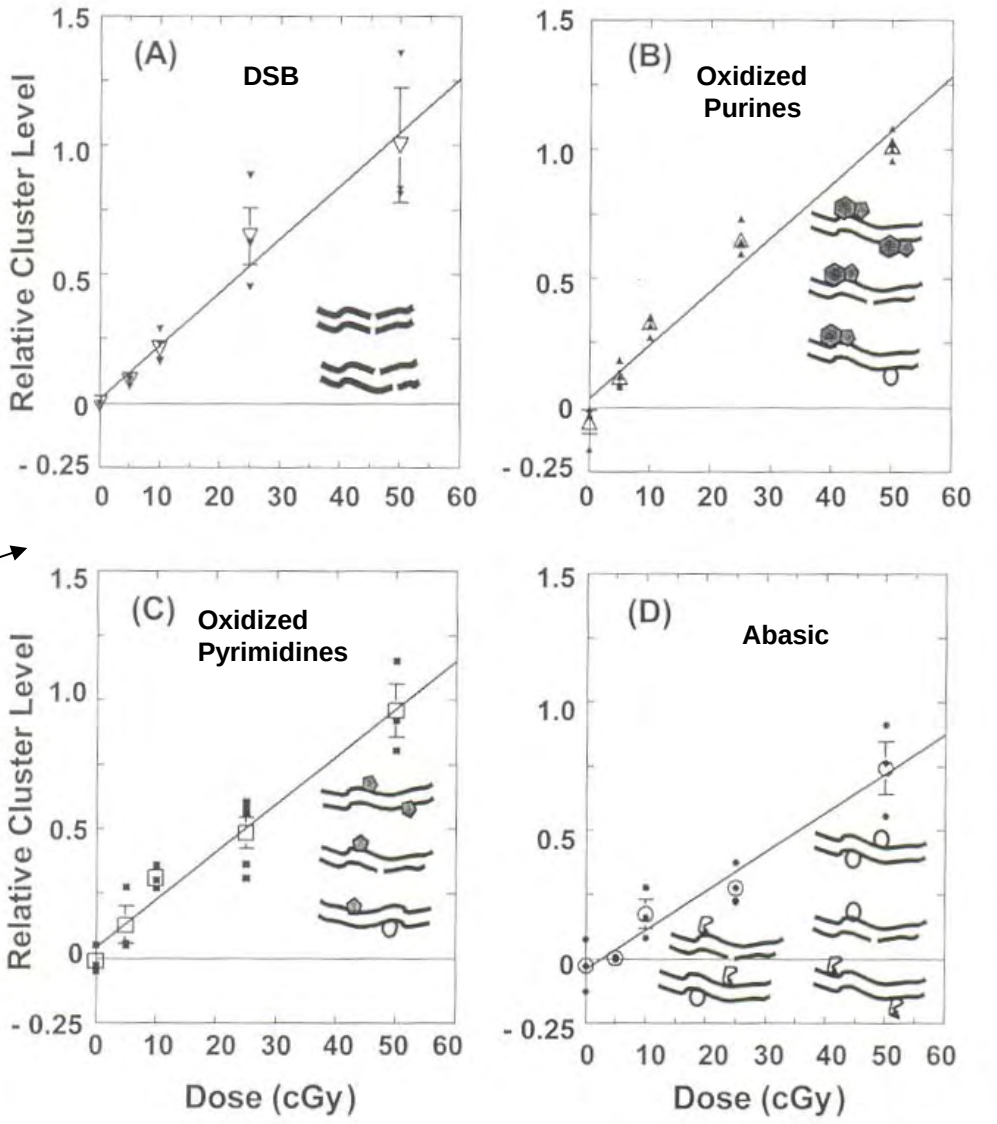
Most emphasis on ~ homogeneous $^{\bullet}OH$ radicals, until

1981 Ward	≳2 local radicals
1985 Ward ↓	Local-multiply-damaged sites (LMDS)

Measurement of (simple) clustered damage in cellular DNA

Linear yields of double-strand breaks (DSB)

and of simple base-damage clusters



After X-irradiation (50 kVp)

Sutherland et al Radiat Res 157, 611 (2002)

But:
Current methods cannot detect complexity of DSB or of base clusters

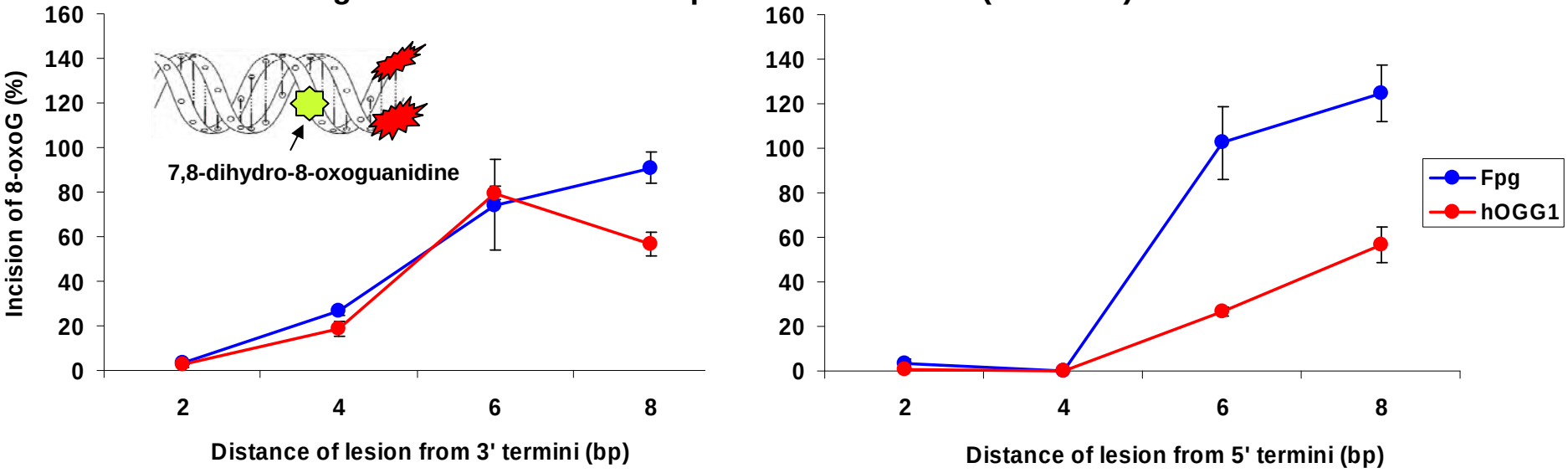
DNA Repair Machinery and Complex DSBs

Synthetic constructs of 3- (or 4-)component clustered damage ('Dirty DSB') show reduced rejoining by repair enzymes.

- Removal of 8-oxoG by Fpg and human OGG1 is retarded close to DSB termini
- When 8-oxoG is in the 5' orientation kinetics of hOGG1 removal are slower even up to 8 bases from the termini

Courtesy of Tracey Dobbs and Peter O'Neill (modified)

e.g. 8-oxoG at 2 to 8 base pairs from the DSB (terminus)



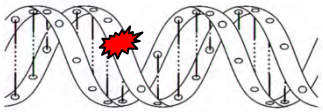
Complex DSBs block glycosylase activity when ≤ 4 bases from termini, potentially creating a persistent DSB

-- Ligation of complex DSBs via NHEJ is retarded

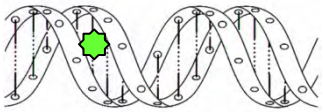
Clustered Damage in DNA

Simple damage (1 component):

Single strand break (SSB)

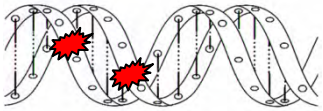


Damaged base (BD)

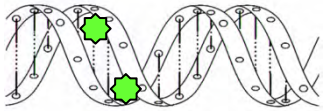


Simple Clustered Damage (2 components):

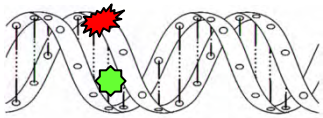
Double strand break (DSB)



Double base damage



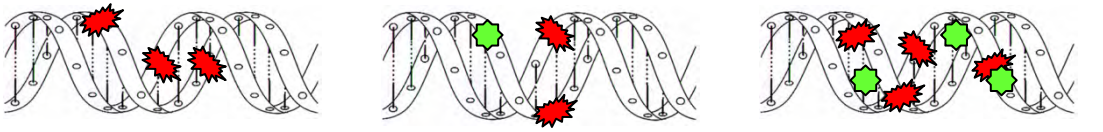
SSB + BD



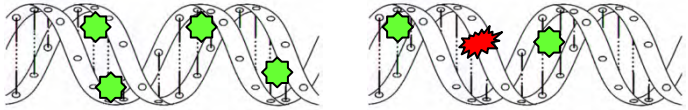
Also pairs on same strand

Complex Clustered Damage (3 or more components):

eg Complex DSB



eg Other combinations



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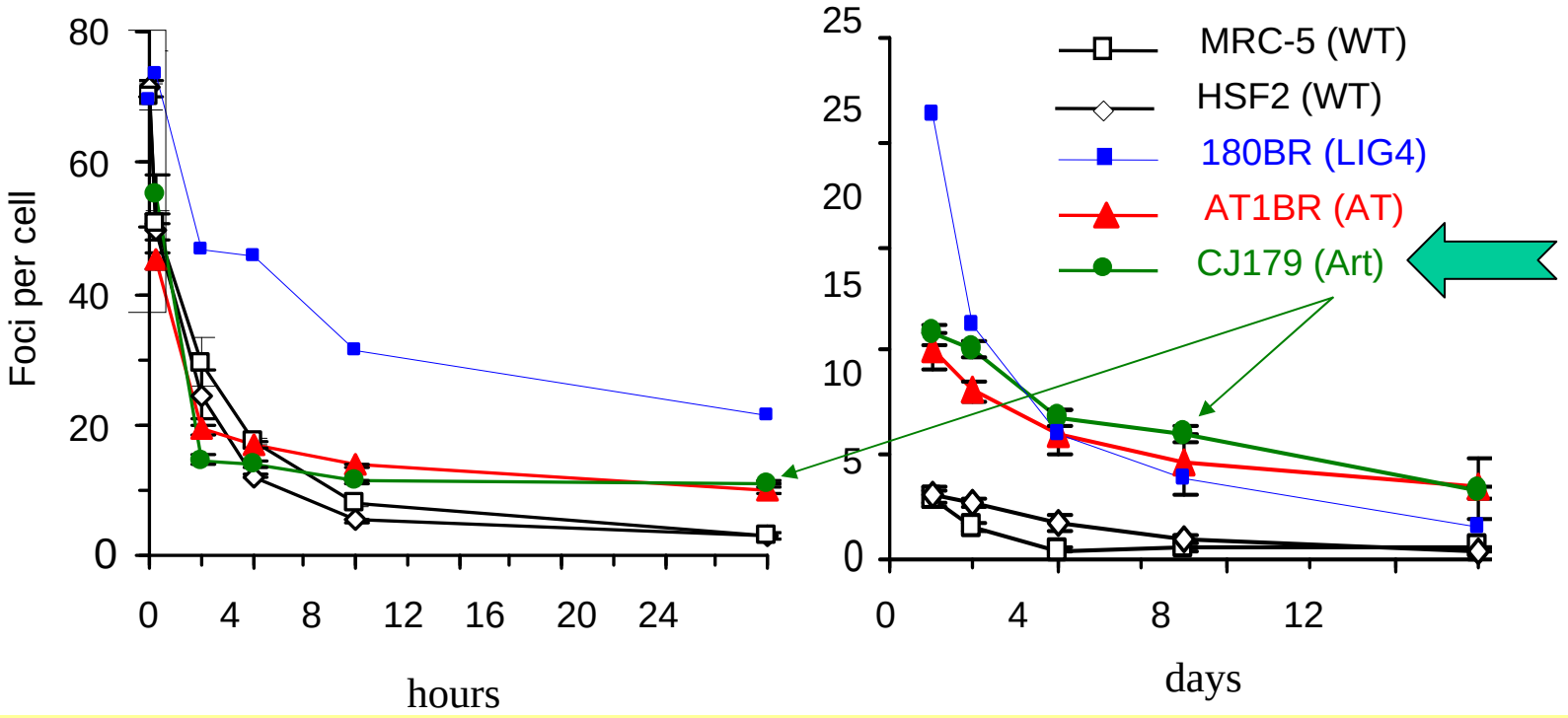
* Nikjoo et al, IJRB 71, 467 ('97); Radiat Res 148, 485 ('97); 156, 577 ('02); Rad Prot Dosim 99, 77 ('02)

Courtesy of Penny Jeggo (modified)

DSB rejoining after 2 Gy X-rays

(γ-H2AX analysis)



90 % DSBs repaired quite rapidly but **10 % repaired with slower kinetics** but they contribute to survival and they **require Artemis nuclease activity** for repair

1. Can radiation produce biologically significant damage to DNA and chromosomes, even at the lowest doses (ie single electron)?

YES

- **~ All ionizing radiations produce low-energy secondary electrons, in abundance (Typically $^1/_4$ to $^1/_3$ of dose from X- or gamma-rays)**

- **Low-energy electrons are efficient at producing clustered DNA damage, notably -- simple double-strand breaks (DSB)**
  -- base-damage clusters
  -- complex double-strand breaks

From track structure simulations

- **Complex DSB are likely to be least repairable and lead to DNA losses/rearrangements → mutations, aberrations, etc**

Endogenous versus Radiation Damage to DNA (1)

T. Lindahl:

"…the driving force in the evolution of DNA repair has been the inherent lability of DNA under conditions *in vivo*."

"Exposure of living cells to ionizing radiation or environmental chemical mutagens has been too recent or insignificant to result in selection of specific DNA repair processes …"

"Human cellular defence capacity against such agents, however, is probably only a side effect of the continuous correction of intrinsic DNA damage.
In consequence, low exposure to most environmental mutagens might be expected to have little or no biological effect: a small … increase in DNA damage above the considerable basal level of endogenous lesions can still be processed effectively by the versatile DNA repair systems."

(Phil Trans R Soc Lond B 351, 1529 (1996)

Endogenous versus Radiation Damage to DNA (2)

Pollycove argues **(with many assumptions)**:

Steady state endogenous base damage = 24,000 per cell

(From exerimental range 24,000 – 1,200,000)

[But Cadet says 2,200 (Chem Res Toxicol 13, 541 (2000))]

Assuming types of damage, $T_{½}$ → Steady state ssb = 480 per cell **[44]**

Hence, probability of opposing pair within 5 base pairs = 10^{-7} **[10^{-5}]**

Hence, endogenous dsb = 0.1 per cell per day **[10^{-3}]**

Compare with 1 mGy per year

low-LET radiation → 10^{-4} dsb per cell per day **(Exper 40 dsb/cell/Gy)**

$$\text{Ratio} \quad \frac{\text{Endogenous dsb}}{\text{Radiation dsb}} = 10^{3}$$ **[10]**

Conclude: Non- radiation- induced damage far outweighs DNA damage from low doses of low- LET radiation, both qualitatively and quantitatively.

(Pollycove and Feinendegen, Human Exper Toxicol 22, 290 (2003))

i.e. Total endogenous damage >>>> Background radiation damage

Endogenous ssb >>> Background radiation ssb

Endogenous dsb >> Background radiation dsb

Endogenous versus Radiation Damage to DNA (3)

Pollycove argues:

$$\text{Ratio} \quad \frac{\text{Endogenous dsb}}{\text{Radiation dsb}} = 10^{3} \qquad \text{(for 1 mGy per year)}$$

BUT: This assumes all dsb are similar

Consider, probability of 3rd break in dsb: Endogenous $p = 10^{-6}$ ($T_{½}$ assumed) [10^{-9}]
Radiation $p = 0.2$ (Low LET track structure)

Hence, for Complex DSB:

$$\text{Ratio} \quad \frac{\text{Endogenous dsb}^{+}}{\text{Radiation dsb}^{+}} = 5 \times 10^{-3} \qquad \text{(3 breaks)} \qquad [5\times10^{-6}]$$

$$\text{Ratio} \quad \frac{\text{Endogenous dsb}^{++}}{\text{Radiation dsb}^{++}} \sim 10^{-7} \qquad \text{(4 breaks)} \qquad [10^{-11}]$$

Conclude: Radiation far outweighs endogenous for complex dsb

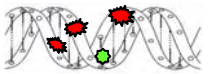
Endogenous dsb >> Background radiation dsb
Endogenous dsb^{+} << Background radiation dsb^{+}
Endogenous dsb^{++} <<<< Background radiation dsb^{++}

Inclusion of base damage, would make radiation even more dominant in producing complex dsb

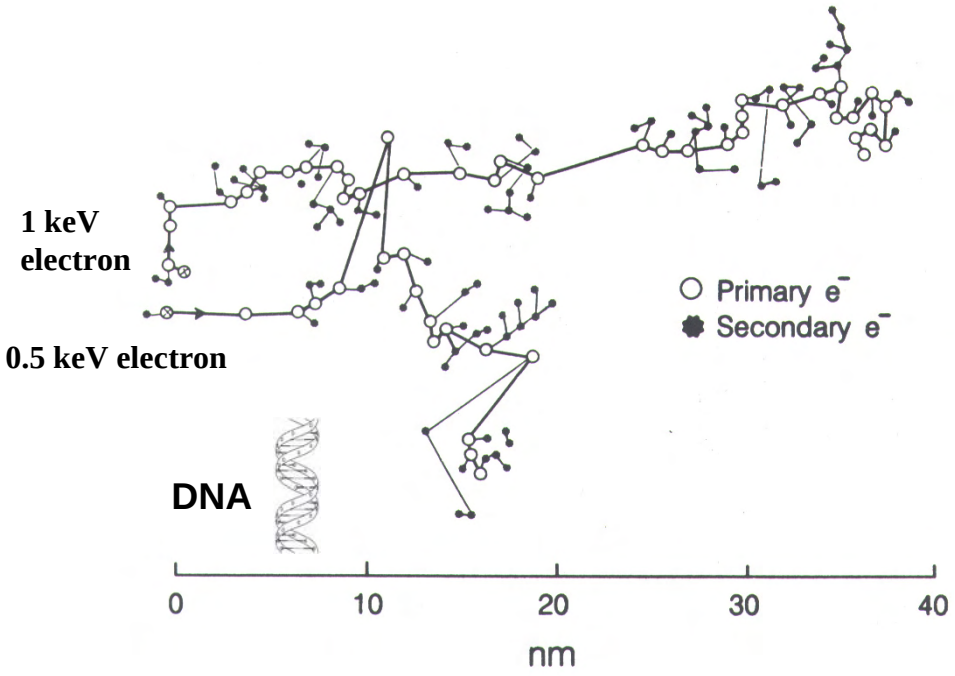
2. Is such damage not swamped by the large amounts of endogenous DNA damage (oxidative processes, etc)?

No

Complex clustered damage is a <u>special feature</u> of ionizing radiation



because of the property of ionization clustering in the tracks of low-energy electrons



Experiments have shown such electrons to be effective at producing 'all' types of biological effect in cells

3. Is a chromosome aberration the key event ('initiation') in radiation carcinogenesis?

Maybe?

- Chromosome rearrangements are major feature of carcinogenesis
- BUT little evidence to confirm any as the key direct radiation event
- Strong case for AML (acute myeloid leukaemia) in CBA mice

  Deletion of Sfpi1 gene (PU.1) in chromosome 2 as early (initial?) radiation event

  Does dose response for these deletions predict AML dose response??

  LOH can result from a single DSB → linear dose response

  Shown elegantly in yeast [Cullen et al, Mol Cell Biol 27, 7745 (2007)

  Does this apply to Sfpi1 deletions and hence AML 'initiation'?

- What about other tumour types; in humans?

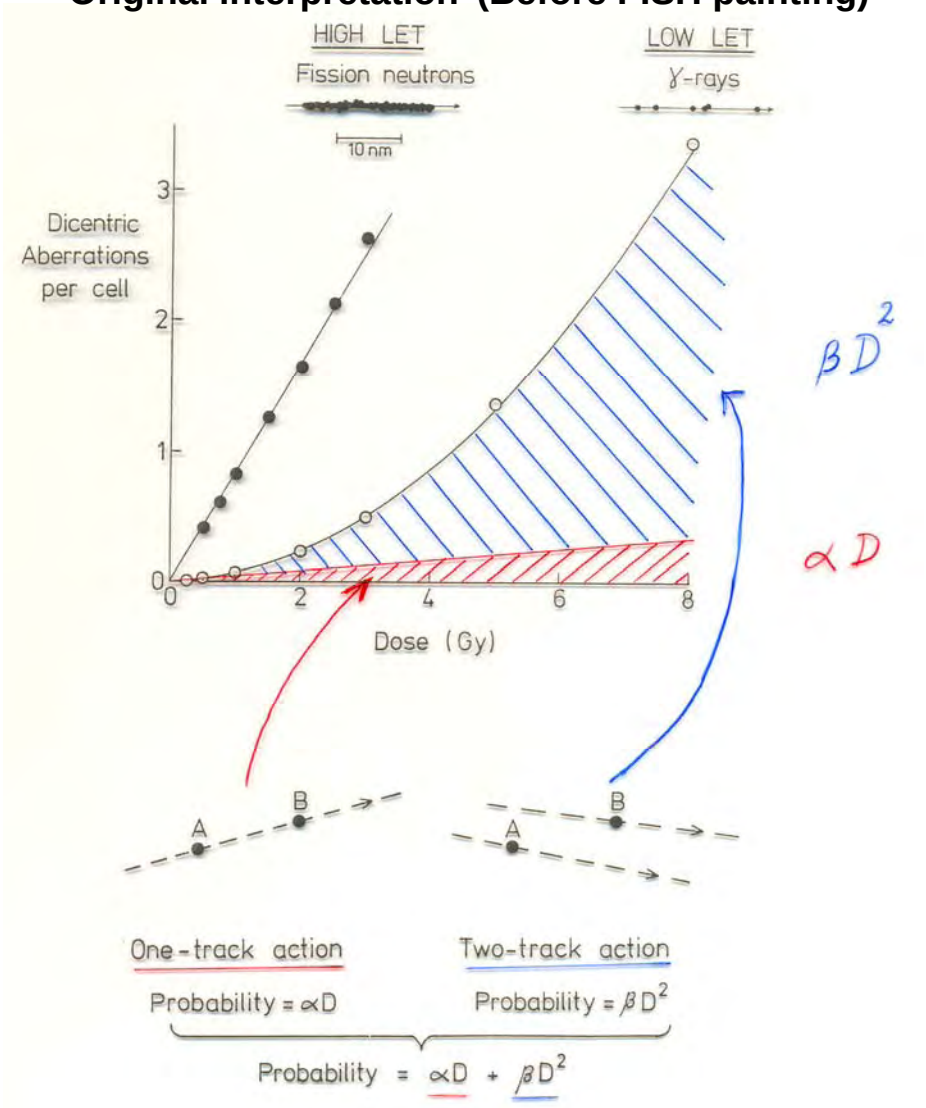
4. Are dose responses for dicentric aberrations reliable guides for analysis of relationships between cancer dose responses?

Are they a reasonable surrogate for the cancer-initiating aberrations?

- **Right type of aberration mechanism?**
- **Cell must be <u>viable</u> to have cancer relevance**

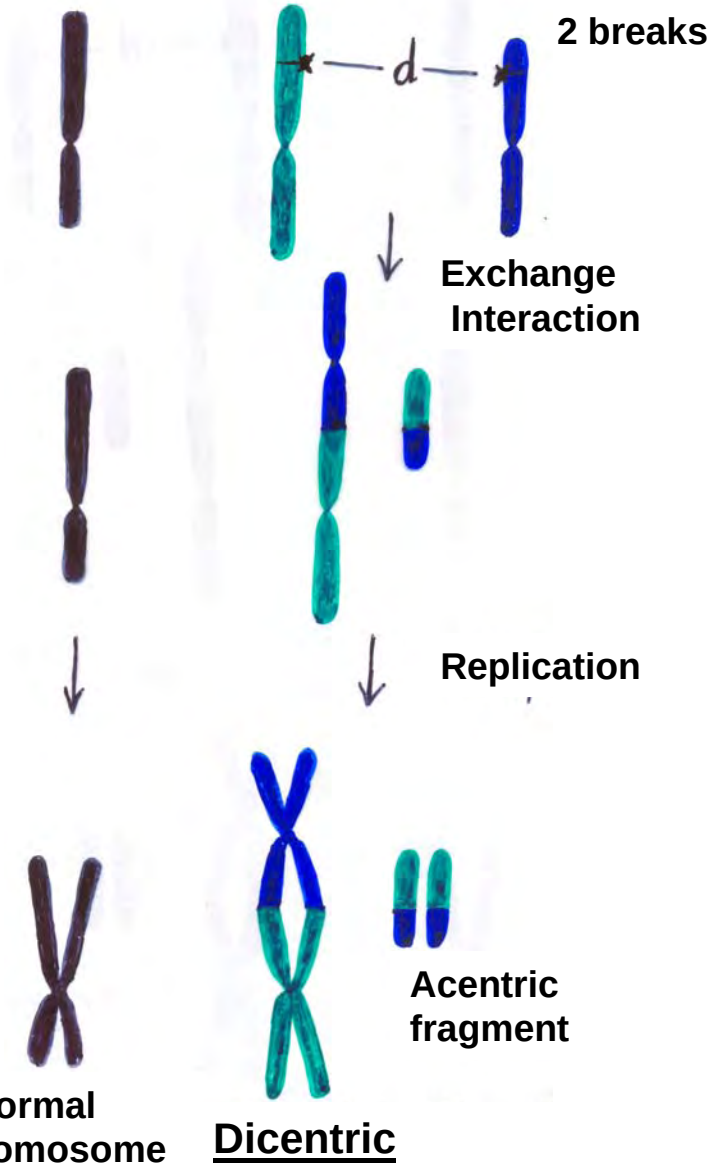
Chromosome exchange aberrations

Original interpretation (Before FISH painting)



Hence linear quadratic dose response

Conventional hypothesis:



Similarly for <u>symmetric</u> exchanges → reciprocal translocations

BUT, with advent of FISH painting of chromosomes:

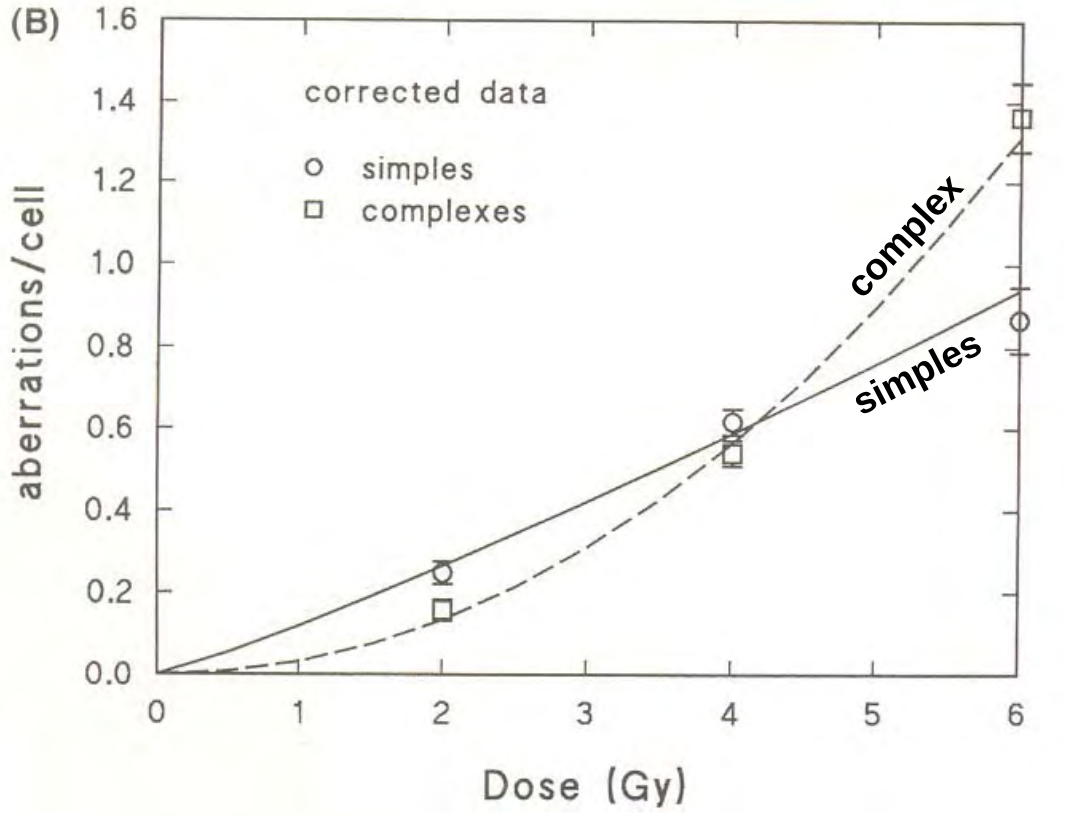
Simpson & Savage, IJRB 69, 429 (1996)

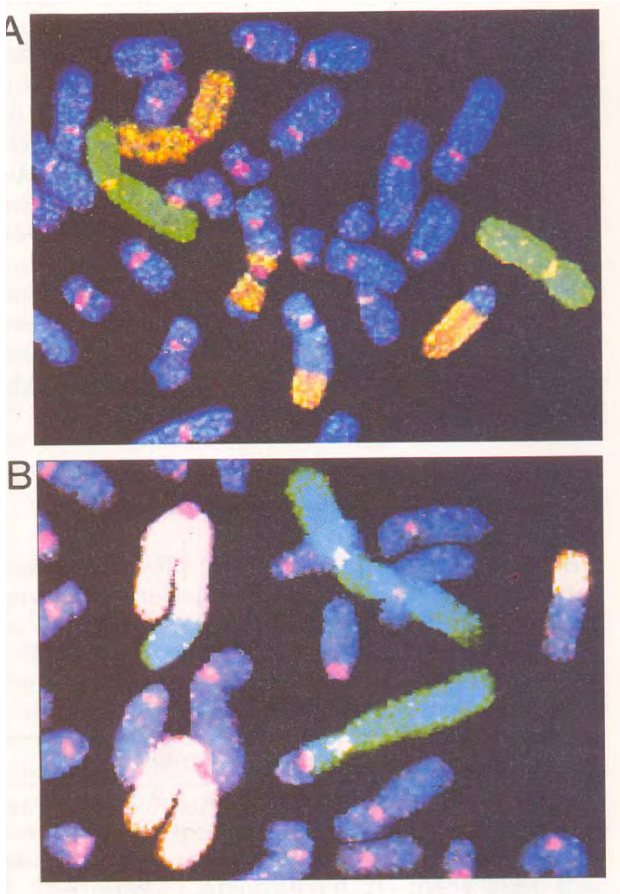
Savage, Mut Res 347, 87 (1995)

Find: Linear term due ~ to simple aberrations

Curvature due ~ to complex aberrations

(mostly non-transmissible, ie non-viable)



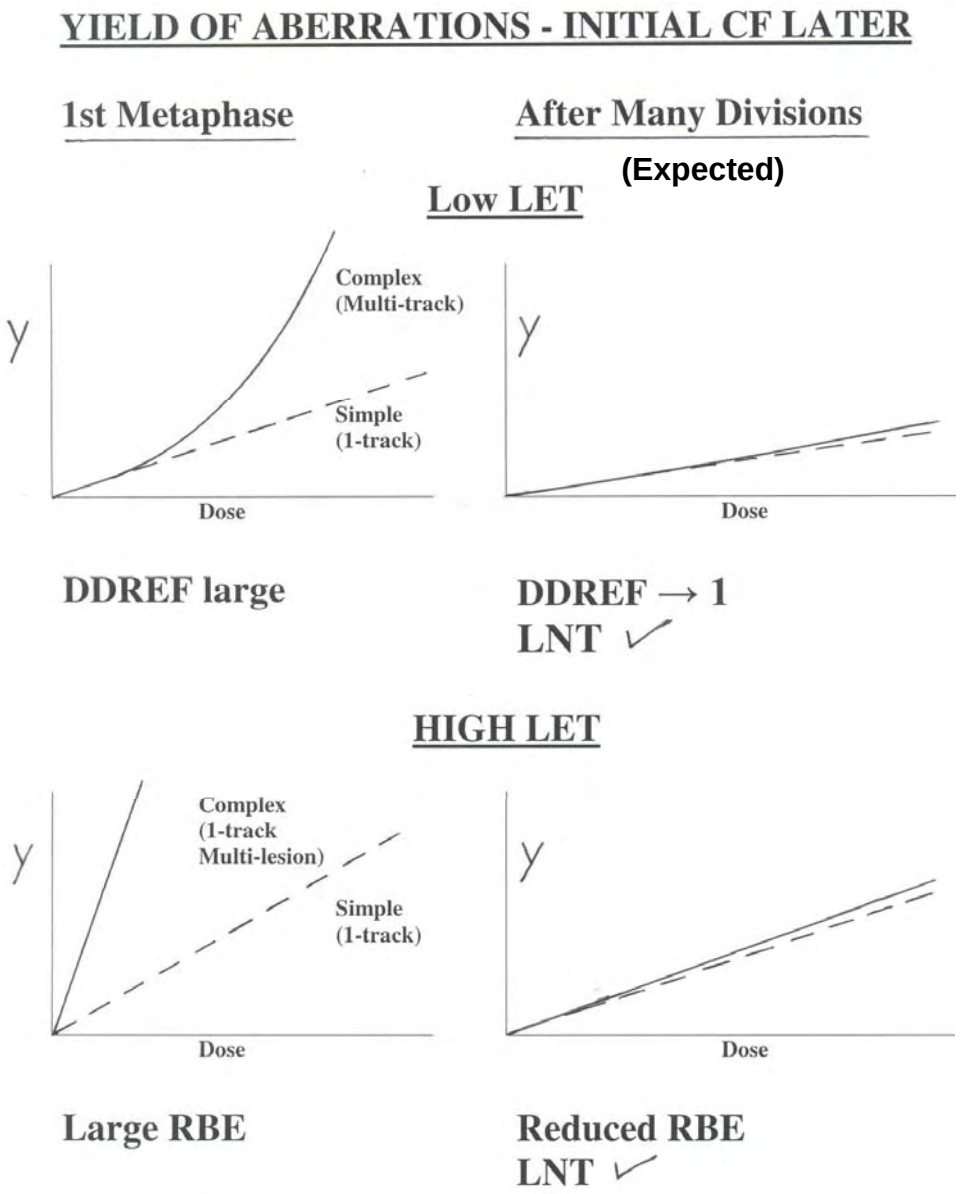


Painted c'somes 1 & 2
Normal Human fibroblasts
250 kVp X-rays

Suggests aberrations in viable cells → ~ linear response

Hence, expect little dose-rate dependence

Cancer can arise only from viable cells, so only viable aberrations can be of relevance

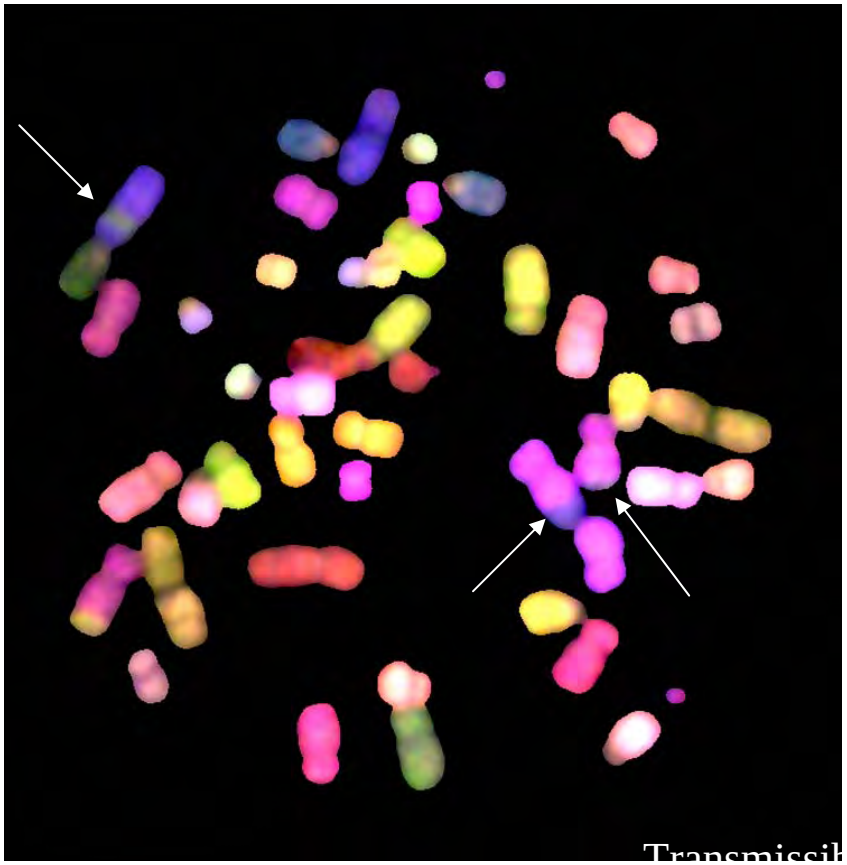


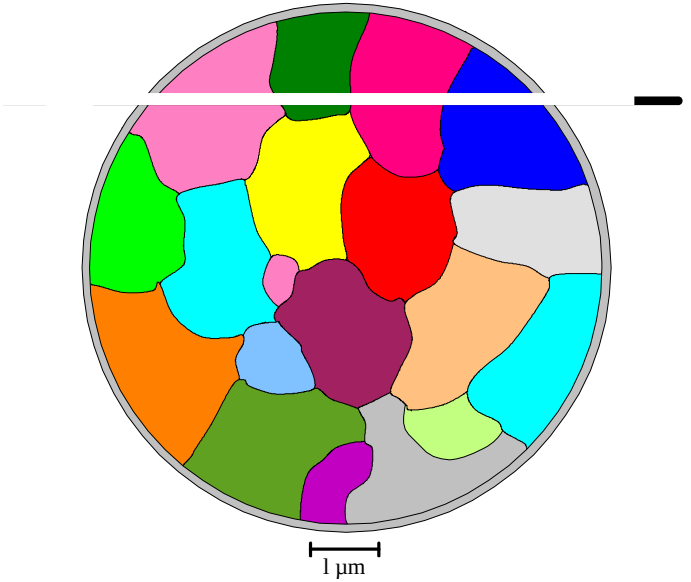
Dose responses for viable aberrations are <u>not</u> well represented by initial aberrations

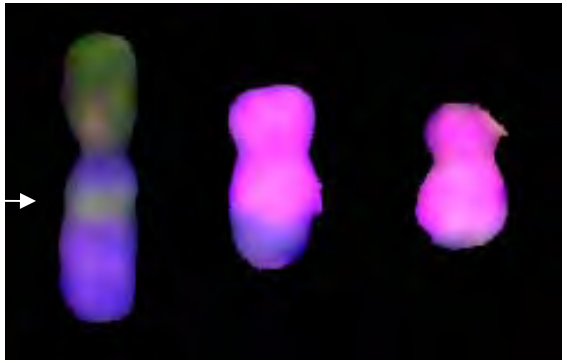
Aside Comment: No surprise if RBE of alpha-emitters is very small for abs in viable cells (in eg haemopoietic cells)

(From Goodhead, 11th ICRR, Dublin 1999)

Example of a viable complex aberration in a human lymphocyte after alpha-particle irradiation



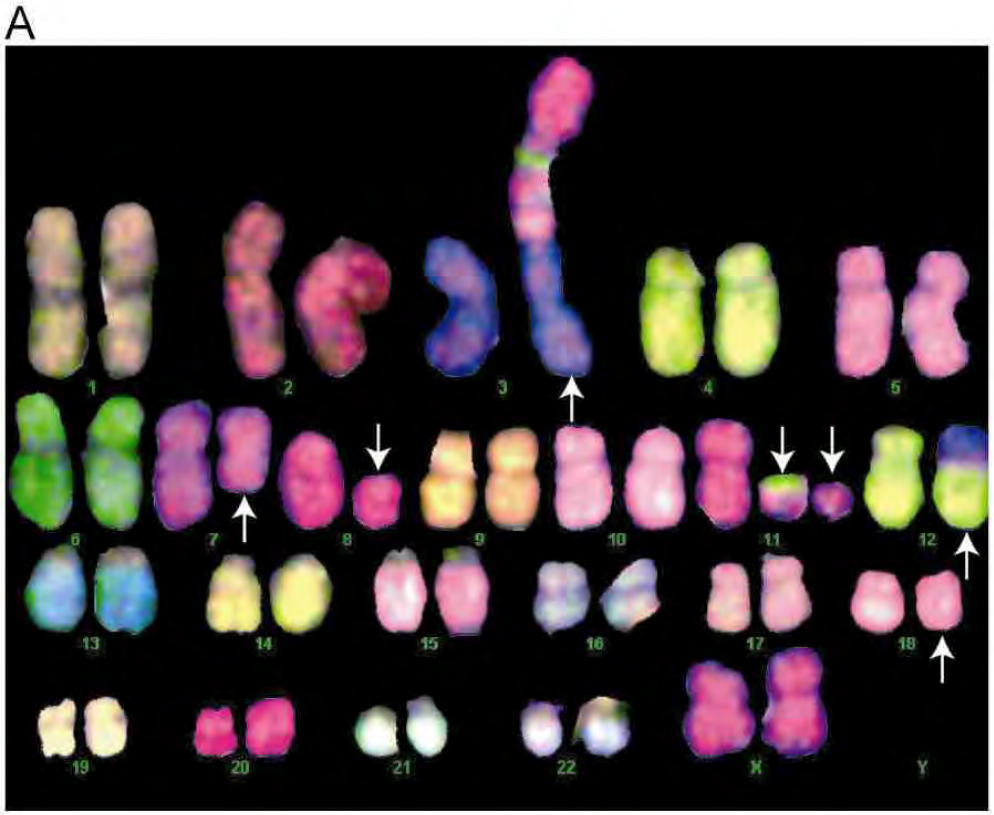


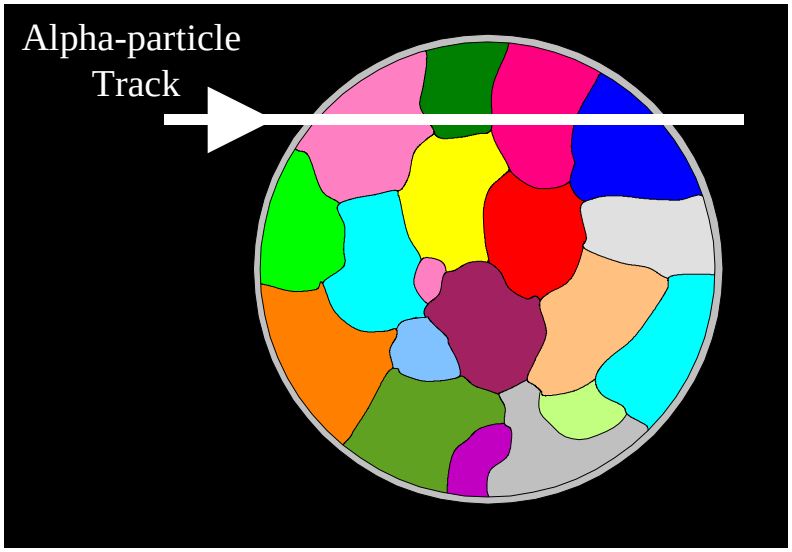


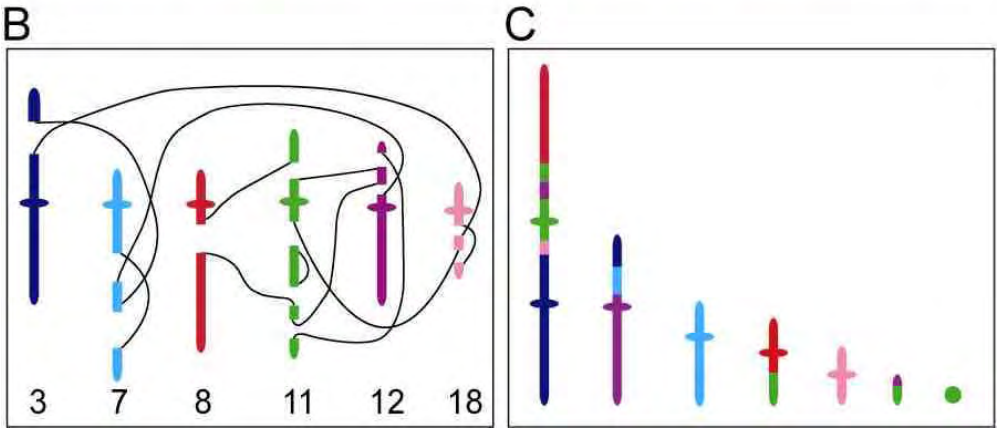
Anderson et al, PNAS 99, 12167 (2002) (*in vitro*)

Anderson et al, Radiat Res 163, 26 (2005) (in humans)

A very complex aberration produced by an α-particle passing through a human lymphocyte







This complex aberration involves at least 6 chromosomes and 12 breaks.

It has been visualized by M-FISH.

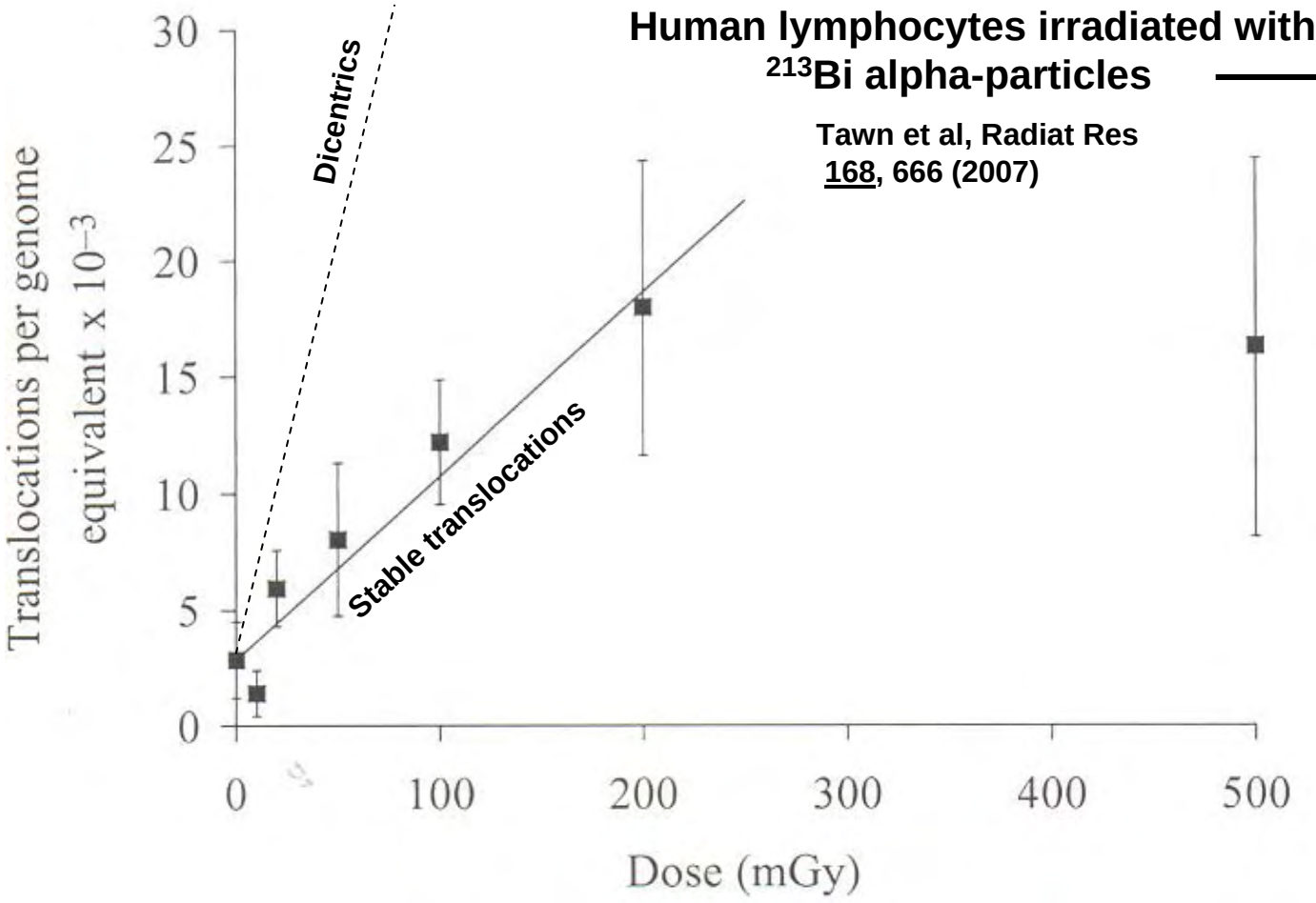
Anderson et al, PNAS 99,12167 (2002)

Most complex aberrations (from X-rays or α-particles) are non-transmissible

eg Human lymphocytes: Anderson et al, Radiat Res 159, 40 (2003)

Human lymphocytes irradiated with ^{213}Bi alpha-particles

Tawn et al, Radiat Res 168, 666 (2007)



Low-dose RBE

Dicentrics = 14

Stable translocations = 3

Dicentrics are a poor surrogate for viable aberrations

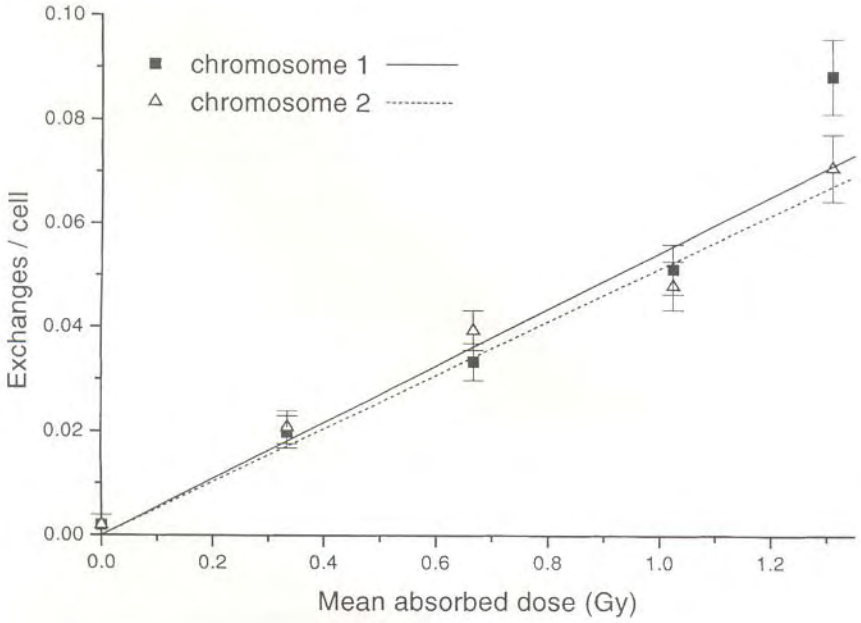
Normal Human fibroblasts

C_K ultrasoft X-rays

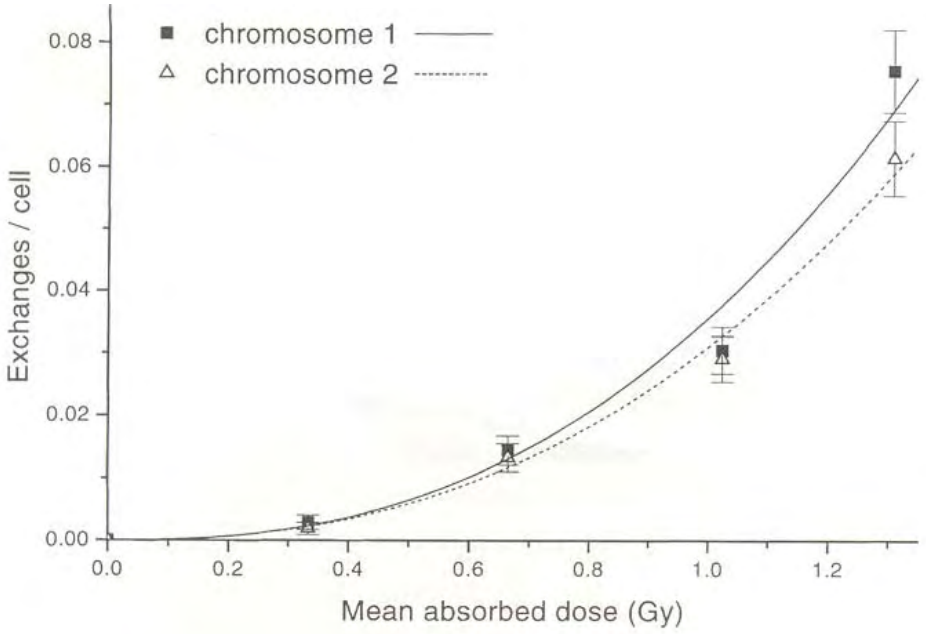
Painting c'somes 1 & 2

Griffin, Hill et al, IJRB 73, 591 (1998)

Simple exchanges



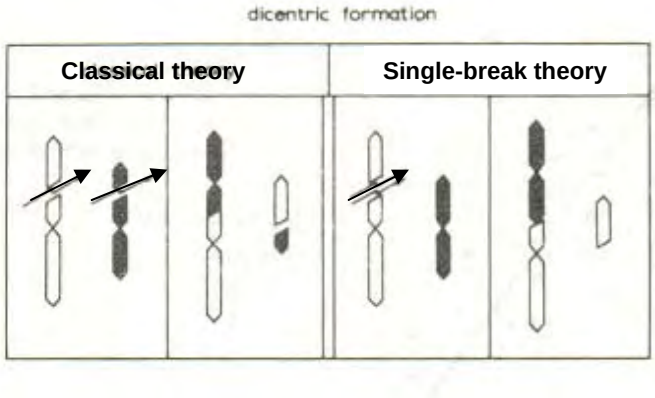
Complex exchanges



Reminds of another issue:

1-break exchanges??

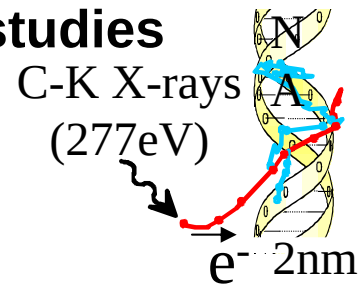
(lesion – nonlesion interaction)



Isolated low-energy electrons produce simple chromosome exchange aberrations, with linear dose dependence.

→ **Strong evidence that a single damaged chromosome (from single track, single dsb) can cause a chromosome exchange**

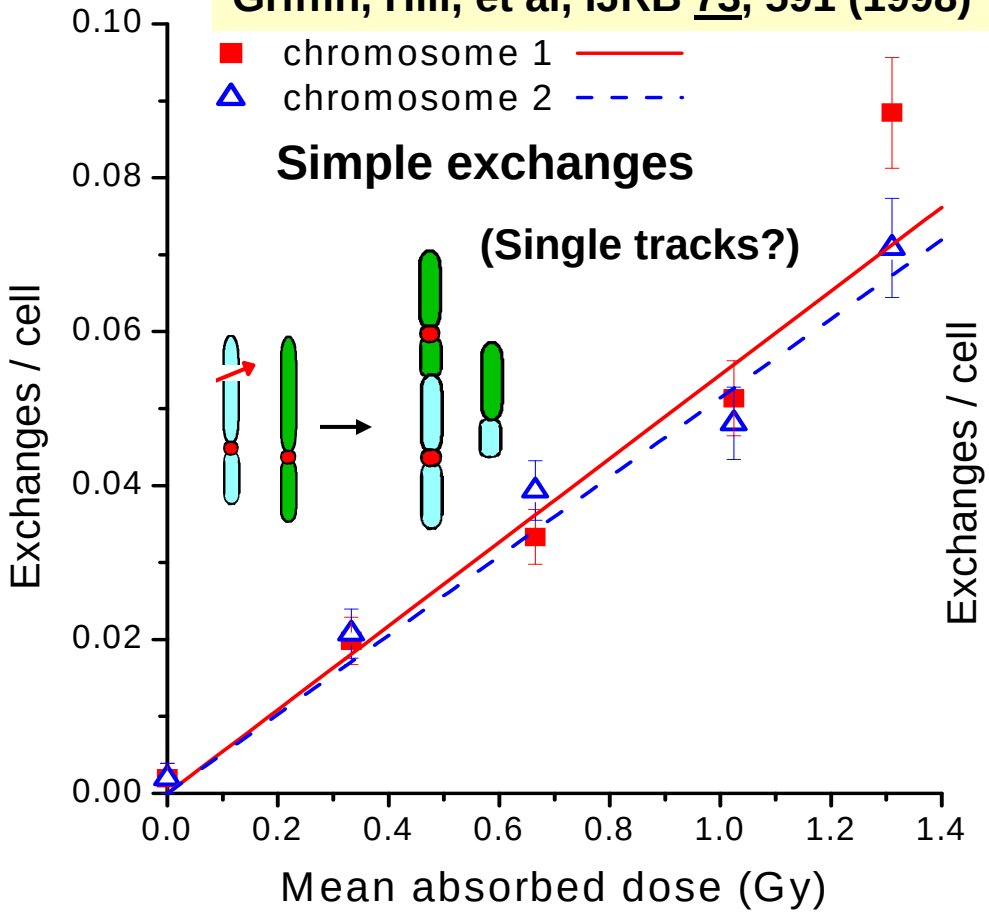
ultrasoft X-ray studies

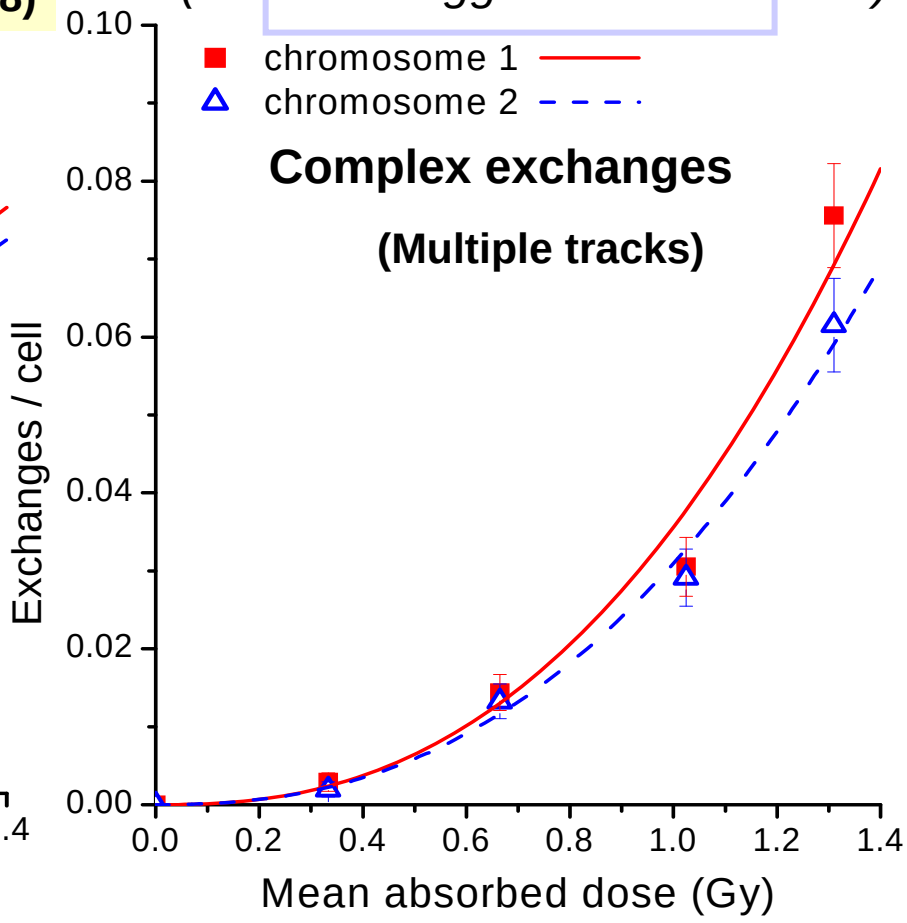


electron range < 7nm

(not much bigger than DNA helix)

Griffin, Hill, et al, IJRB 73, 591 (1998)





4. Are dose responses for dicentric aberrations reliable guides for analysis of relationships between cancer dose responses?

Probably not

Must be transmissible aberrations
ie in viable (stable) cells

Deletion vs simple exchange mechanisms?

Summary comments

Single electron:

- Can produce clustered DNA damage
- Full range of stochastic consequences to cells
- Stands out above endogenous damage
- Supports LNT, right down to a single electron

Chromosome aberrations:

- Beware extrapolation guidance from aberration dose responses
  - Type of aberration
  - Cell must retain viability
  - LNT intact
  - But beware DDREF and w_R extrapolations

Conclusions

- Expect LNT
- Beware DDREF and w_R extrapolations

<u>ASSUMING</u> direct chromosome aberration is prime determinant of cancer dose response

BUT

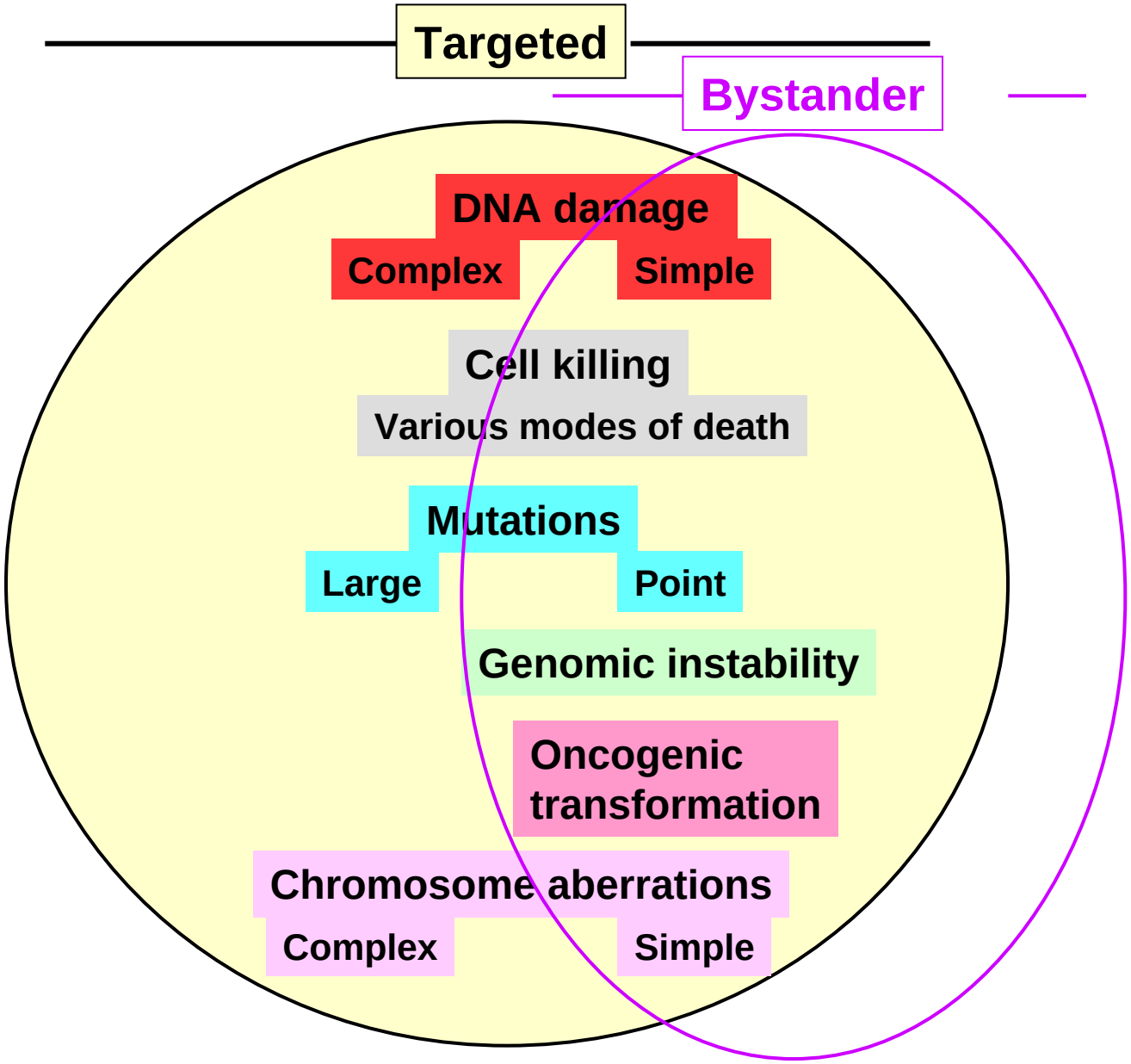
Clearly, there are other radiobiological processes that may modify, or even largely replace, the conventional paradigm.

These may include:

- **Bystander effects**
- **Radiation-induced instability**
- **Modifications to cell/tissue microenvironment**
- **Cell signaling (intra- and inter-cell)**
- **Adaptive responses**
- **Hormetic/stimulatory effects**
- **Promotional effect of radiation**
- **Germline minisatellite mutations**
- **……. etc, etc.**

Any of these might modify standard expectations at low and/or high doses, including the LNT assumptions.
Roles not yet clear; research continues; committees deliberate!

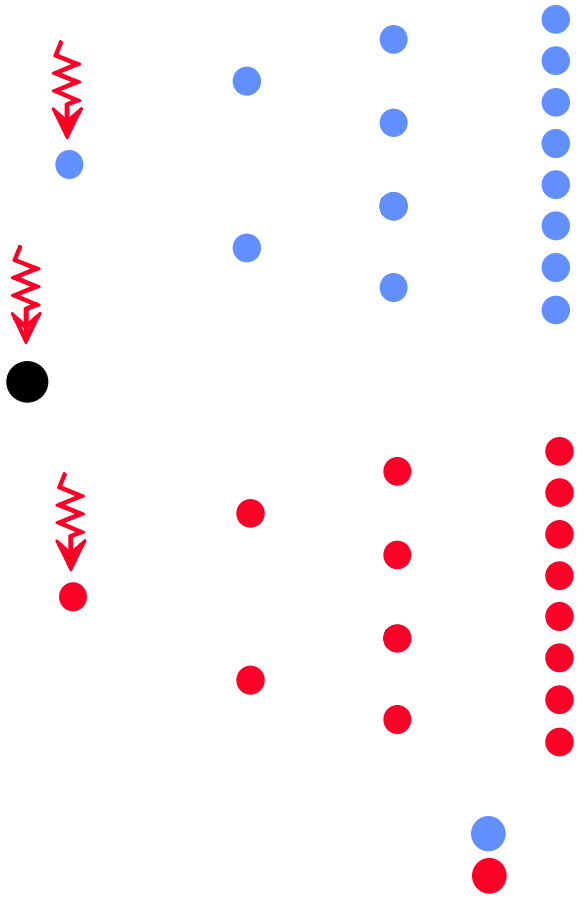
Much overlap --- but notable differences



[Courtesy of Munira Kadhim]

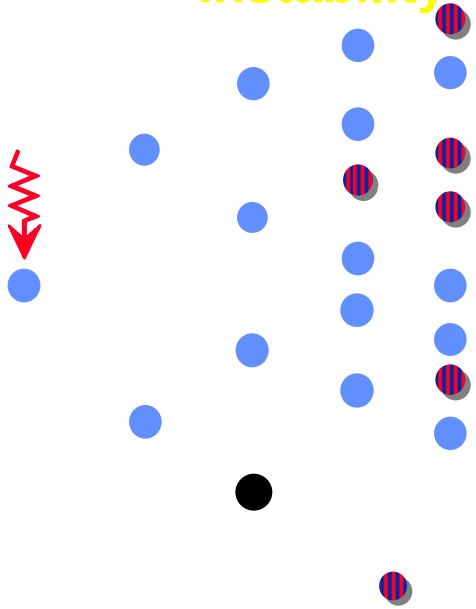
Paradigm Shift

Conventional Paradigm



Low Frequency, Immediate, Clonal Expression

New Paradigm
Radiation Induced Genomic Instability



High Frequency, Delayed, Non-clonal Expression

Reviews:

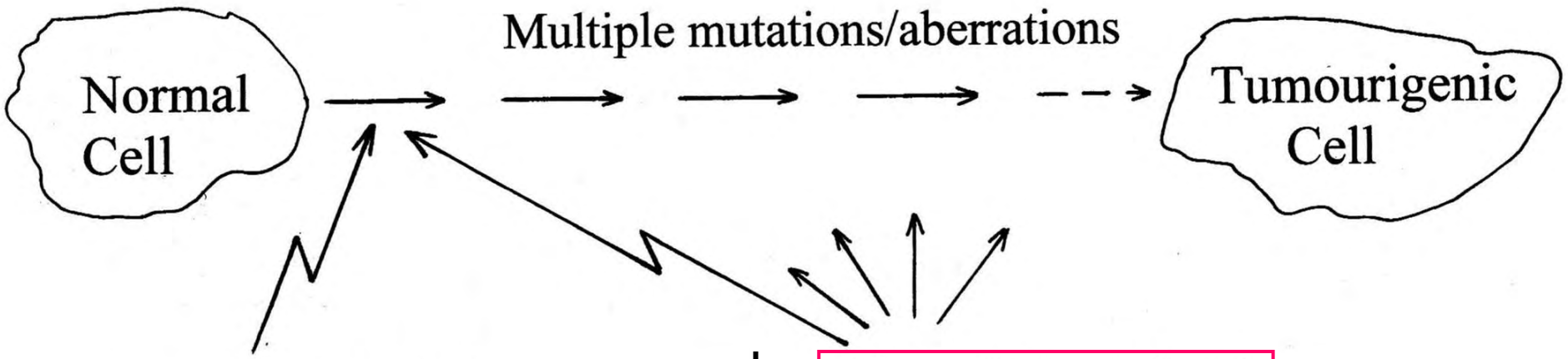
Morgan, Radiat Res 159, 567 (2003)

Little, J Radiol Prot 23, 173 (2003)

Kadhim, Oncogene 22, 6994 (2003)

After: Kadhim et al, Nature 355, 738 (1992)

TWO PARADIGMS FOR RADIATION TUMOURIGENESIS:



(1) Radiation initiation (mutation/aberration) [Conventional paradigm]

(2) Radiation-induced instability

In *Radiation and Homeostasis*, Eds Sugahara et al (Elsevier) p508 (2002)

From damage directly to DNA ('targeted').
Very low frequency event.

Even a single track carries some risk
(ie no dose threshold)

From what damage???
(untargeted).
Very high frequency event.

Dose threshold for low-LET???
No threshold for high-LET.

Bystander processes?

BUT **Clearly, there are other radiobiological processes that may modify, or even largely replace, the conventional paradigm.**

These may include:

- **Bystander effects**
- **Radiation-induced instability**
- **Modifications to cell/tissue microenvironment**
- **Cell signaling (intra- and inter-cell)**
- **Adaptive responses**
- **Hormetic/stimulatory effects**
- **Promotional effect of radiation**
- **Germline minisatellite mutations**
- **……. etc, etc.**

BUT

No effect on risk assessments

BEIR VII (2006)
ICRP (2007)
UNSCEAR '2006' (2008)?

Contrast

French National Academies (Medicine & Science)

Any of these might modify standard expectations at low and/or high doses, including the LNT assumptions.
Roles not yet clear; research continues; committees deliberate!

Standard assumption:

Cancer is dominant risk from low-level radiation

(also small germ-line hereditary risk)

What of cardiovascular disease?

- **Substantial dose-dependent risk in A-bomb survivors** **(Shimuzu et al 1992; Preston et al 2003)**
- **Also evidence from some other exposed groups**
  - **-- convincing at high acute doses** **(Reviews: McGale & Darby 2005; Little et al 2008)**
  - **-- Is this a threshold effect?** **(Tissue damage, inflammation?)**
- **BUT, also significant associations reported after chronic protracted exposures**

  (McGeoghegan et al 2008: The non-cancer mortality experience of male workers at British Nuclear Fuels plc, 1946-2005 (Int J Epidemiol))

  -- Magnitude comparable to radiation-cancer mortality
- **Some evidence that plaque formation may be monoclonal, with mutational origin**

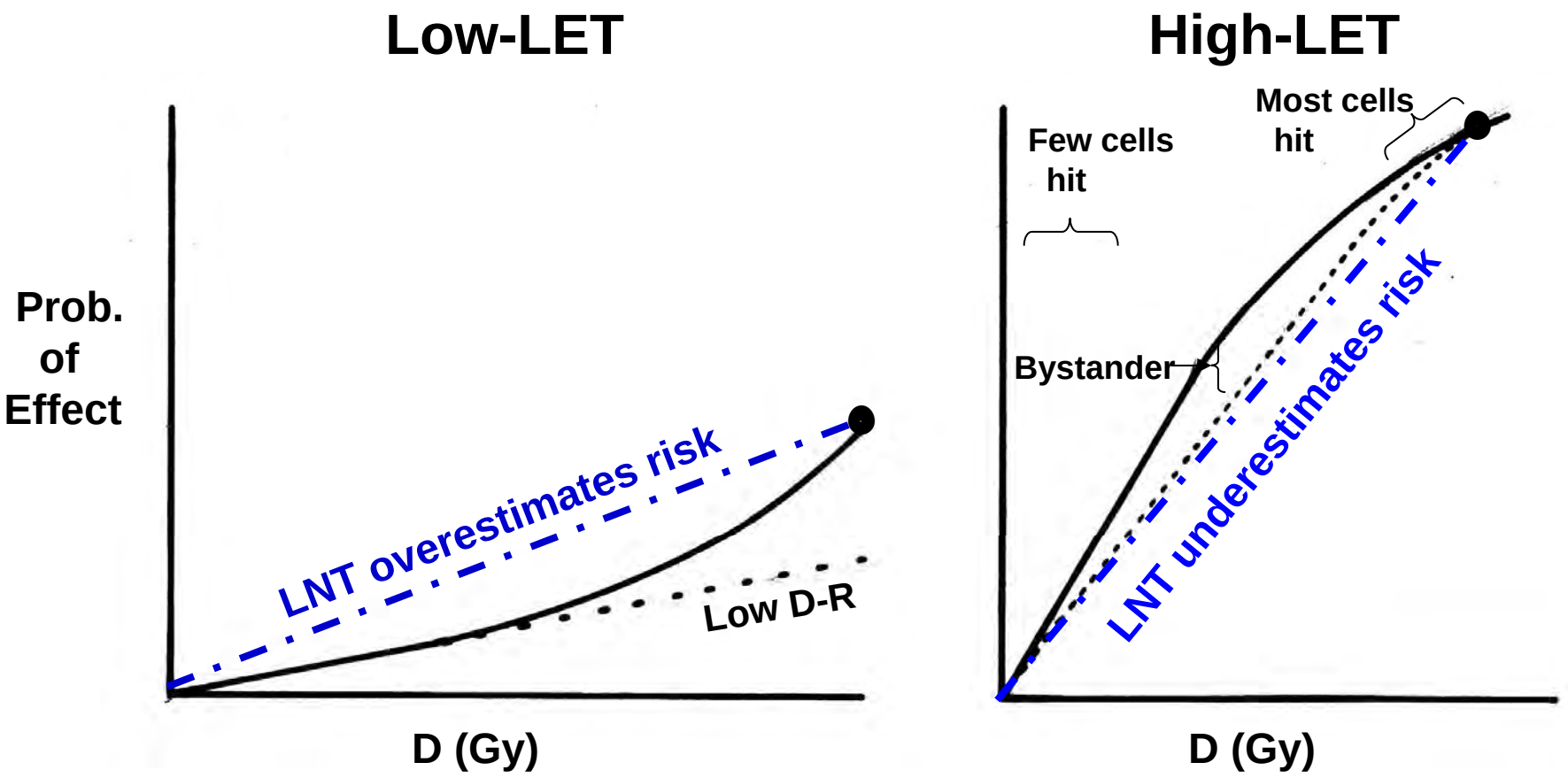
  --- could imply non-threshold, DNA-damage, single-track effect??

Big Question: Might similar issues arise as for cancer risk??

-- mechanism, shape of dose response, LNT or not??

(1) Assume conventional carcinogenesis mechanism

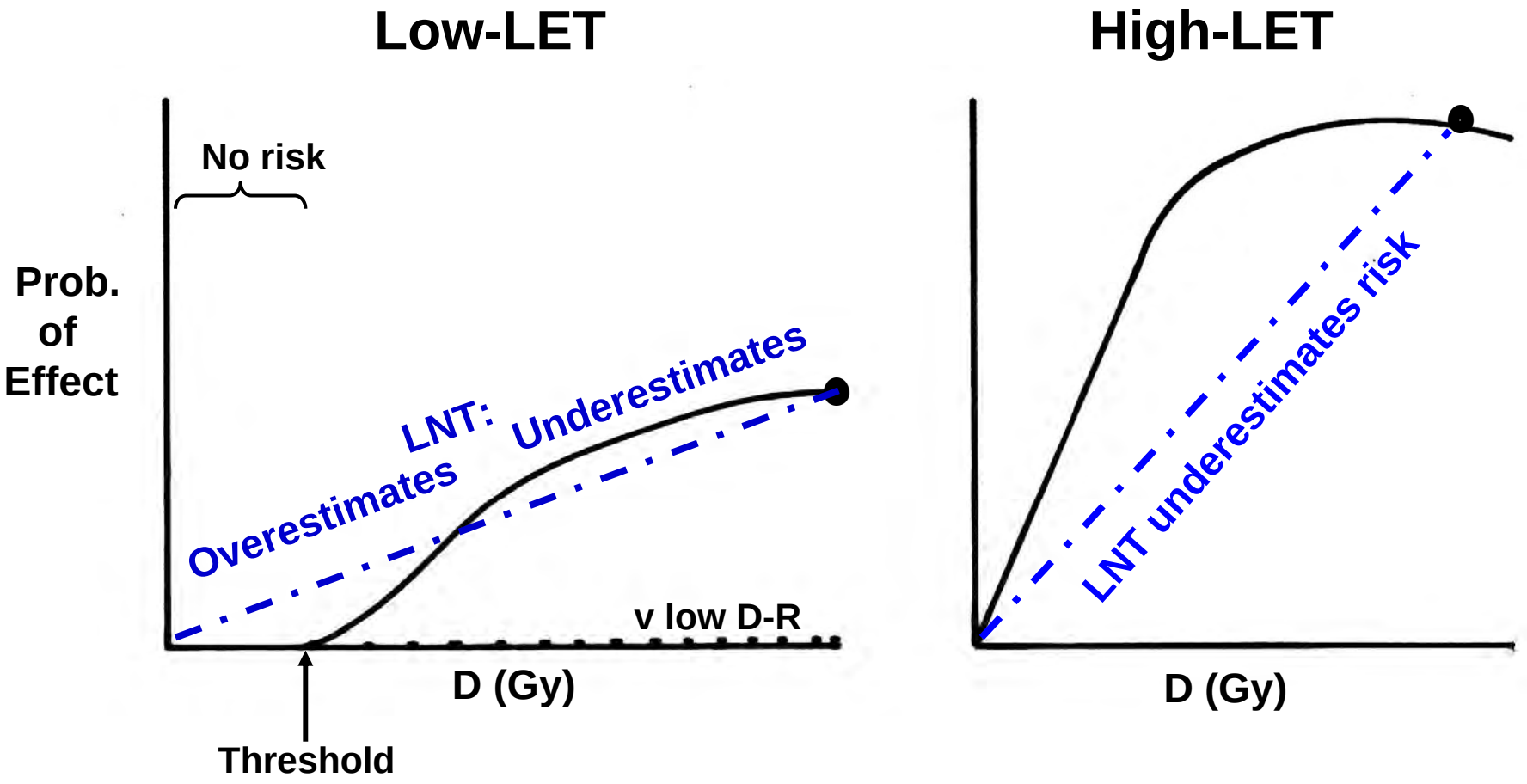
(ie immediate 'initiating' mutation from radiation)



(2) Assume instability carcinogenesis mechanism

(ie radiation induces ongoing instability → ongoing increased mutation rate)

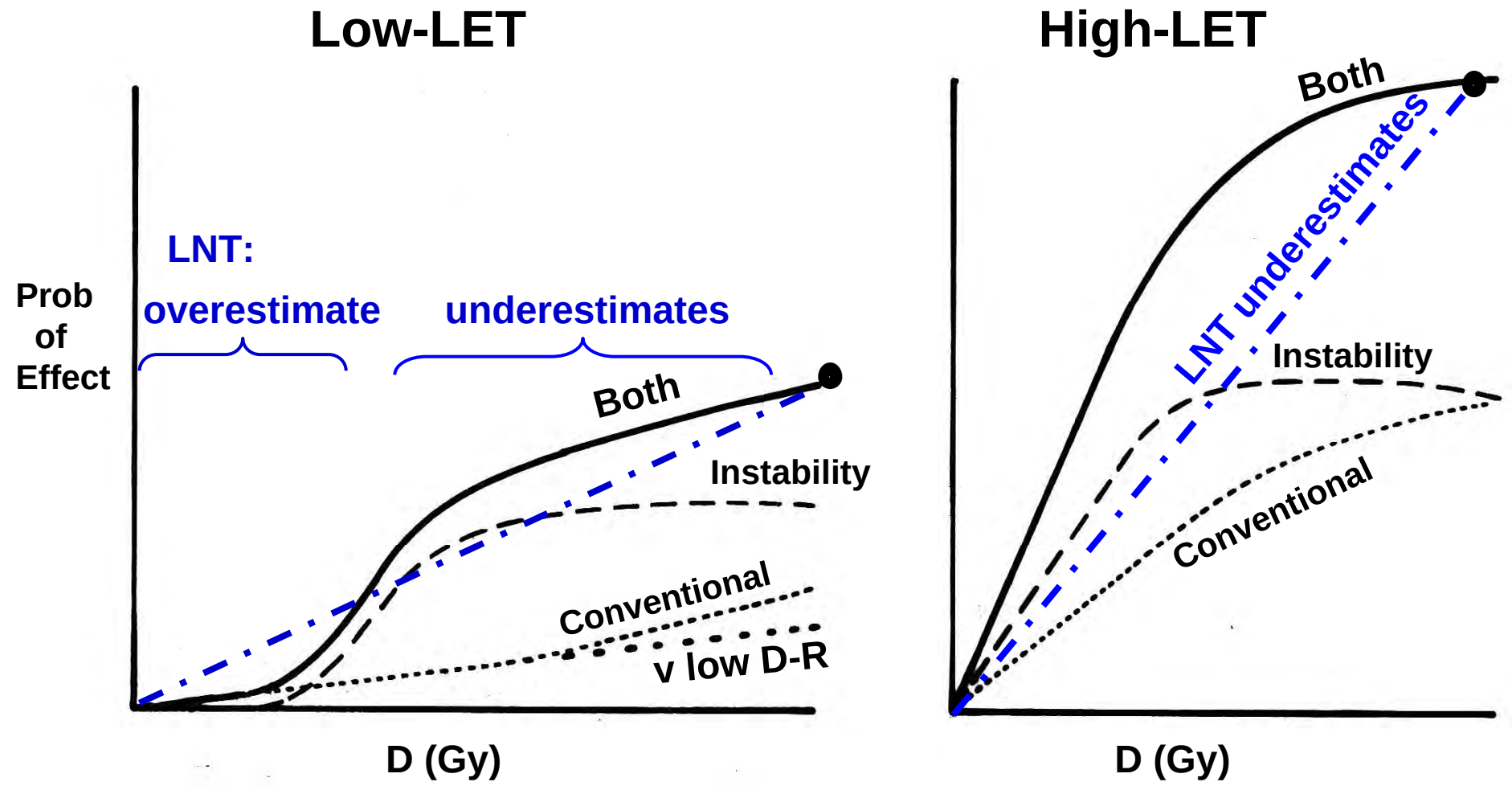
+ Assume threshold for Low-LET radiation



(3) Assume both mechanisms contribute, independently

ie conventional mechanism
or instability mechanism
} → radiogenic cancer

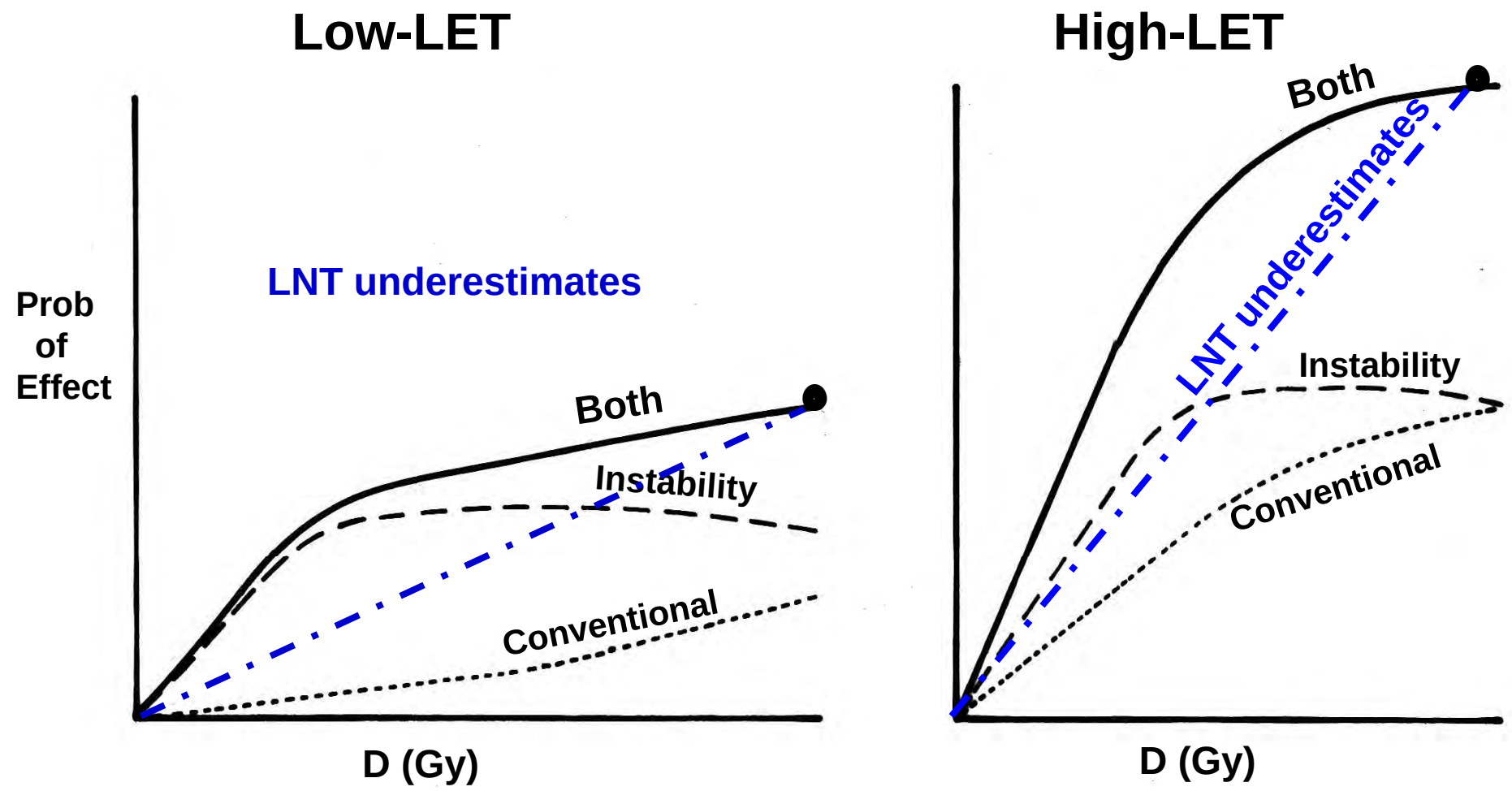
(with threshold)



(4) Assume both mechanisms contribute, independently

ie conventional mechanism
or instability mechanism
} → radiogenic cancer

(no threshold)



Low Dose and Low Dose-Rate Radiation Effects and Models

Antone L. Brooks
Washington State University Tri-Cities
Richland WA, 99354

44th Annual Meeting of the NCRP
Bethesda, MD
April 14-15, 2008

Members of Program Area Committee 1

- Thanks for organizing this important meeting!!!
  - Antone L. Brooks
  - 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
  - Gayle E. Woloschak

Widespread Interest in Low Dose Radiation Effects and Policy

- Large number of recent scientific publications
- Working Group on the Effects of Low Radiation Doses-Science and Policy (Neil Coleman)
- Strengthening Scientific and Industry Cooperation for Contributing to International Deliberations on Risk from low-Dose Ionizing Radiation (Sylvain Saint-Pierre)
- EPRI Literature Survey on LNT (Phung Tran)

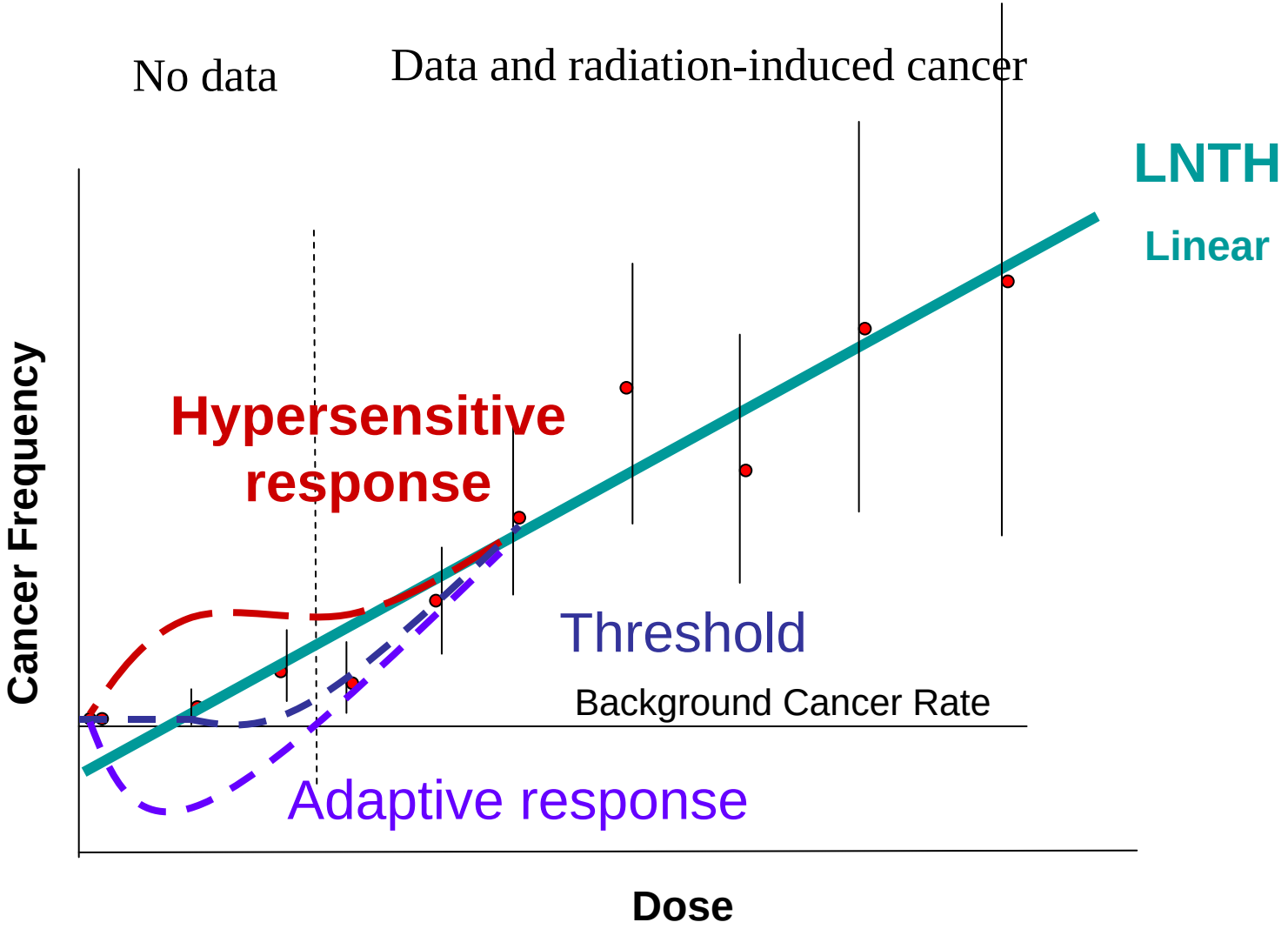
Strengthening Radiation Standards to Provide Adequate and Appropriate Radiation Protection

- Understand the history and basis for the current standards
- Evaluate the strengths, weaknesses and uncertainty associated with standards
- Provide a strong scientific basis for the standards
- Interact and inform both the public and those who make regulatory decisions concerning the potential scientific, medical, social and economic impact of regulations
- Provide appropriate forums for input and modification of regulations and actions associated with radiation events

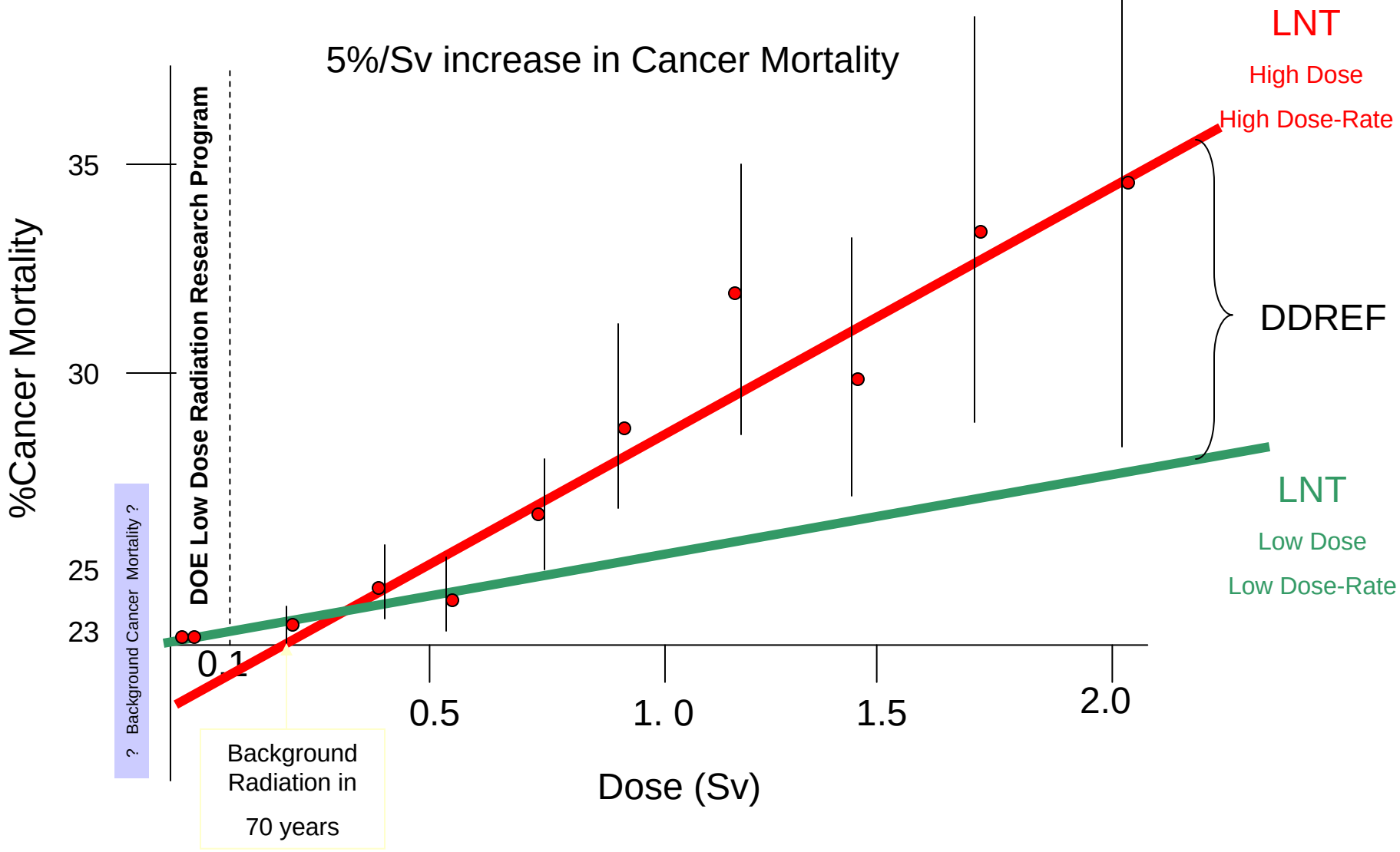
History and Basis for Current Standards

- Standards rely very heavily on the A-bomb data
- Animal studies used to modify standards for low dose rate and non-uniform dose distribution associated with internally deposited radioactive material. Some recent human data.
- Use of cell and molecular data to develop biophysical models for low dose extrapolation.

Radiation Dose-Response Models



A-Bomb Experience



Strengths, Weaknesses and Uncertainty for Current Standards

- Review of the most recent human studies to evaluate the impact on standards
- Discussions on the limitations associated with the human studies
- Discussion of the magnitude and use of the DDREF in low dose region
- Uncertainty associated with the biophysical model used for low dose extrapolation

NCRP Annual Meeting

Low Dose and Low Dose-rate Radiation Effects and Models

April 14-15, 2008

Molecular, Cellular, Tissue and Animal Radiation Responses of Relevance to Radiation Protection

- DNA damage and repair contribution to risk
- Effects of dose and dose-rate on gene expression
- Non-targeted cell and tissue responses
- Factors that modify radiation induced cancer
- Radiation sensitivity among individuals
- Biophysical models and systems biology approaches

The LNT Model for Low Dose Radiation Risk Extrapolation

DEBATE

David Brenner (BEIR VII)

and Dietrich Averbeck

(French Academy Report)

Human Epidemiology Studies

- As a basis for risk estimates
- Status and issues
- Uncertainty in dose estimates

Low Dose Effects, Regulatory Policy and Impacts on the Public

- What would it take to change regulations?
- Use of scientific information in decision making and regulations
- Public beliefs about radiation
- Public programs for reimbursement

Questions?

- Are the mechanisms of action different following high and low doses of radiation?
- Are low doses of radiation protective or harmful?
- What research would be needed to alter radiation standards?
- How can we best communicate low dose radiation risk?
- Are the current standards supported by scientific data and are they adequate and appropriate?

National Cancer Institute

Low Dose Extrapolation of Radiation Health Risks

Some implications of uncertainty for radiation protection at low doses

Charles Land

Division of Cancer Epidemiology & Genetics
Radiation Epidemiology Branch

April 14, 2008

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Background

- "Quantitative uncertainty analysis"
  - A well-established field of study
  - Underlies what follows
- A Guide for Uncertainty Analysis in Dose and Risk Assessments Related to Environmental Contamination
  - (NCRP Commentary No. 14 (1996))
  - Evaluations based on combination of statistical and subjective sources of uncertainty
- Uncertainties in Fatal Cancer Risk Estimates Used in Radiation Protection
  - (NCRP Report 126 (1997))
  - "New paradigm" for expression of radiation-related cancer risk
  - And for dealing with what we don't know well but can't ignore

Some “New Paradigm” Examples

- Report of the NCI-CDC Working Group to Revise the 1985 NIH Radio-epi Tables
  - NIH pub. 03-5387 (2003)
- Low-dose Extrapolation of Radiation-related Cancer Risk
  - ICRP Report 99 (2005)
- Health Risks from Exposure to Low Levels of Ionizing Radiation (BEIR VII)
  - NAS/NRC (2006)

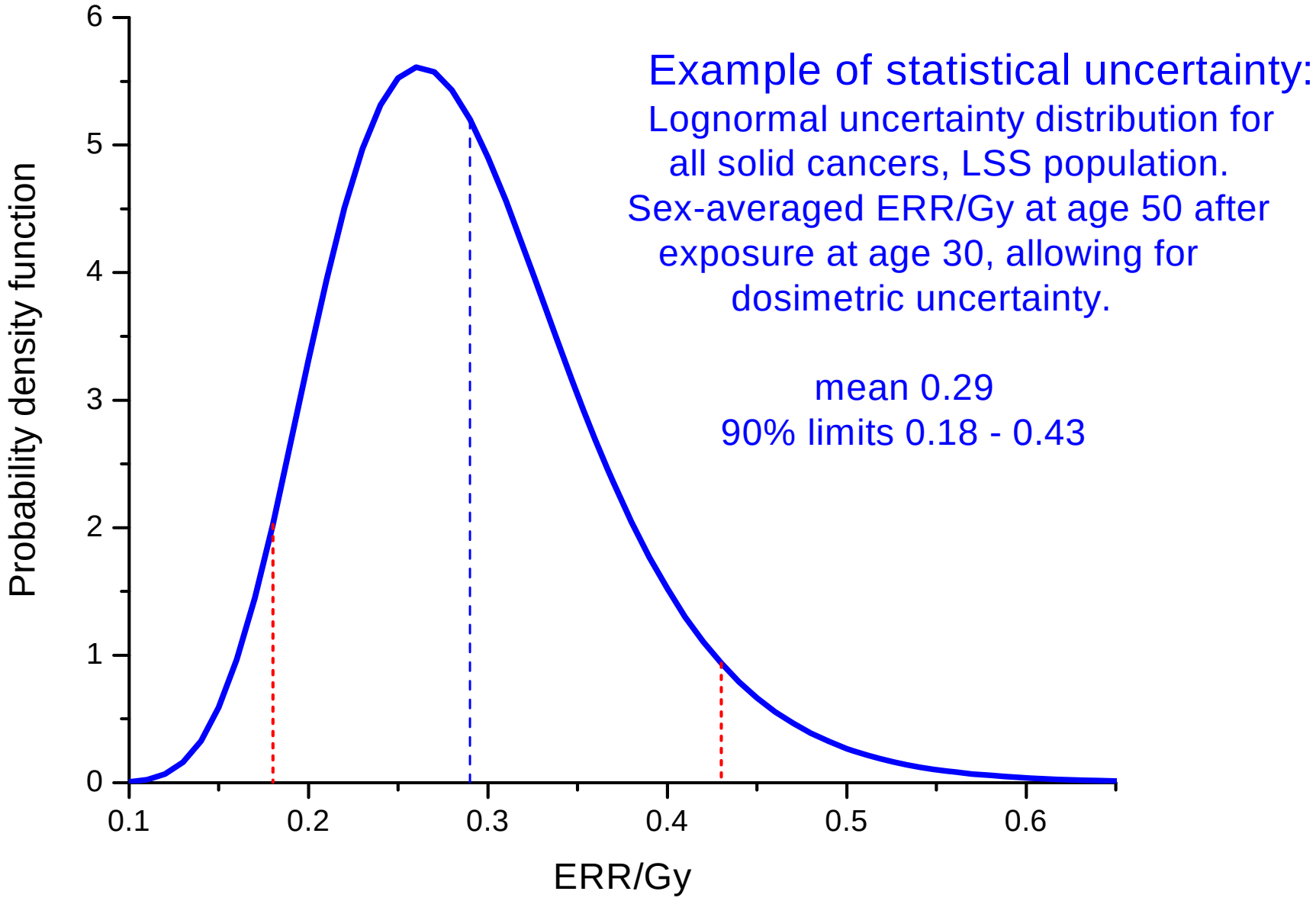
How the “New Paradigm” works

- Statistical analysis of epidemiological data
  - Corrected for dosimetric uncertainty in the data
- Yields estimated excess risk per Gy (if linear), with confidence limits (statistical uncertainty distribution)
- Takes a quantitative uncertainty analysis approach to necessary, but uncertain, assumptions needed to apply the statistical information to risk analysis

Technical notes

- "Risk" is an actuarial concept
  - It can be estimated and verified only on the basis of population rates
  - And applied to an individual as a property of a population to which he or she is assumed to belong

- Excess risk can be expressed in relative terms, as a multiple of baseline (ERR), or absolute terms, as an addition to baseline (EAR)
  - Thus, EAR = baseline $\times$ ERR, ERR = EAR / baseline
  - Age-specific graphs for EAR and ERR are the same, except for scale



* Based on 1958-1987 LSS Tumor Registry Data, Thompson et al, Rad Res 1994

Other sources of uncertainty

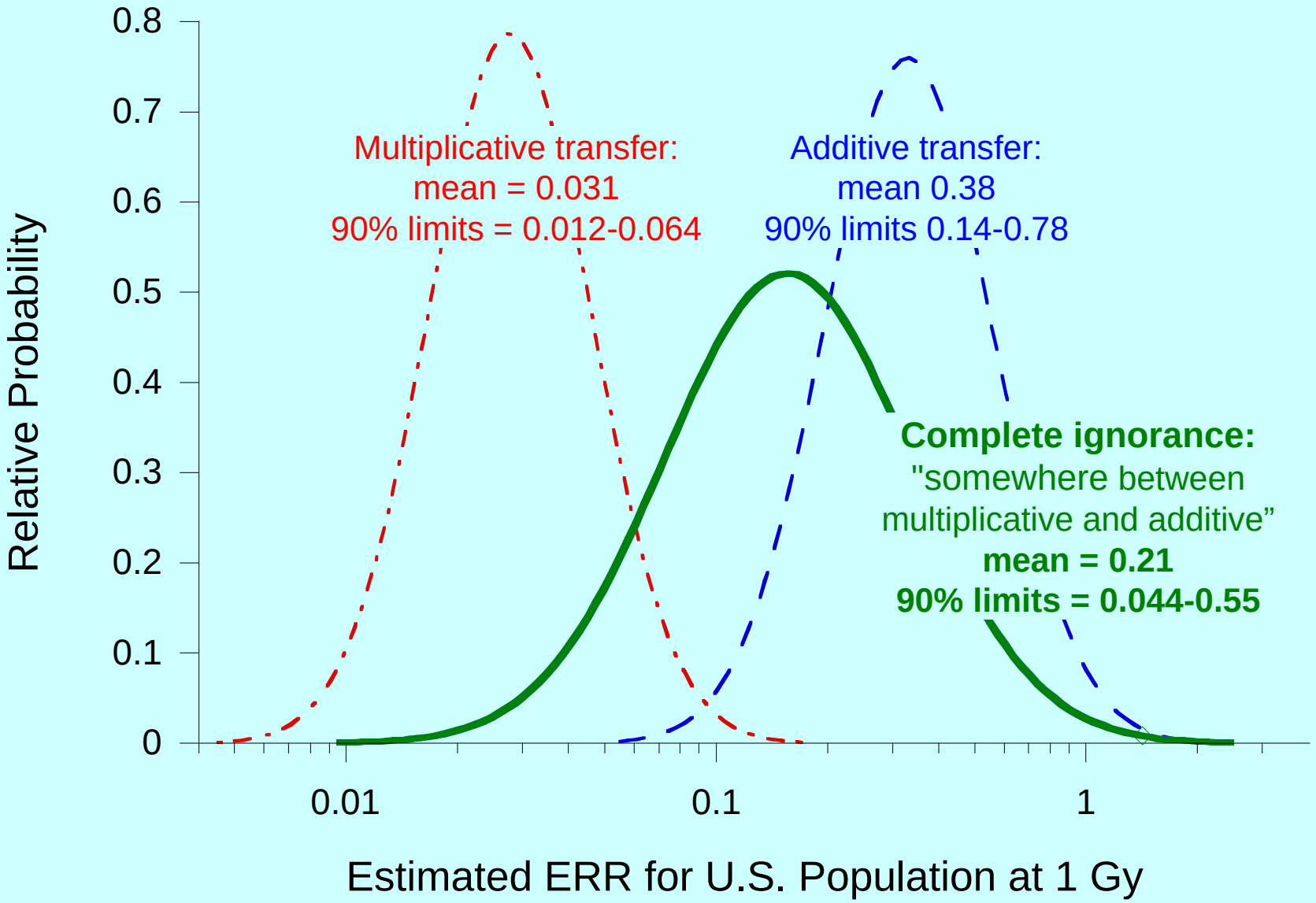
- 1. Transfer of risk estimates between populations
  - Not a big problem for all solid cancers combined, the subject of the previous slide
  - But can be a big problem if the baseline cancer rates differ greatly between populations
    - Example: stomach cancer rates in Japan are about 12-fold higher than those in the US
    - Multiplicative transfer: ERR(US) = ERR(Japan)
      - Implies that EAR(US) = EAR(Japan)/12
    - Additive transfer: EAR(US) = EAR(Japan)
      - Implies that ERR(US) = ERR(Japan) $\times$ 12

Population transfer (cont.)

- **Very few data on how to do it: we don't know enough to resolve this problem, but we can't ignore it**
- **One approach is to treat multiplicative and additive transfer as the extremes**
- **And incorporate the uncertainty into the estimation process**
  - **E.g., ERR = $p \times$ multiplicative + (1 – p) $\times$ additive,**
  - **Where p is uniformly distributed between 0 and 1**

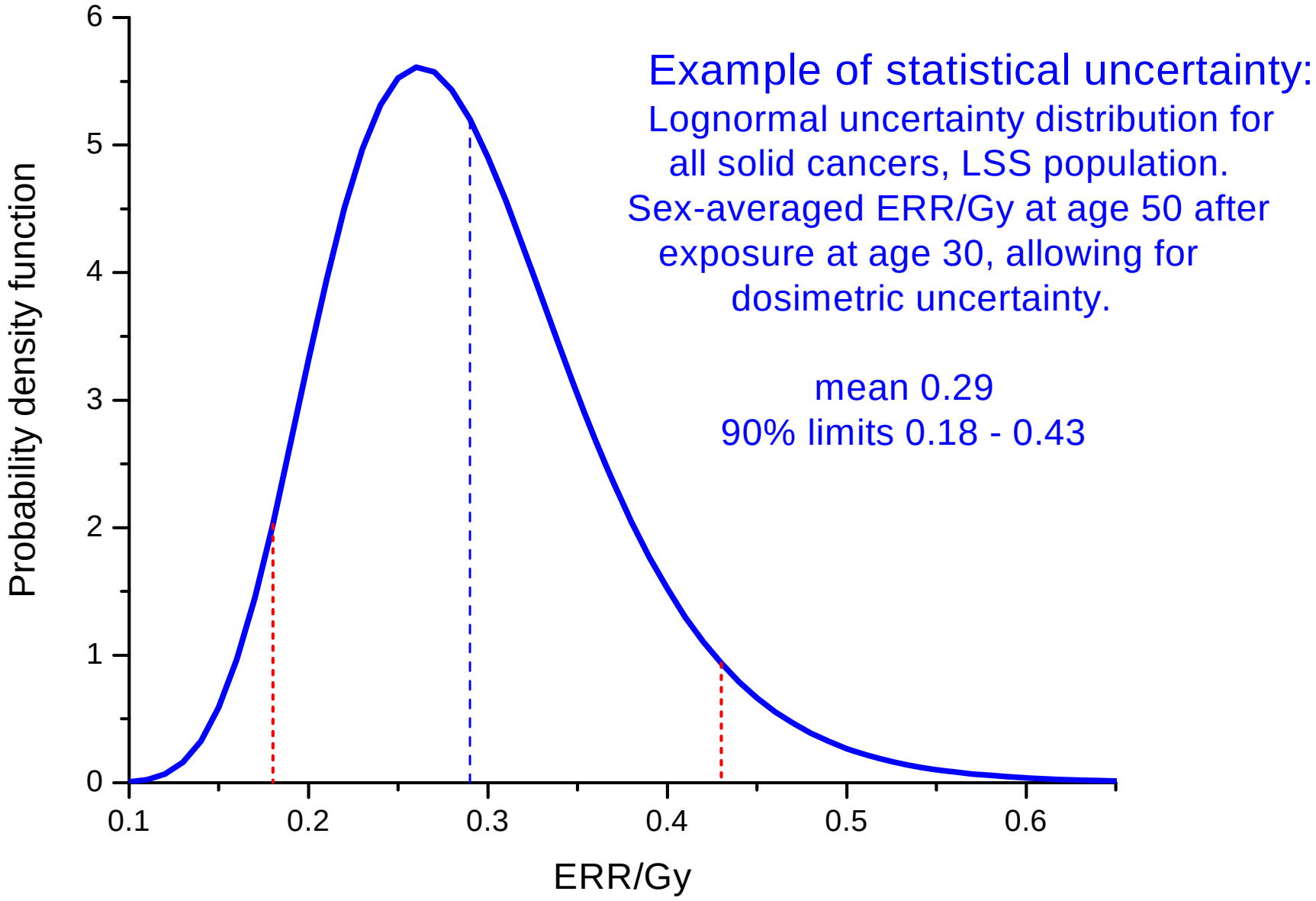
- In this example, we identify a crucial problem (transfer between populations)
- We don’t know which, if either, of the two (additive and multiplicative) approaches is correct
- But we believe that the truth is somewhere between them
- We formalize that assumption as subjective information about uncertainty
- And proceed from there

Stomach Cancer Example: Comparison of ERR Uncertainty Distributions for Different Japan-to-US Transfer Models

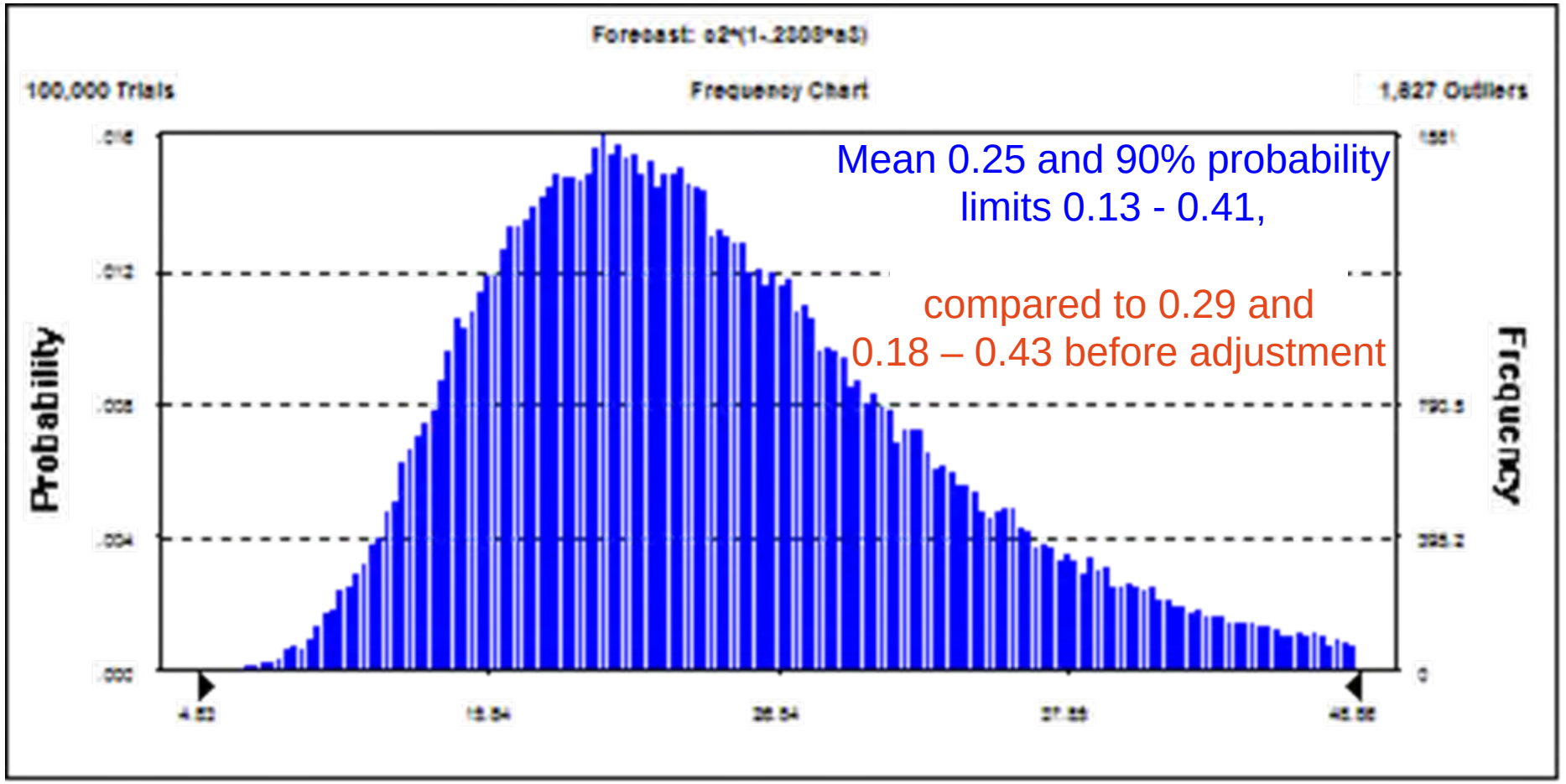


For all solid cancers combined

- Japanese baseline rates are a little lower than US rates
- The difference is far less than for stomach cancer, but it still requires adjustment
- Result is a widening of the uncertainty distribution and a small shift to the left
  - The mean ERR/Gy changes from 0.29 to 0.25,
  - 90% limits change from 0.18 – 0.43 to 0.13 – 0.41



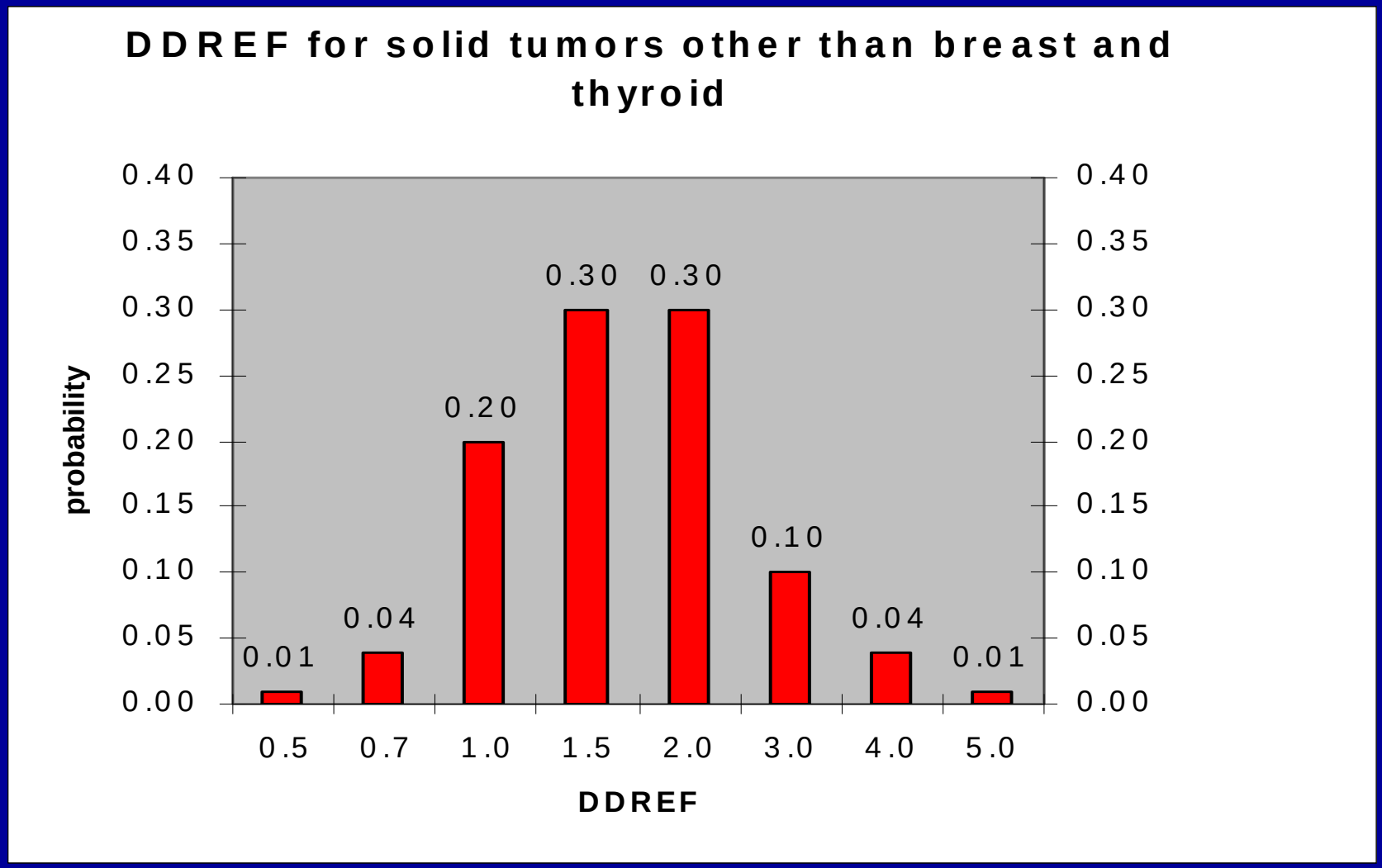
* Based on 1958-1987 LSS Tumor Registry Data, Thompson et al, Rad Res 1994

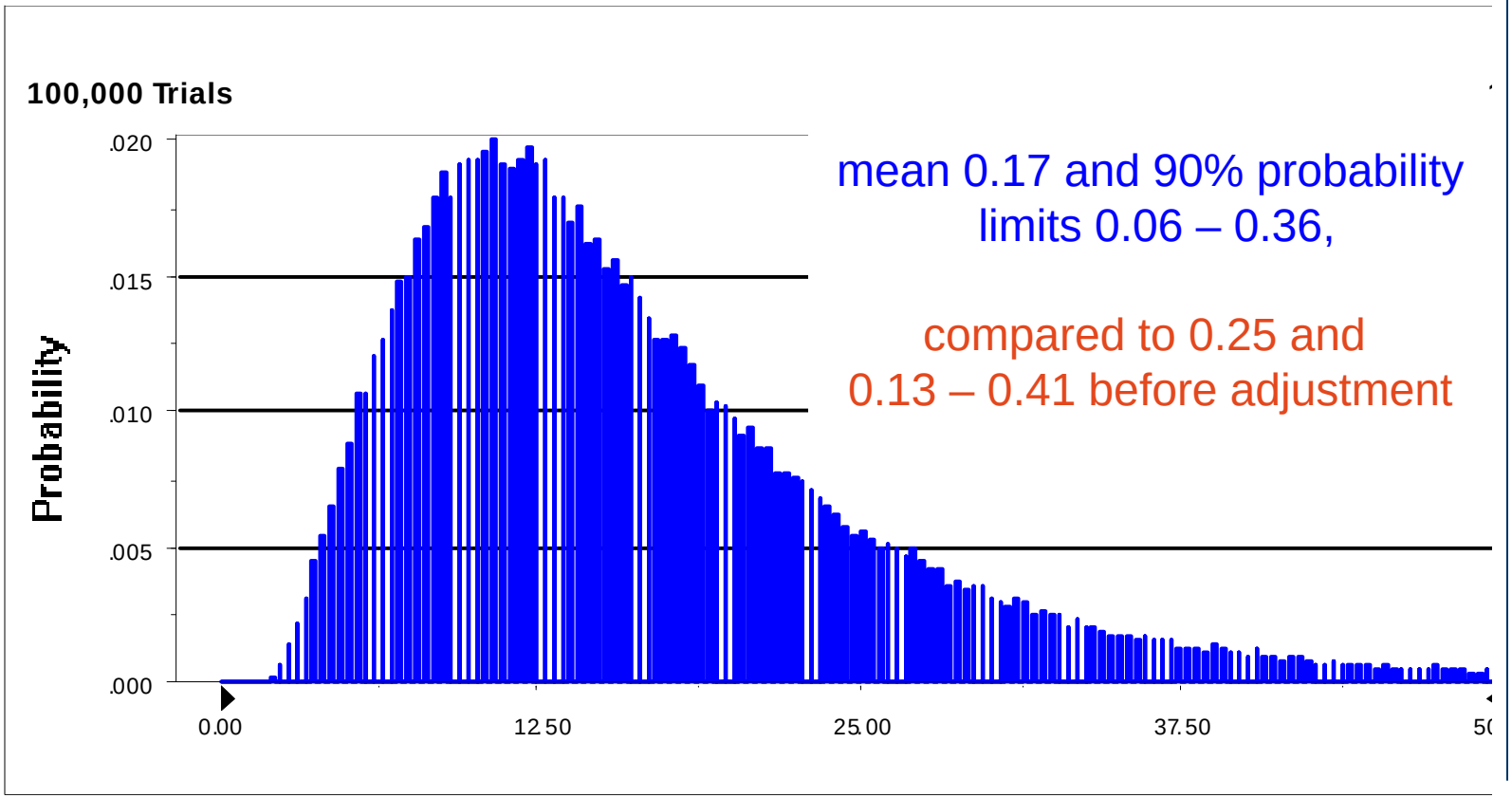


Monte Carlo simulation of the uncertainty distribution for all solid cancer: ERR at 1 Gy, after transfer to a U.S. population: the simulated distribution is approximately lognormal

Uncertain DDREF for low-dose extrapolation

(for example) this subjective uncertainty distribution:





Monte Carlo simulation of the uncertainty distribution for low-dose cancer ERR per Sv,

after division by an uncertain DDREF: the simulated distribution is roughly lognormal

.

Recap

- The “new paradigm” approach uses objective and subjective information about radiation-related cancer risk
- The approach is transparent
  - It highlights crucial uncertain factors
  - And requirements for more information, i.e., more research
- It also provides an interim basis for making decisions

Radiation Protection

- A political process, with stakeholders
  - Who may feel threatened by radiation exposure
  - Or who may value certain benefits that involve radiation exposure to themselves and/or others
  - Most of us belong to some extent to both groups
- Useful to address stakeholders' concerns from their particular viewpoints
  - What actual or potential benefit to you or others is associated with the exposure?
- What is the highest acceptable risk level?
  - With a benefit?
  - Without a benefit?

The new paradigm

- The methodology can provide:
  - The average value of risk
  - A highest plausible risk
  - A lowest plausible risk
- Allows comparison of these risks with other risks
  - That a stakeholder may tend to disregard
  - Or strenuously avoid
- And with a known or uncertain benefit

Linear, no-threshold theory

- Currently, radiation protection practice is based on the LNT theory
- The theory states that, at low doses, excess risk is proportional to dose
- It doesn’t require linearity of dose response over the entire dose range, just at low doses

Implications of the LNT theory: Collective dose

- If the estimated risk from 100 mGy to 10,000 people is 10 excess cancers, then (ignoring DDREF)
  - The estimated risk from 10 mGy to 10,000 people would be 1 excess cancer,
  - The risk from 10 mGy to 1,000,000 people would be 100 excess cancers
  - And the estimated risk from 1 mGy to 1,000,000 people would be 10 excess cancers

- We'd never be able to prove it by studying the million people (if the risk is indeed 10 per million)
- Nor would we be able to prove that the risk is much lower (if indeed it is)
- It might be helpful to show that we can be reasonably confident that the risk isn't as high as (say) 1 per 10,000 (industrial standard)

The low-dose threshold theory

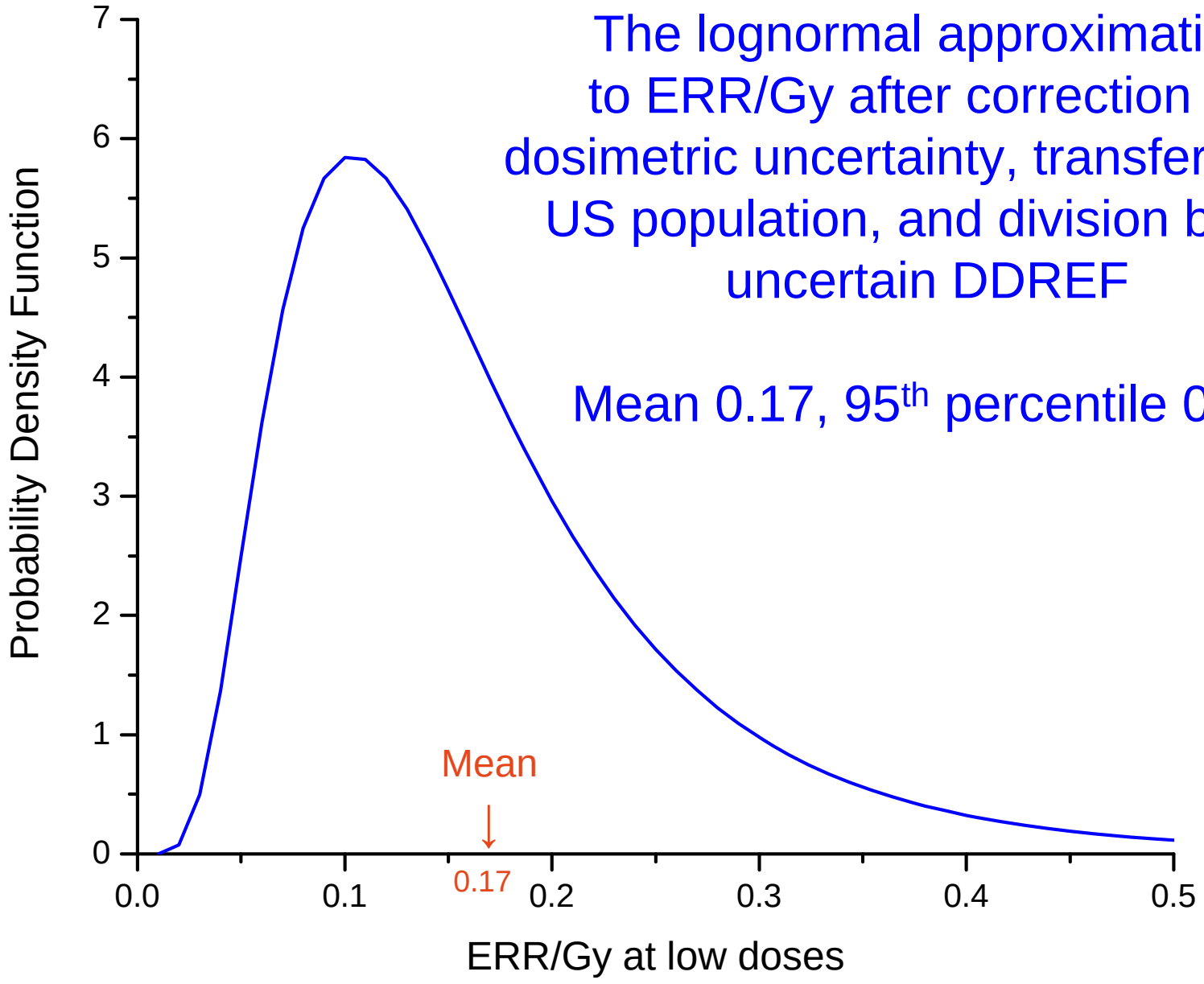
- **If we could agree that there is *no* radiation-related cancer risk associated with doses below (say) 2 mGy, the 1 million people exposed to 1 mGy could relax**
- **Radiation protection might be cheaper and easier than it is today**
- **But a low-dose threshold at (say) 2 mGy would be difficult to prove, for the same reasons that make it difficult to demonstrate the opposite**

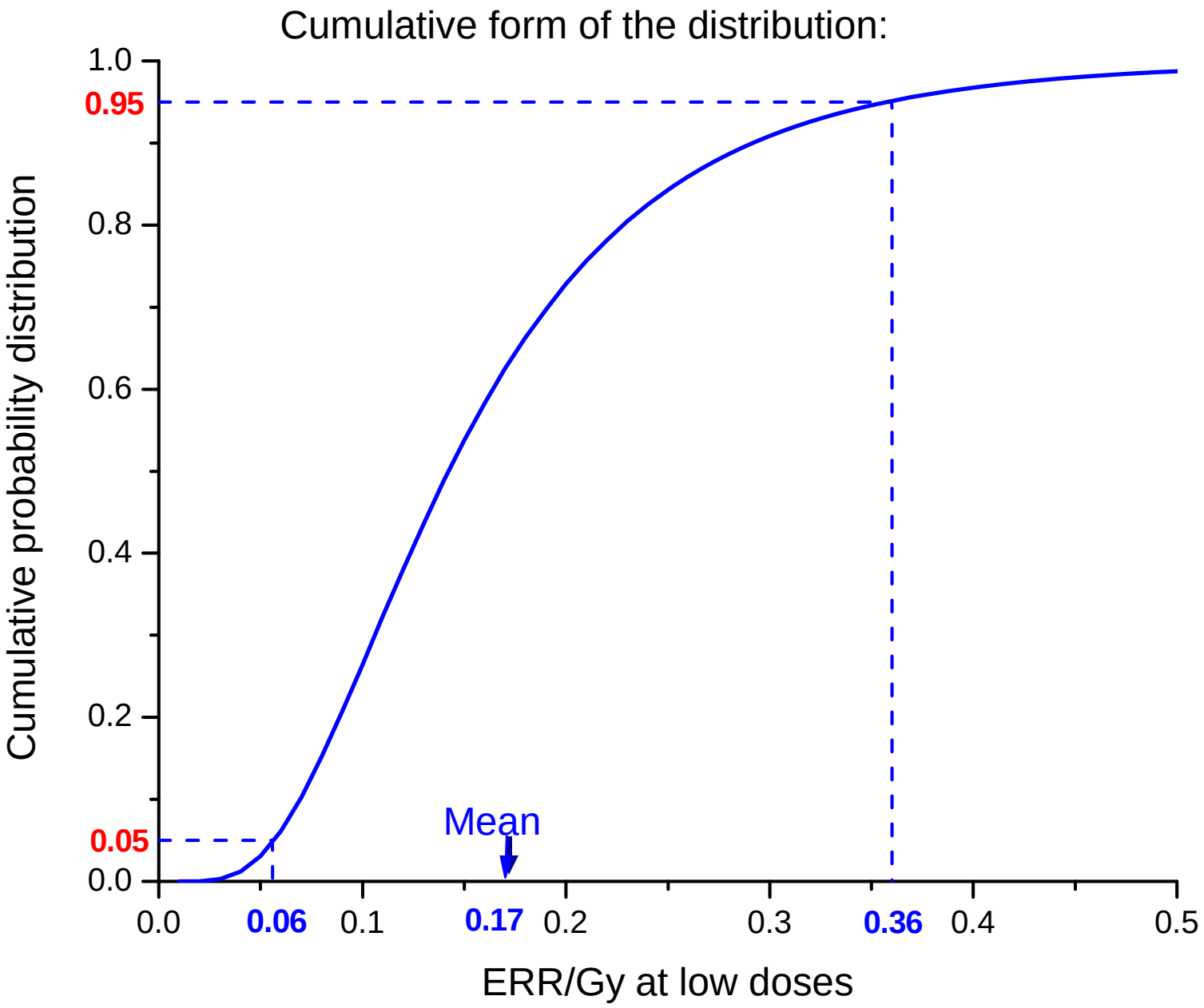
- **Experimental and epidemiological evidence doesn’t preclude tissue-specific thresholds**

- **But also, it doesn’t support existence of a universal threshold, operating in all or most tissues**

- **(Which is what would be needed to influence radiation protection policy)**

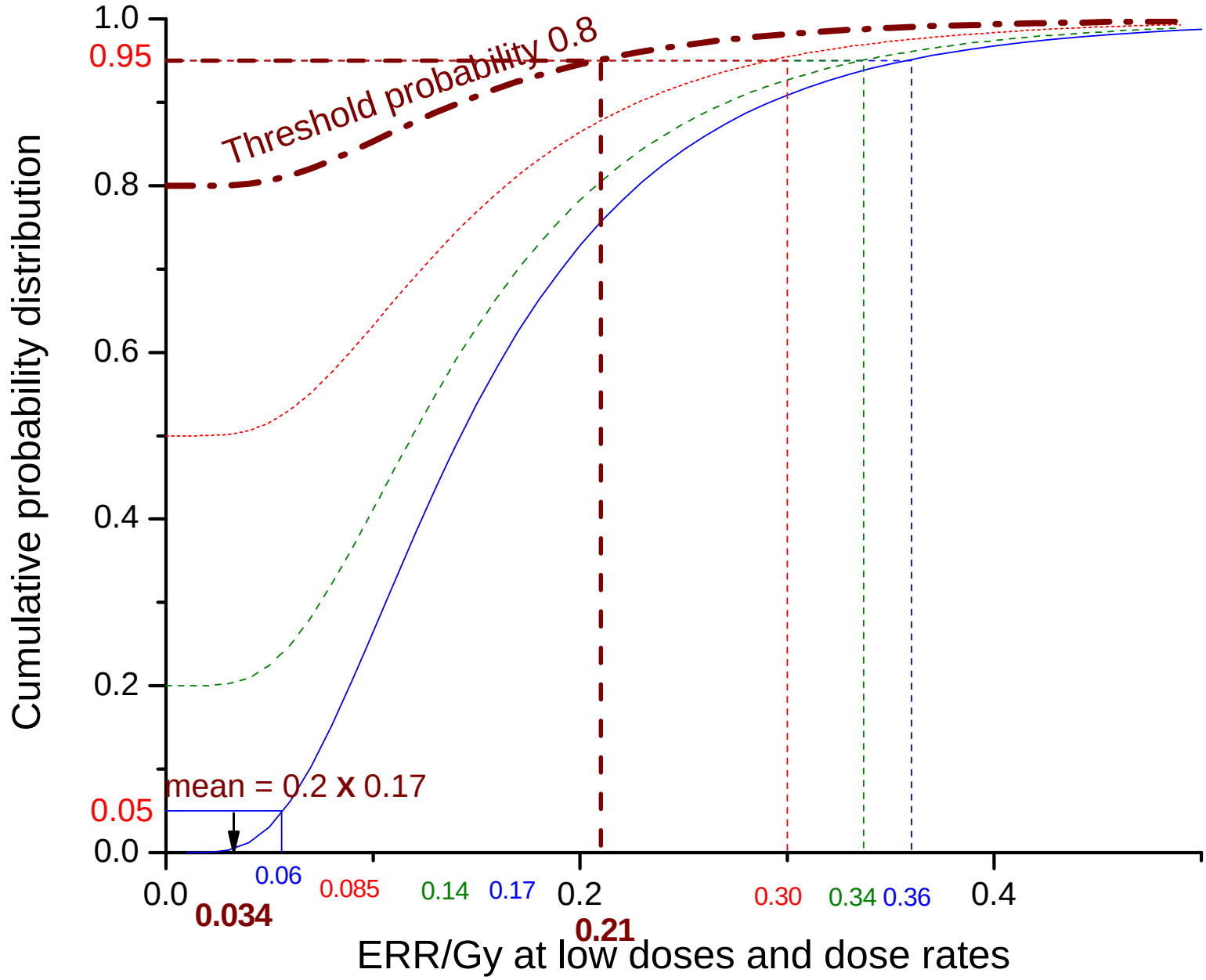
What would be the implications for radiation risk assessment of acknowledging some likelihood of a low-dose threshold?


The lognormal approximation to ERR/Gy after correction for dosimetric uncertainty, transfer to the US population, and division by an uncertain DDREF
Mean 0.17, 95th percentile 0.36
Probability Density Function
ERR/Gy at low doses
Mean
0.17
0
1
2
3
4
5
6
7
0.0
0.1
0.2
0.3
0.4
0.5

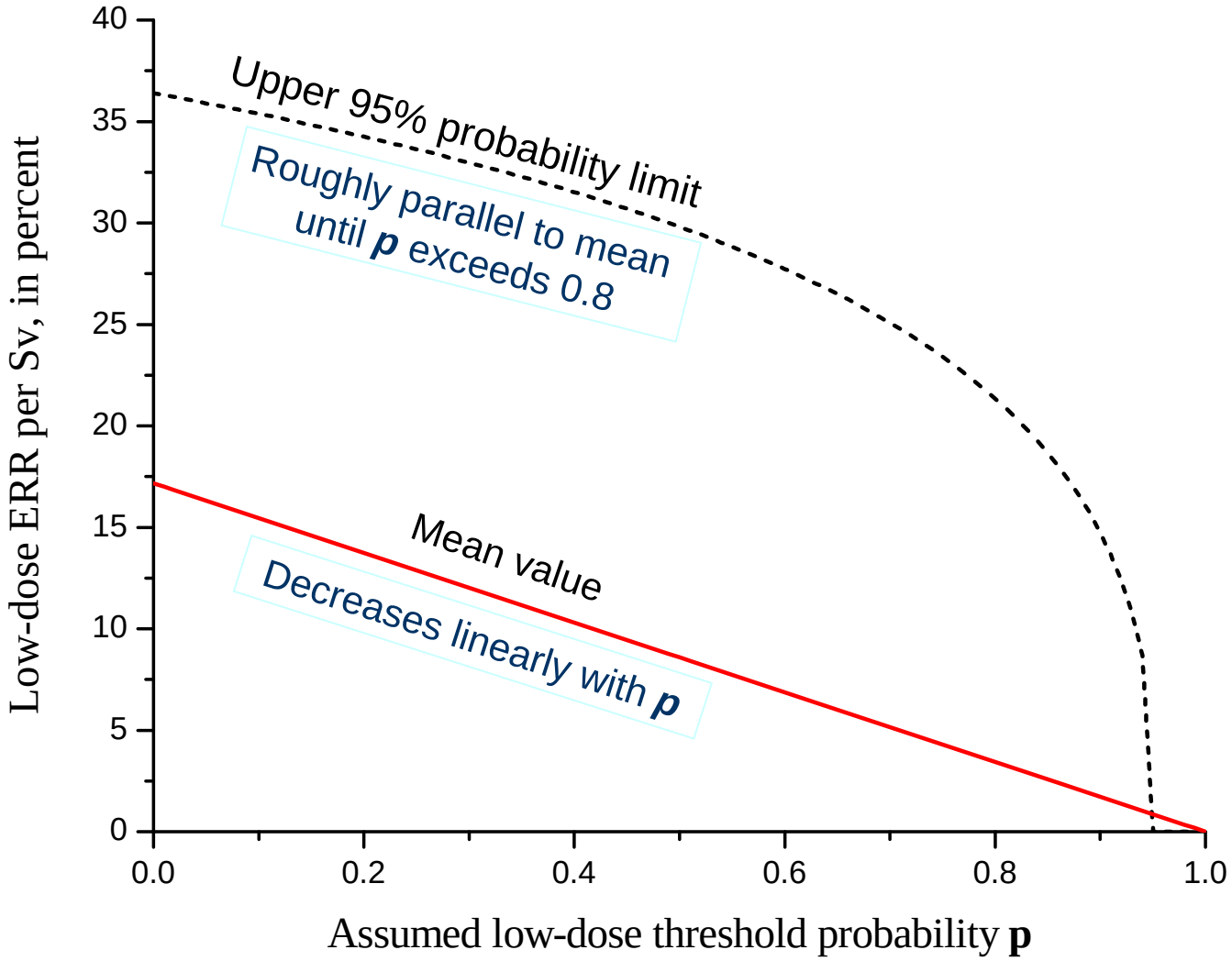

Cumulative form of the distribution:
Cumulative probability distribution
1.0
0.95
0.8
0.6
0.4
0.2
0.05
0.0
Mean
0.0
0.06
0.1
0.17
0.2
0.3
0.36
0.4
0.5
ERR/Gy at low doses

Suppose we allow for the uncertain possibility of a threshold

- At some dose greater than the one we're interested in now
- e. g., suppose that, for doses below the assumed threshold level
  - With 20% probability, there is ***no*** excess risk
  - And with 80% probability, the previous cumulative graph applies


Threshold probability 0.8
1.0
0.95
0.8
0.6
0.4
0.2
0.05
0.0
Cumulative probability distribution
mean = 0.2 x 0.17
0.0
0.034
0.06
0.085
0.14
0.17
0.2
0.21
0.30
0.34
0.36
0.4
ERR/Gy at low doses and dose rates

Effect of uncertain threshold assumption on a lognormal (mean 0.17, upper 95% limit 0.36) uncertainty distribution for ERR per Sv



Implications of an uncertain threshold for radiation protection

- For threshold probability ***p***
  - The effect on the mean of increasing ***p*** is like dividing ERR/Gy by a fixed DDREF value = 1/(1-*p*)
  - The 95% limit increases considerably, relative to the mean, until *p* exceeds 0.8
- The epidemiological and radiobiological information available does not suggest a high value for ***p*** at any threshold dose level high enough to matter.
- **Thus, allowing for the *possibility* of a threshold should make very little difference to radiation protection**

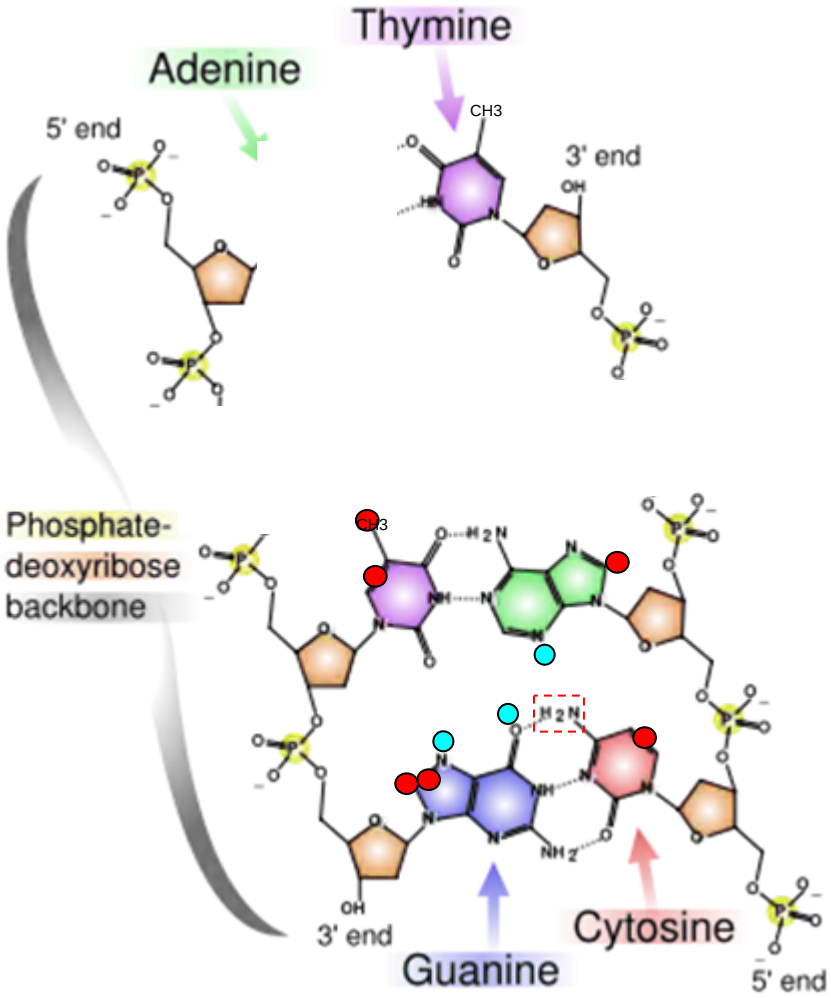
Conclusions

- Probably, most people would object to exposure
  - Unless the potential benefit clearly outweighs the potential risk
  - Or they judge that the risk is truly “negligible”
- Information, and upper probability limits on risk in particular, are important to this process
- If the scientific consensus were that a threshold is ***very*** likely, we should take that into account
- Otherwise, the threshold possibility is mostly a distraction and can be largely ignored in radiation risk protection

MRC | Genome Damage and Stability Centre

University of Sussex

The impact of low dose and dose rates: from the DNA damage response perspective



Endogenous DNA damage

>50,000 lesions per cell per day

20,000 single-strand breaks

10,000 depurination/depyrimidation

5,000 alkylating lesions

2,000 oxidative lesions

600 deamination events

10-20 double strand breaks

• Cells have evolved excellent **DAMAGE RESPONSE MECHANISMs** to prevent harmful effects of endogenous damage –

•**QUESTION**: can they prevent harmful effects of radiation induced lesions at low levels.

• Will focus on the response to **DSBs** because its most significant lesion induced by IR.

Damage response to

DNA double strand breaks

2 Strategies:

DSB

REPAIR

NHEJ/HR

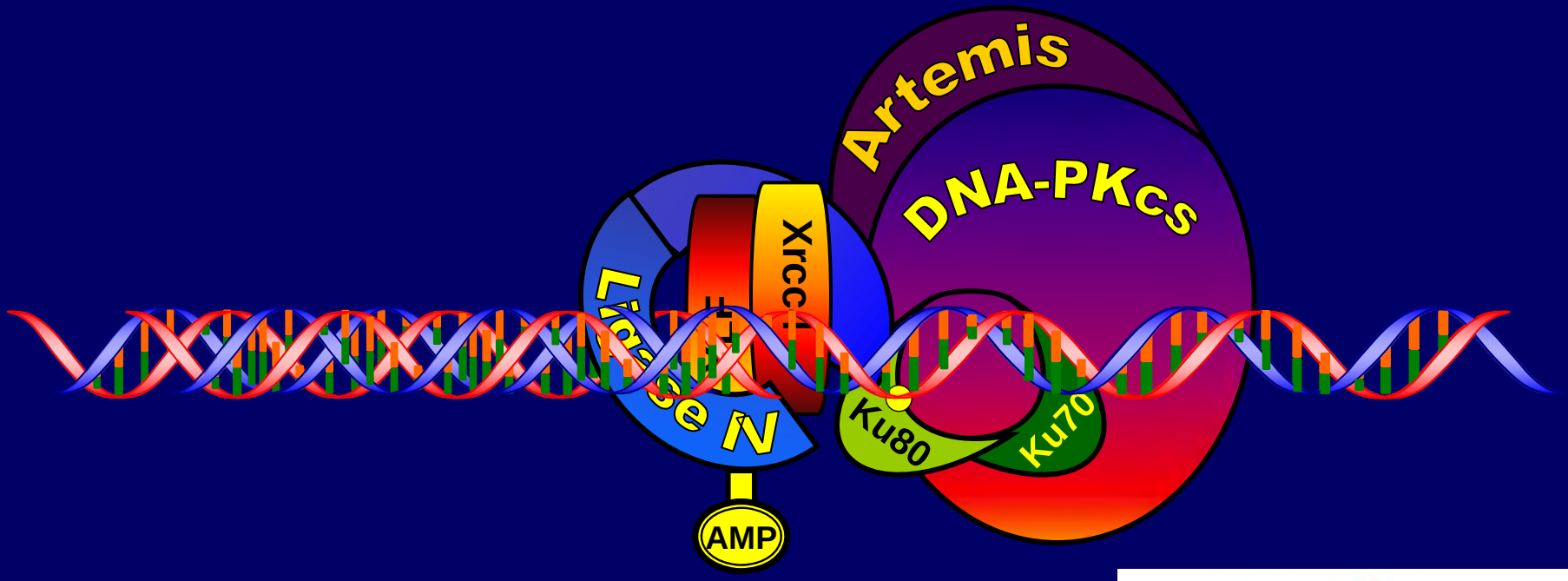
SIGNAL TRANSDUCTION

ATM

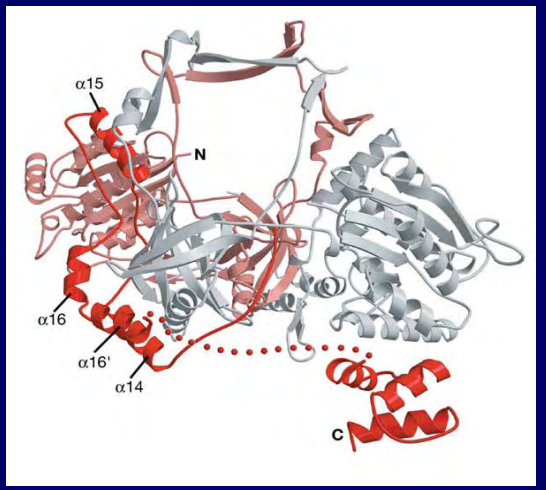
cell cycle checkpoint arrest

apoptosis

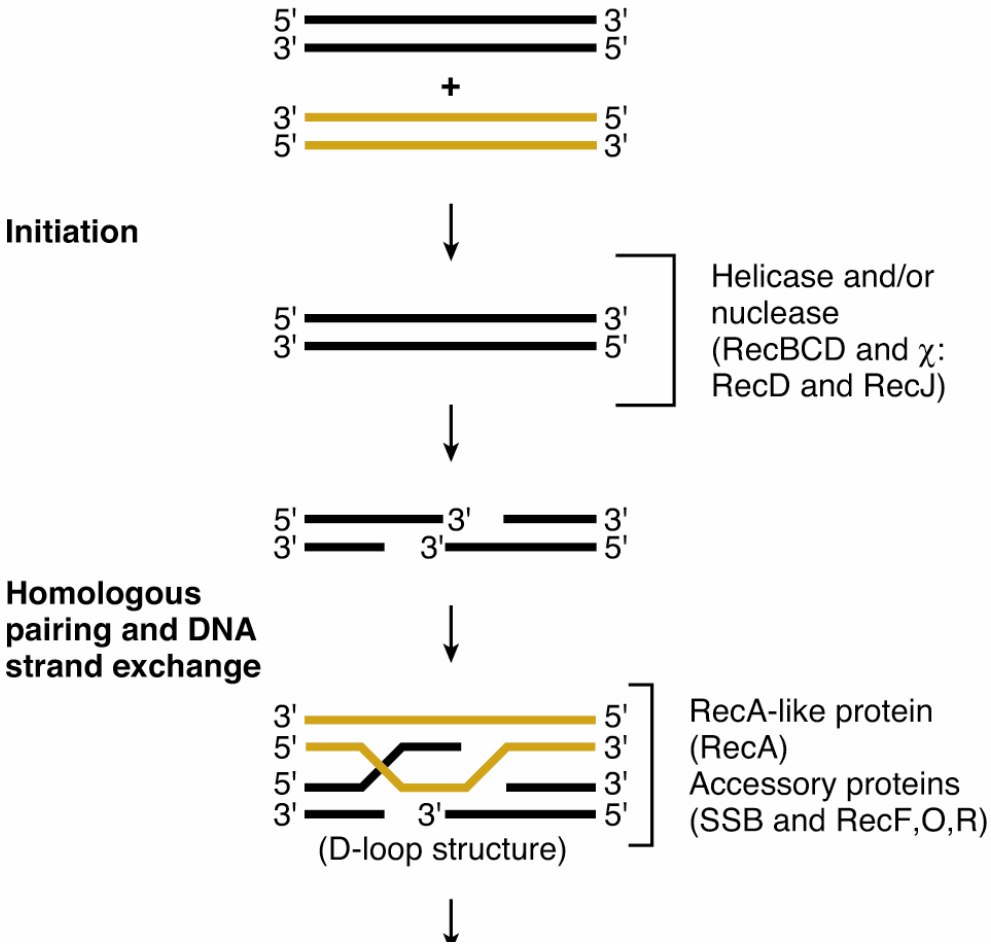
Non-Homologous End-Joining



1. DSB protection
2. DSB remodelling
3. DSB processing
4. DSB ligation
5. DSB resealed



Homologous Recombination is another DSB repair process. This processes uses an undamaged template to restore information lost at the DSB site



- In mammalian cells, although there are two copies of every chromosome (homologues), HR does not function in G1 using the homologous chromosome.

- Instead HR functions following replication (in late S/G2 phase) using the replicated sister (sister chromatid) for information

Role of HR in the repair of IR induced DSBs.

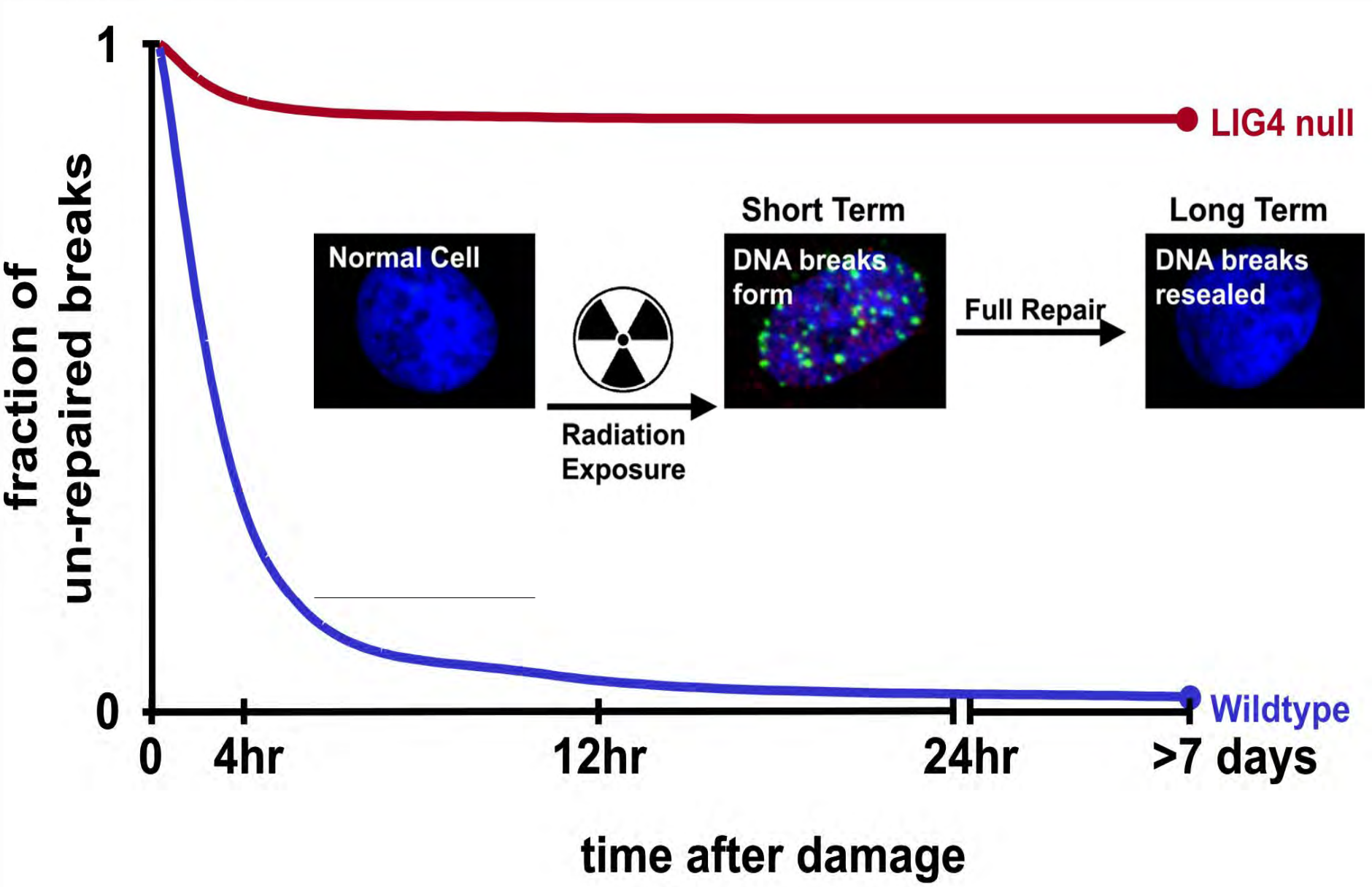
- HR only functions in late S/G2 phase.
- Even in G2 phase only contributes to the repair of 10-20 % of the DSBs
- In S phase, main function is to repair collapsed/stalled replication forks
- NHEJ repairs most non-replication DSBs even in S phase.

Hence, although HR has the capacity to accurately repair complex DSBs, there is little evidence that is represents a major DSB repair pathway.

What is the probability of repairing a radiation induced DSB accurately.

- Currently unknown.
- If sequence information is lost, then it is unlikely to be reconstituted accurately by NHEJ.
- how frequently is coding information lost – likely frequent for DSBs induced by high LET radiation
- Dose may influence the fidelity of DSB repair – by allowing wrong ends to be rejoined.
- Can HR compete with NHEJ for repair of complex DSBs (NO??).

DSB REPAIR MAY BE MONITORED BY H2AX QUANTITATION

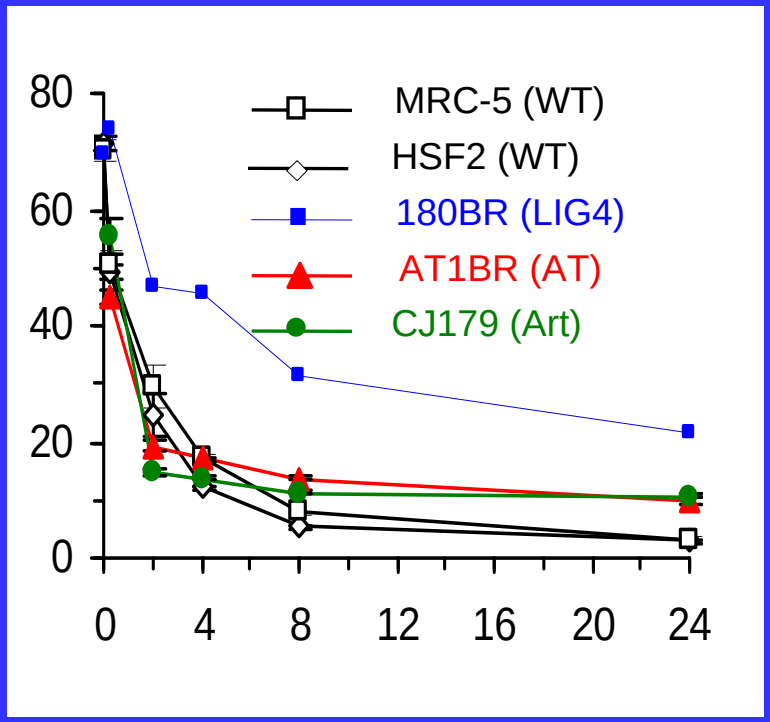


Does the complexity of the end influences the repair

Alpha particle irradiation generates MORE complex breaks

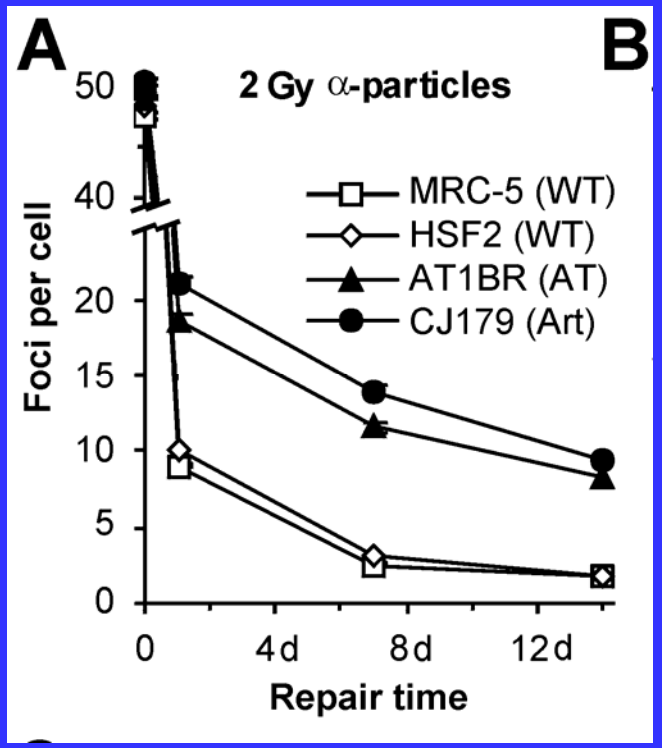
And the DSBs are repaired more slowly

γ-H2AX analysis after 2 Gy X-rays



NHEJ mutants are dramatically sensitive to X-rays

2 Gy α- particles



NHEJ mutants show same sensitivity as wild type cells to alpha particle irradiation

1. Hence alpha particle DSBs must be repaired with low fidelity since their rejoining does not enhance survival.

2. Thus, its likely that low LET radiation will also be inaccurately repaired although maybe less frequently.

3. Inaccurate repair is likely to lead to survival with rearrangements/deletions on some occasions.

Hence available evidence suggests that low LET radiation DSBs will be carcinogenic even at low frequency

DNA Damage response

2 Strategies:

DSB

REPAIR

NHEJ/HR

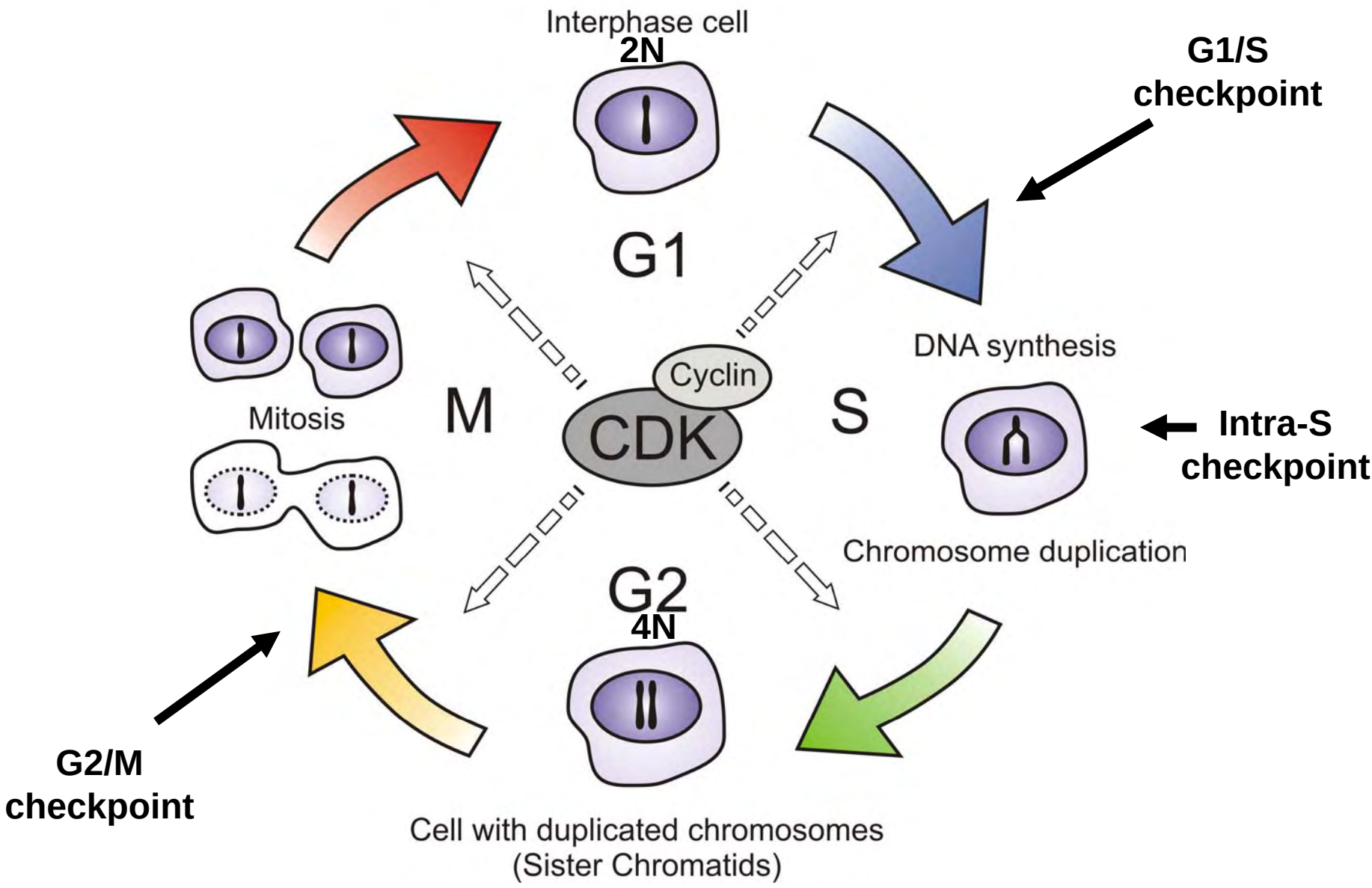
SIGNAL TRANSDUCTION

ATM

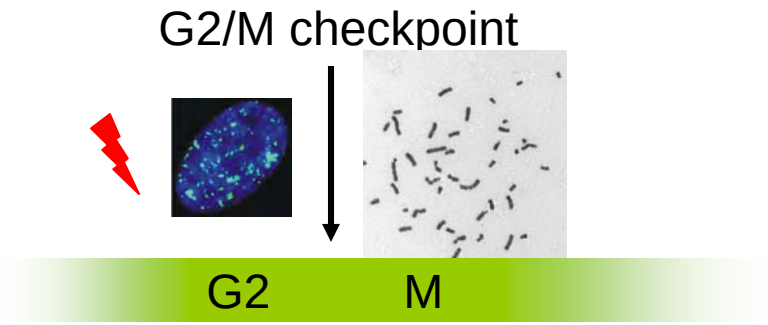
cell cycle checkpoint arrest

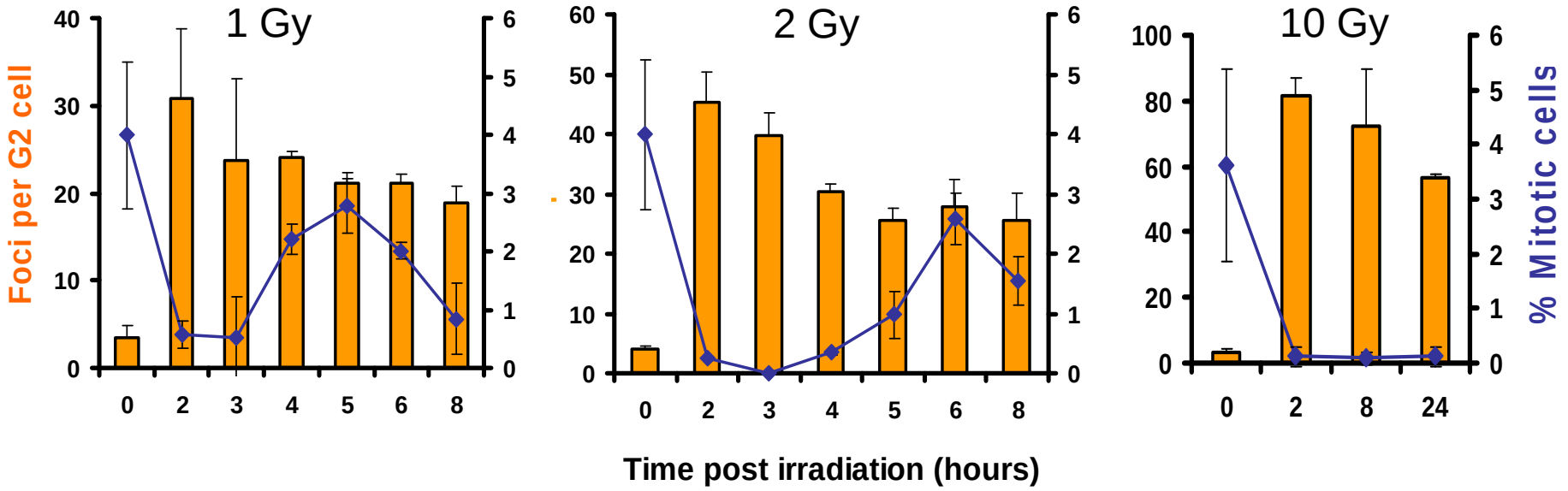
apoptosis

The Cell Cycle



Cells commence entry into mitosis even though ~ 10-20 foci remain





At each dose, entry into mitosis occurs when there are ~20 foci.

Artemis cells delay longer but still enter when 10-20 foci remain

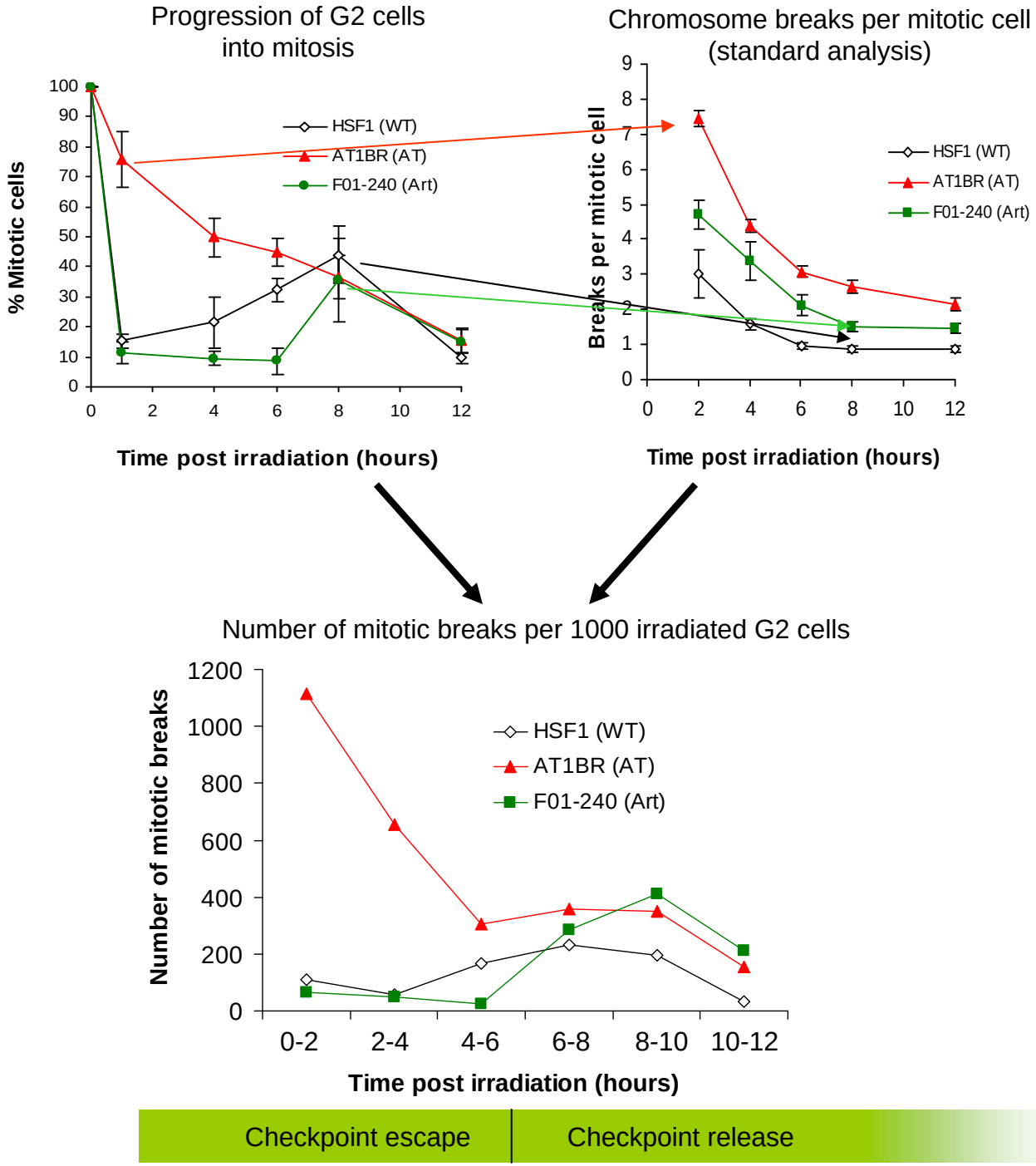
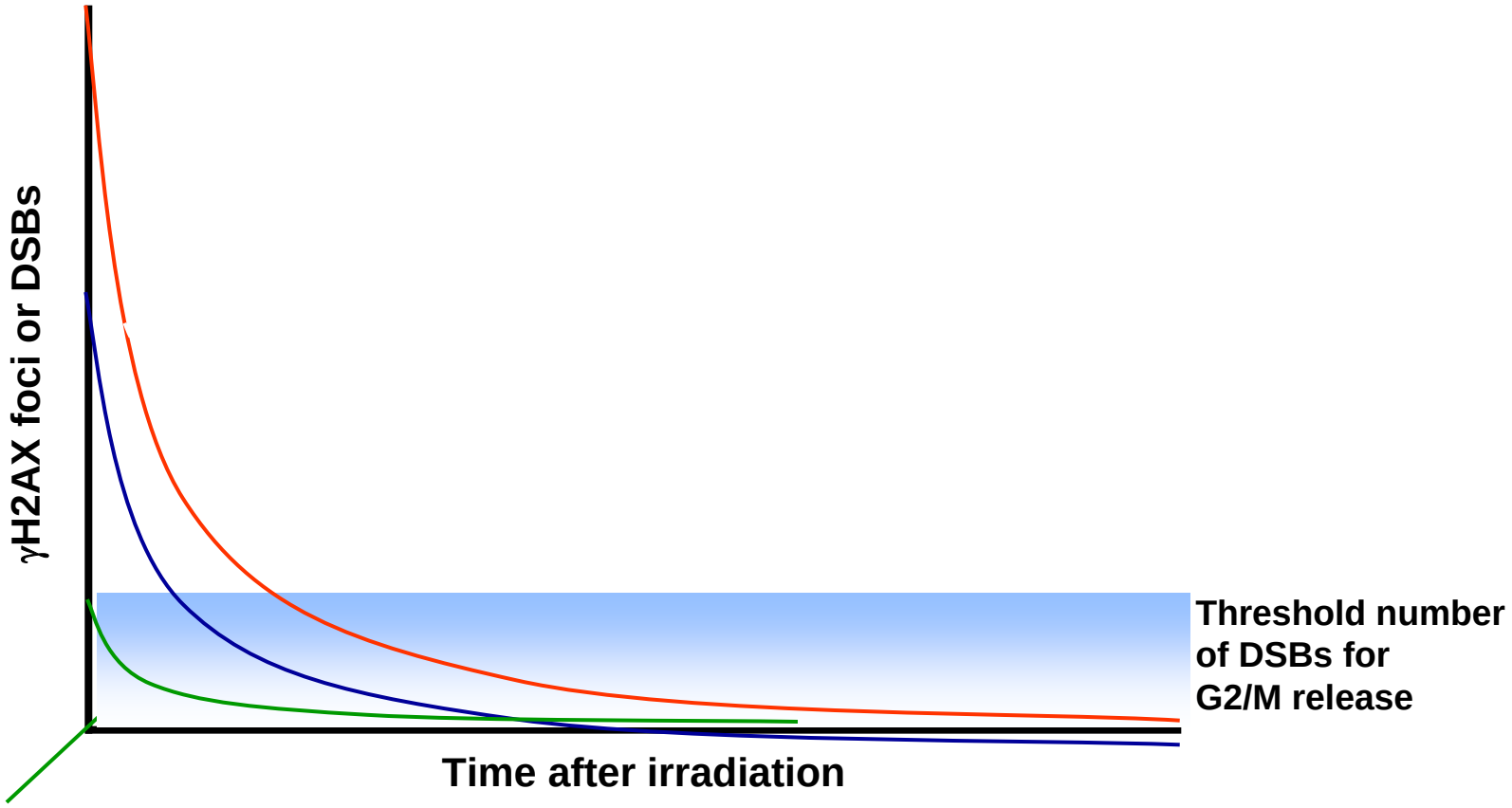

Progression of G2 cells into mitosis
% Mitotic cells
HSF1 (WT)
AT1BR (AT)
F01-240 (Art)
Time post irradiation (hours)
Chromosome breaks per mitotic cell (standard analysis)
Breaks per mitotic cell
HSF1 (WT)
AT1BR (AT)
F01-240 (Art)
Time post irradiation (hours)
Number of mitotic breaks per 1000 irradiated G2 cells
Number of mitotic breaks
HSF1 (WT)
AT1BR (AT)
F01-240 (Art)
0-2
2-4
4-6
6-8
8-10
10-12
Time post irradiation (hours)
Checkpoint escape
Checkpoint release

Figure 6

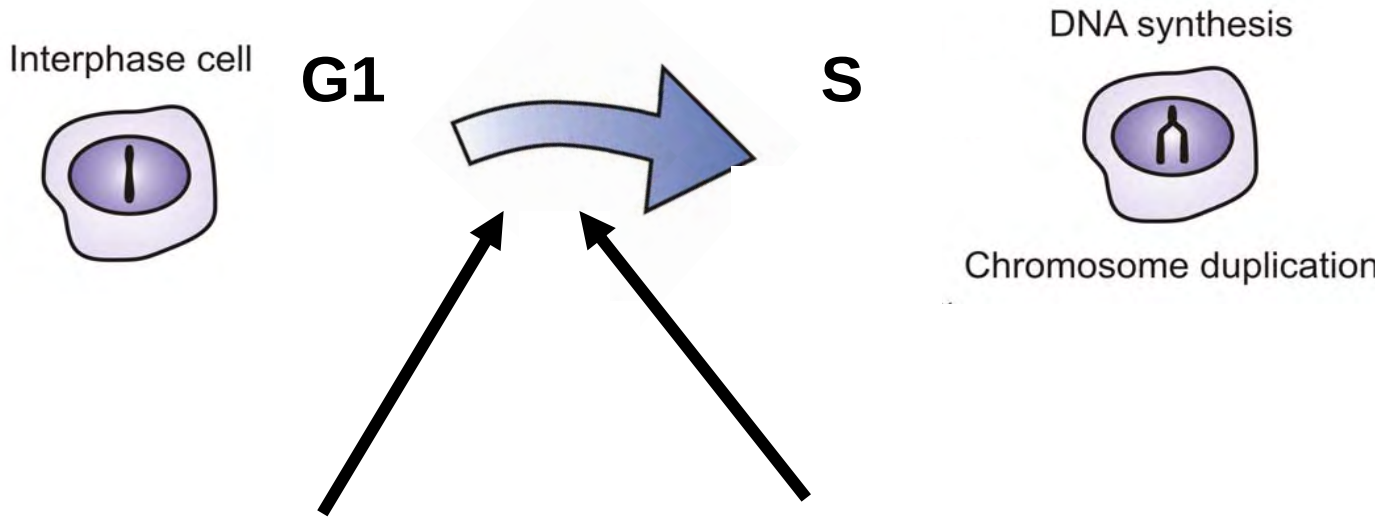


Duration of checkpoint arrest is DOSE not TIME dependent; longer delay in repair defective cells – therefore checkpoint machinery monitors the magnitude of DSB repair.

G2/M checkpoint is not sensitive to a single DSB – probably 10-20 DSBs

- Chromosome aberrations form in the cells RELEASED from checkpoint arrest.
- At low doses Checkpoint arrest is not initiated
- likely underlies low dose hypersensitivity.
- If cells progress through G2/M checkpoint and through mitosis then may loose acentric fragments and decrease possibility of accurate repair
- Therefore not only hypersensitivity but maybe low dose impact on accurate repair

What is the sensitivity of the G1/S checkpoint



G1/S checkpoint similar to G2/M checkpoint – likely insensitive

P53 dependent G1/S checkpoint – more sensitive but depends on transcirption therefore slow to activate

BUT: Artemis defective cells (defective in repairing some DSBs) irradiated in G1 have chromosome breaks in mitosis – therefore they can traverse G1/S and G2/M checkpoints

Apoptosis: another pathway to prevent proliferation of damage cells – what is the sensitivity?

STEM CELLS

- What processes function in Stem cells.
- NHEJ can function and is major DSB repair pathway
- Some stem cells have a low threshold for apoptosis – eg HSCs, embryonic neuronal cells, crypt stem cells – all are highly radiosensitive tissues.
- If stem cells die after IR, then progenitors dedifferentiate – how sensitive are they?
- How sensitive are checkpoints in stem cells

CONCLUSIONS.

- IR induces DSBs that are more complex than endogenous DSBs and more difficult to repair.
- NHEJ represents the major DSB repair process
- NHEJ can rejoin complex IR-induced DSBs - but unlikely to maintain fidelity all the time
- BUT – level of accuracy not known.
- What is the interplay between HR and NHEJ??
- G2/M checkpoint is insensitive
- G1/S checkpoint is more sensitive but unclear if a single DSB can cause cell cycle arrest
- Critical issue for cancer induction is HOW SENSITIVE ARE THESE PROCESSES IN STEM CELLS AND EARLY PROGENITORS.

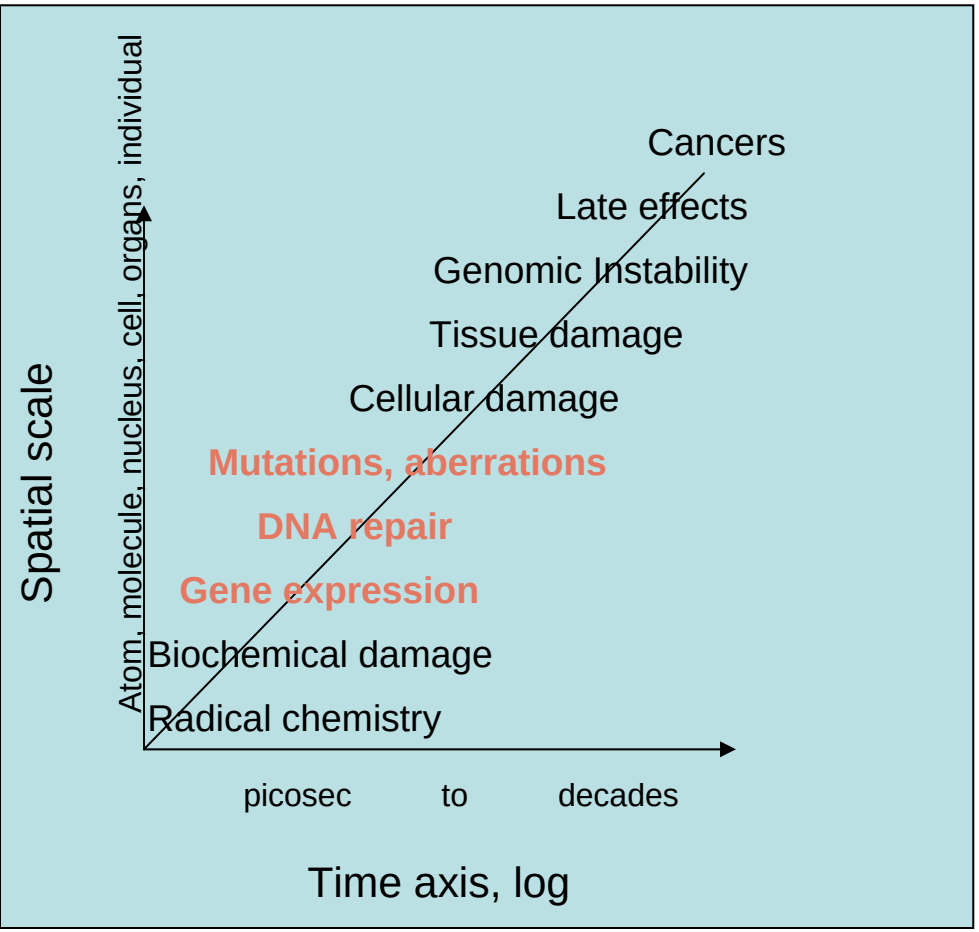
Low-Dose Gene Expression Phenotyping

Molecular Pathways for Radioprotection Against DNA Damage and Chromosomal Abnormalities in Tissues

NCRP Annual Meeting, April 14, 2008

Andrew J. Wyrobek
Department of Radiation Biosciences
Life Sciences Division
Lawrence Berkeley National Laboratory

Molecular targets of low-dose radiation damage and the search for low-dose non-linearities



- Critical molecular targets
- **Predictive signaling pathways**
- **Low-dose non-linearity in responses cancer target cells and cells of the microenvironment**
- Molecular modifiers of radio-resistance and sensitivity
- Integrated disease-risk model

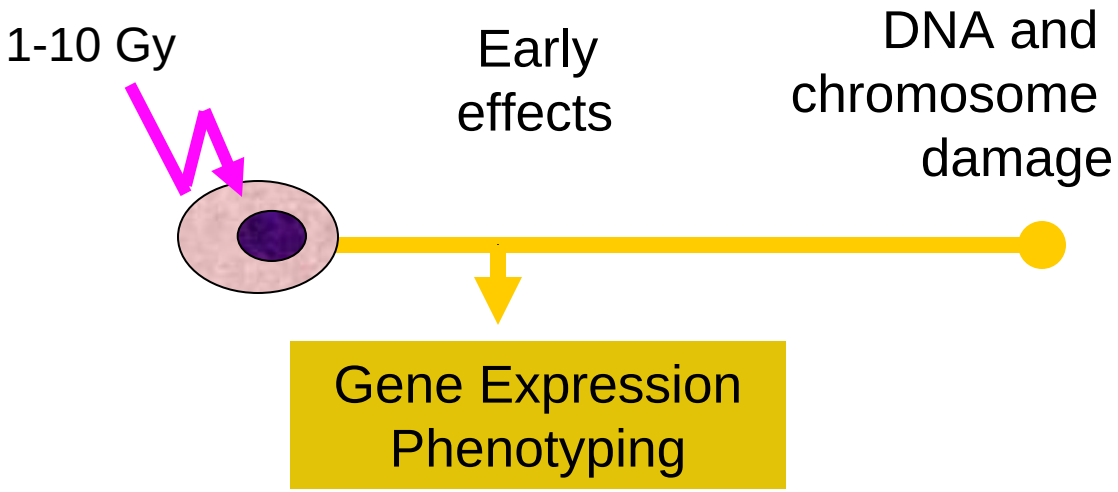
Are there CONSERVED low-dose response pathways?
Are there TISSUE-SPECIFIC response pathways?
Are there ADAPTIVE-RESPONSE pathways that might be controllable?

Range of sensitivity for radiation-induced cell killing

Insensitive

Mature Red Blood Corpuscles
Liver Cells
Neural Cells
Pituitary Cells
Thyroid Cells
Muscle Cells
Bone and Cartilage Cells
Epithelium
Cornea
Renal Tubules
Lung-Tissue Cells
Lens
Gonadal Germ Cells
Small intestine epithelium
Bone-Marrow Cells
Lymphocytes

Sensitive



Human In Vitro
- Lymphoblastoid cells
- Keratinocytes
- Umbilical Vein Endothelial cells

Mouse in vivo
- Brain tissue
- Comparative Tissue Study

Outline

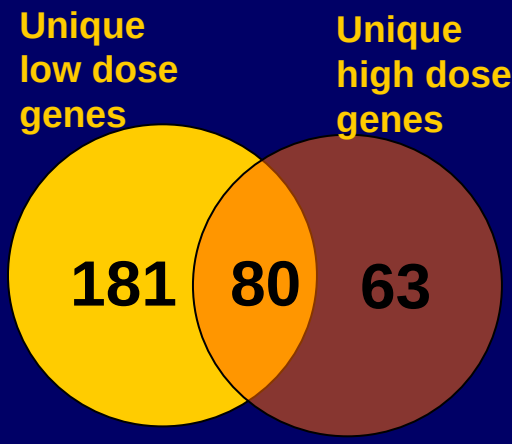
Low-dose “gene expression phenotyping”

- robust responses across human cell types
- tissue variation in responses in mice

Adaptive response networks and pathways

- human cells in vitro
- mouse model - tissue variation in adaptive responses for chromosomal damage and cancers

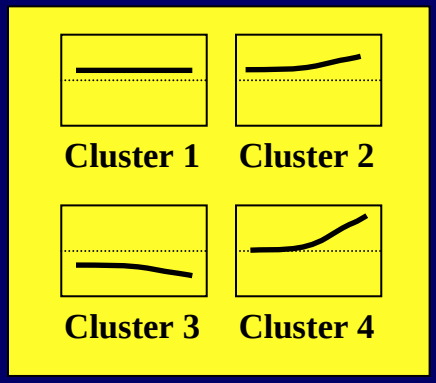
Low-dose expression profiles differ from high-dose profiles in at least four ways



Low dose genes have unique biological functions, networks, and pathways

- **dose response analyses**
- **robust responses among transcript data sets**

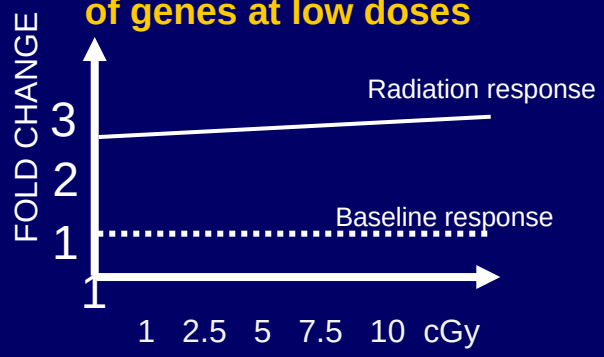
Differing shapes of the dose response curves



Doses 1-400cGy

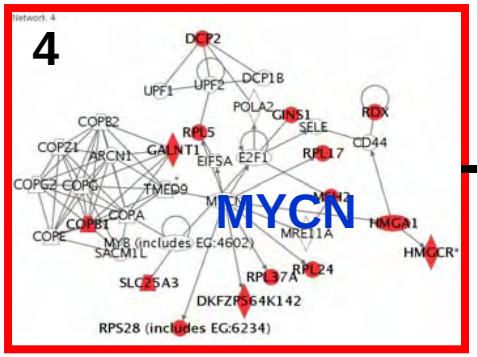
Transcript induction at doses <1cGy

"Plateau-like" responses of genes at low doses



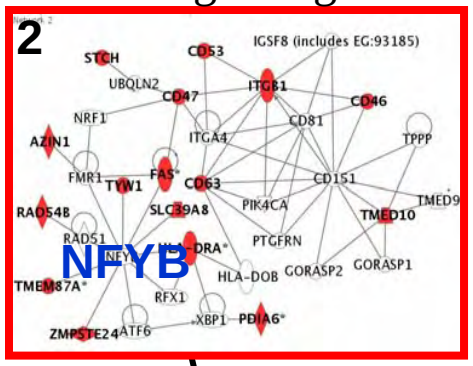
Example for human Lymphoblastoid cells

The low-dose response networks represent diverse biological functions



TMED9

Cell-Cell Signaling Interaction

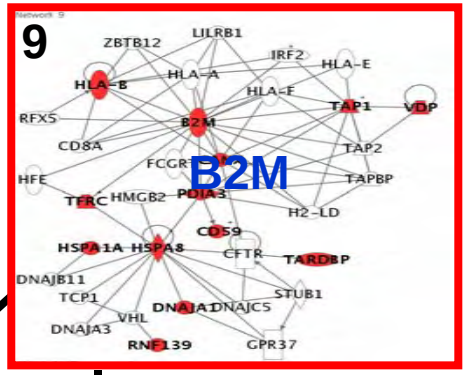


HSP8

TAP1

IRF2

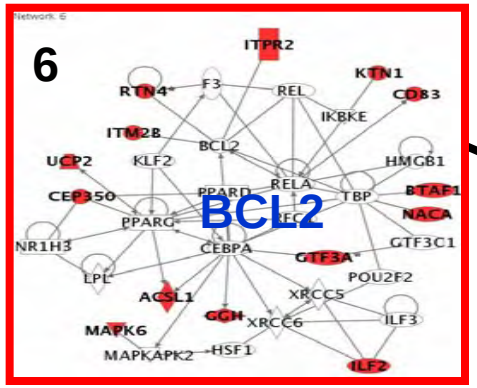
Heat Shock/Oxidative stress



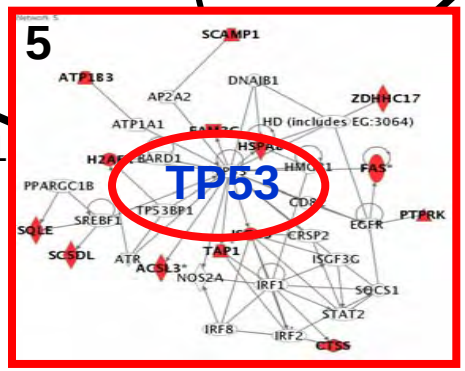
FAS2

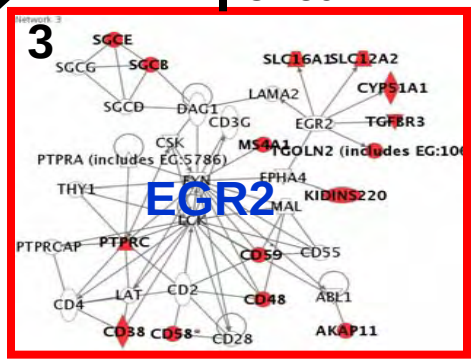
CD59

TFRC



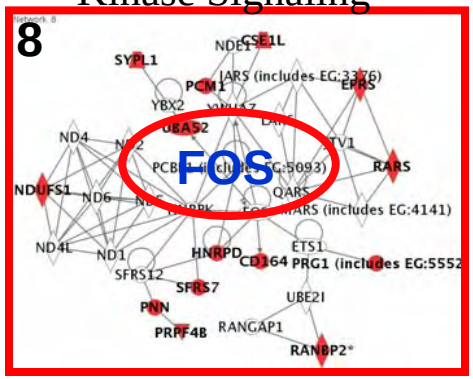
HMGB1

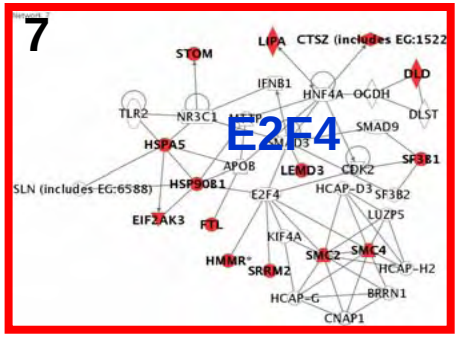


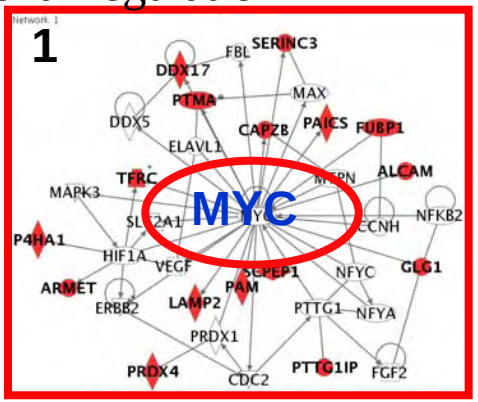


Cell Cycle Regulation
Kinase Signaling

Transcriptional regulation





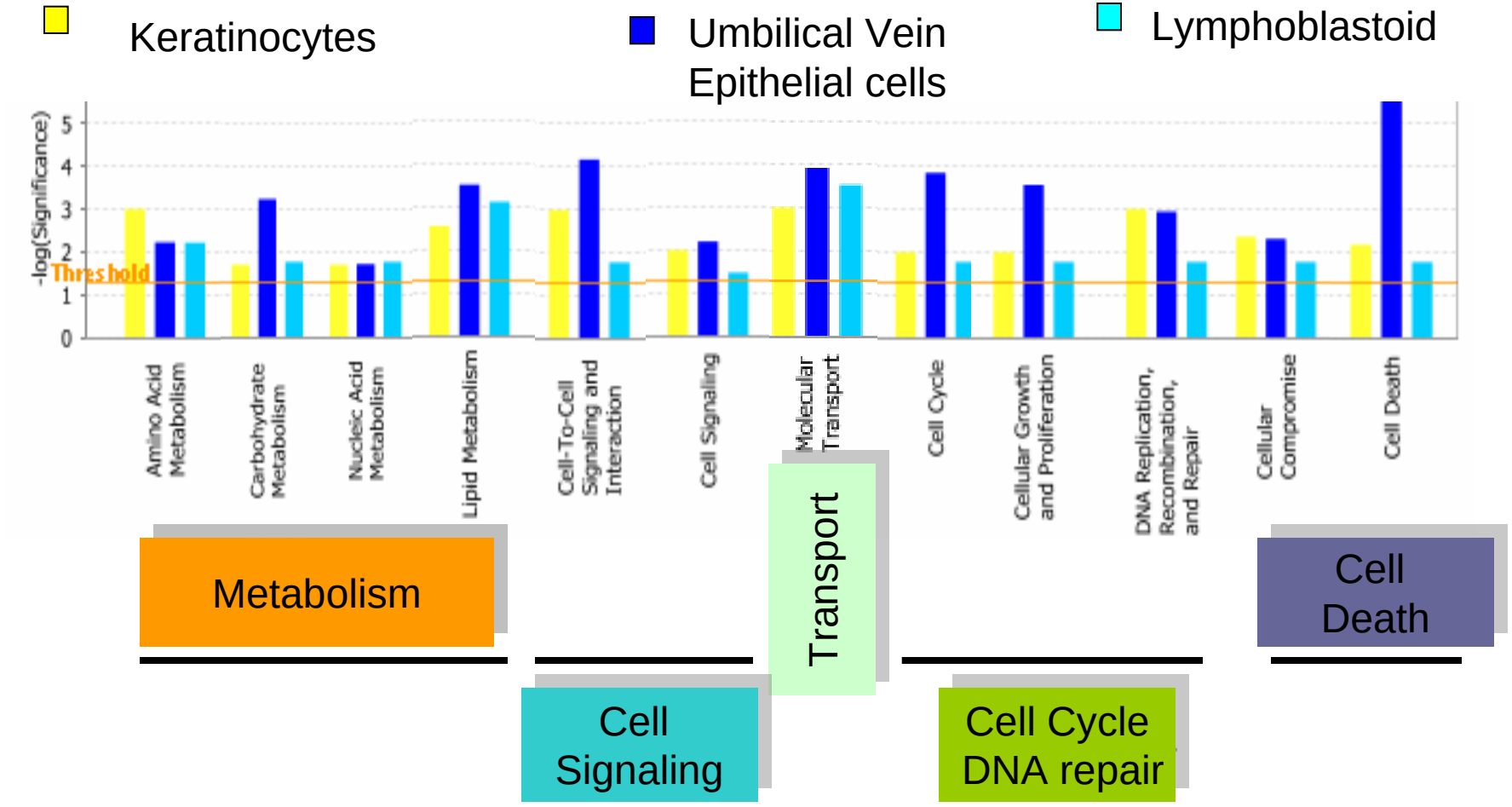


Fatty acid metabolism

Translational regulation

Cell to Cell Signaling

Example gene functions that were consistently modulated in 3 human tissues after low-dose exposures



Ingenuity functional category

Human lymphoblastoid cell model:

Gene Ontology (GO) analyses suggest that low-dose responses are different from high dose responses

Biological Process	Unique High	Unique Low
apoptosis	0.0039	
cell death	0.0052	
death	0.0054	
DNA repair	0.0086	
programmed cell death	0.0040	
protein folding	0.0065	
response to stress	0.0003	0.0005
chromosome condensation		0.0065
protein biosynthesis		0.0060
proteasomal ubiquitin-dependent protein catabolism		0.0097
signal peptide processing(Peptide Metabolism)		0.0011

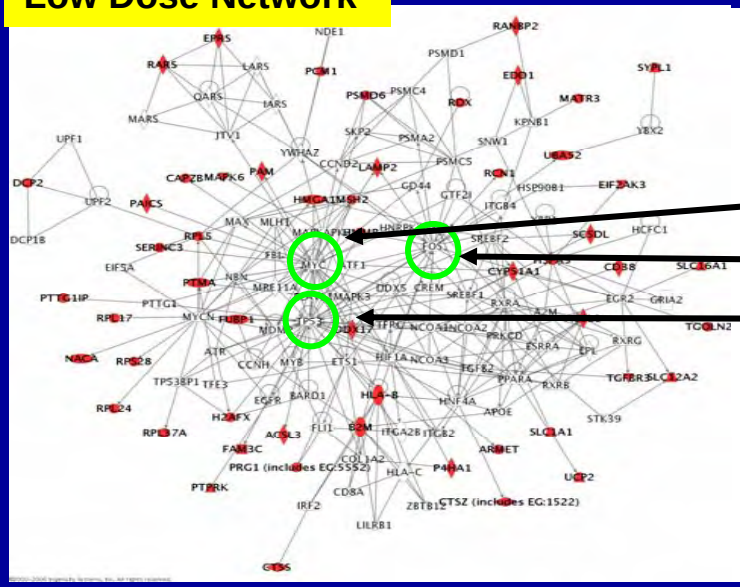
Conserved networks among low- and high-dose "gene expression phenotypes" in three different human cell types

	LOW DOSE			HIGH DOSE	
	HUMAN			HUMAN	
Network*	Lympho-blastoid cell lines	Umblical vein endothelial cells	Keratinocytes	Lympho blastoid cell lines	Umbilical vein endothelial cells
TP53	X	X	X	X	X
MYC	X	X	X	X	X
FOS	X	X	X		
SRC	X		X		
RELA				X	X

*Networks are defined by their primary node

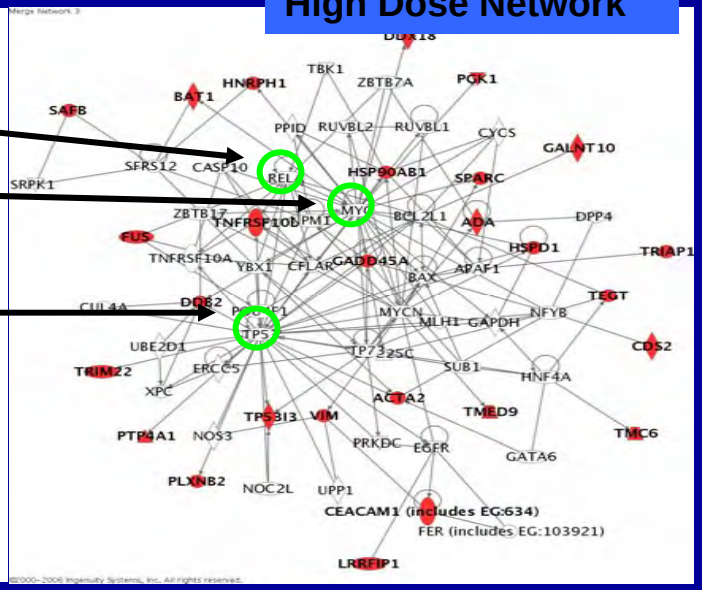
Low- and high-dose networks contain TP53 and MYC nodes, but induce different signaling pathways

Low Dose Network

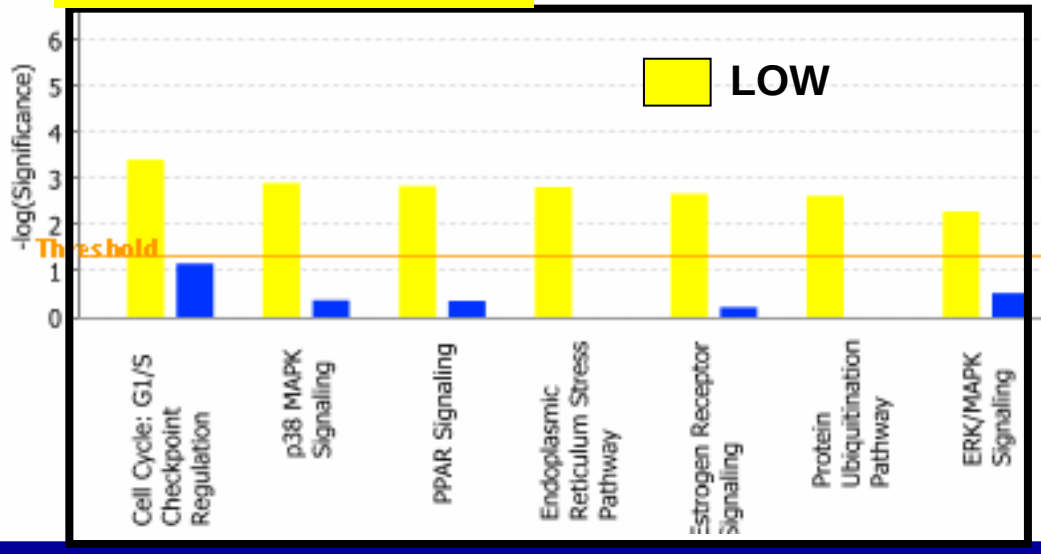


RELA
MYC
FOS
TP53

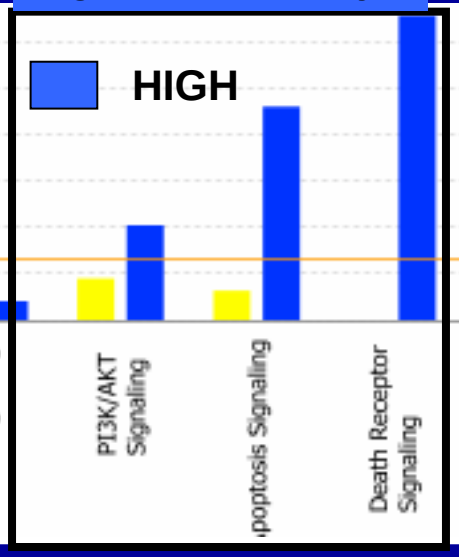
High Dose Network



Low Dose Pathways



High Dose Pathways

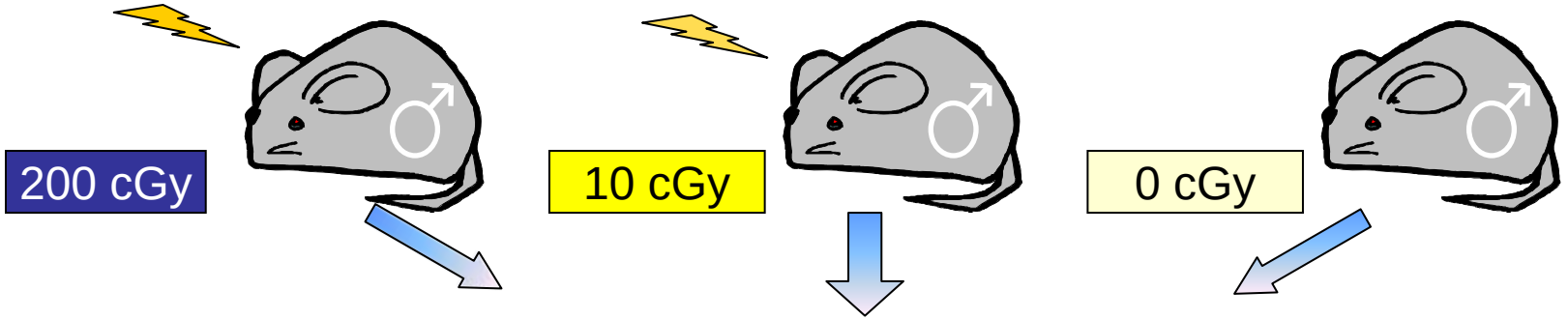


Whole body exposures
Differential effects of low vs. high dose

Male B6C3F1 mice, 7 weeks old

Mouse brain: experimental design

Whole Body Radiation Exposure



Total RNA was collected from brain after 4 hrs

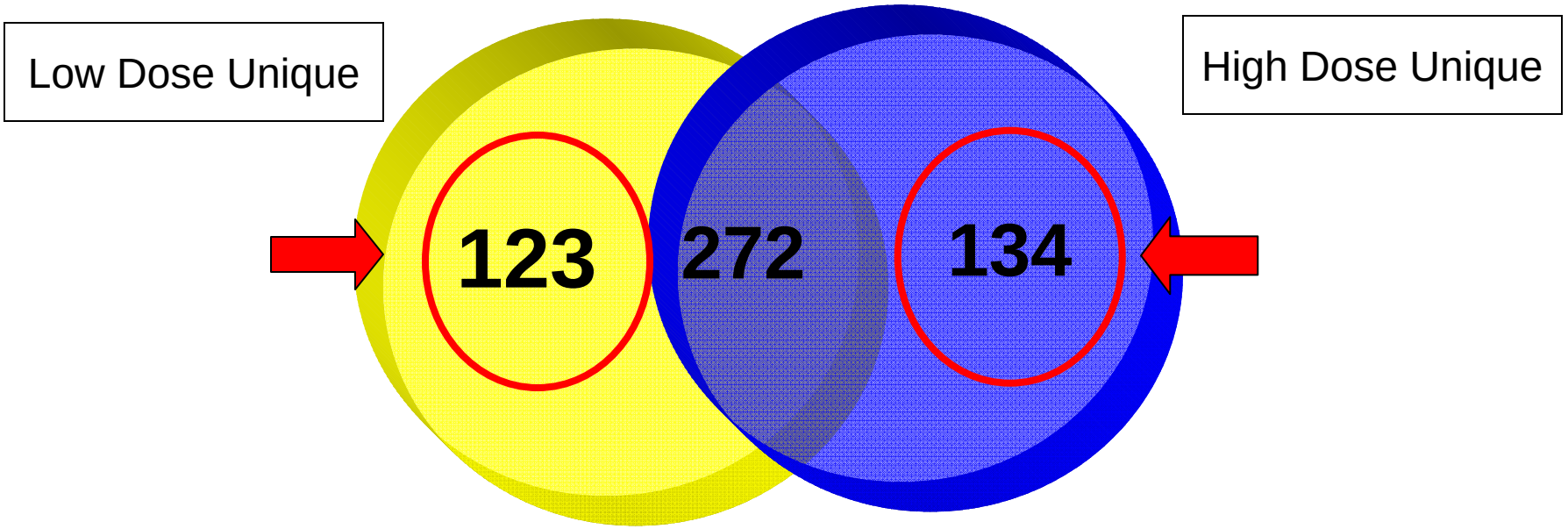
Transcript profiling on Affymetrix oligo arrays (MGU_74 Av2)

Bioinformatics approaches to find unique genes, networks, pathways, and functions

MOUSE BRAIN: *Low-Dose versus High-Dose Gene Expression Phenotypes*

Low Dose 10 cGy

High Dose 200 cGy



MOUSE BRAIN: Gene Ontology identified unique low-dose enriched processes, functions, and cellular locations

	High dose unique	Low dose unique	Common
Biological Process			
Protein biosynthesis	0.0001		
Protein metabolism	0.0040		
Negative regulation of neurogenesis	0.0088		
Small GTPase mediated signal transduction		0.0059	
Rho protein signal transduction		0.0002	
Ribosome biogenesis and assembly			0.0095
Amino acid metabolism			0.0079
DNA metabolism			0.0032
Oxigen and reactive oxigen metabolism			0.0049
Molecular Function			
rRNA binding	0.0008		
Transferase activity	0.0042		
Structural constituent of ribosome	0.0000		
Fatty acid binding		0.0014	
GTP binding		0.0019	
GTPase activity		0.0003	
Actin binding			0.0094
Transcription coactivator activity			0.0048
Oxidoreductase activity			0.0027
6-phosphofructokinase activity			0.0034
Electron transporter activity			0.0014
Cellular Component			
Mitochondrion	0.0001		
Ribosome	0.0000		0.0024
Synaptic vescicle		0.0045	
Chromatin remodeling complex		0.0044	0.0047
Synapse		0.0011	
Neuron projection			0.0005
Dendrite			0.0047
Secretory granule			0.0005

HUMAN and MOUSE COMPARISONS: Common Low-dose gene interaction networks and nodal genes

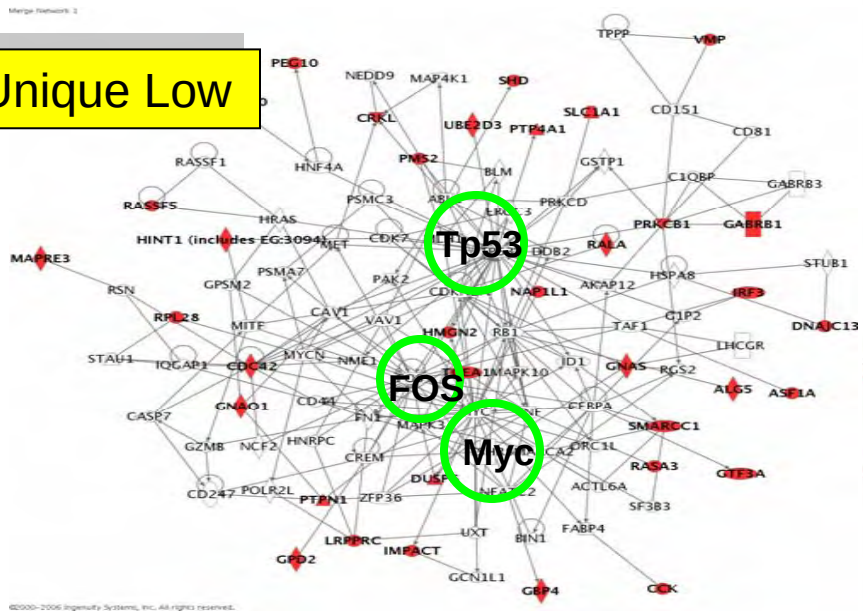
	LOW DOSE				HIGH DOSE		
	HUMAN*			MOUSE**	HUMAN		MOUSE **
Network Nodes	Lympho-blastoid cells	Umblical vein endothelial cells	Keratino-cytes	In Vivo Brain	Lympho blastoid cell lines	Umbilical vein endothelial cells	In Vivo Brain
TP53	X	X	X	X	X	X	X
MYC	X	X	X	X	X	X	X
FOS	X	X	X	X			
SRC	X		X	X			
RELA					X	X	X

* Human cell cultures, log growth and growth arrested

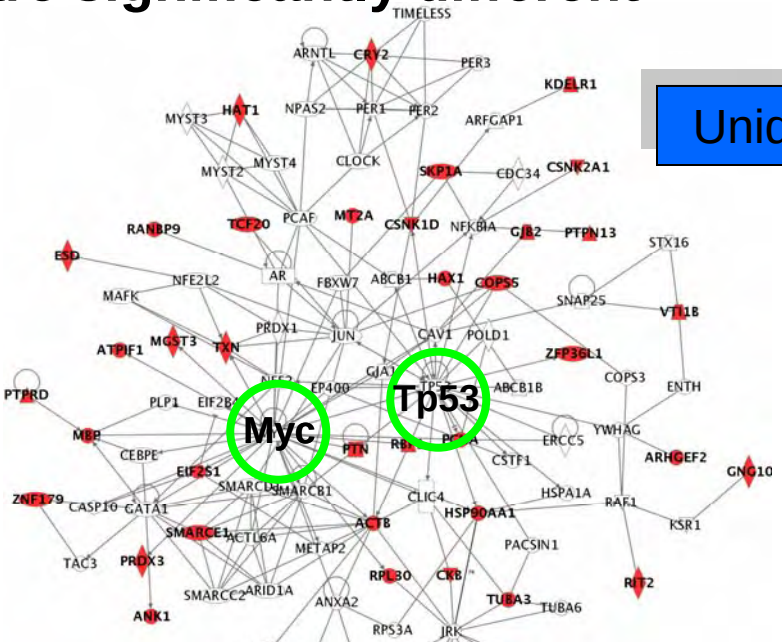
** whole body exposure (mouse brain)

MOUSE BRAIN: Tp53 and myc are mayor nodes in both low- and high-dose networks. However, the functions associated with these networks are significantly different

Unique Low

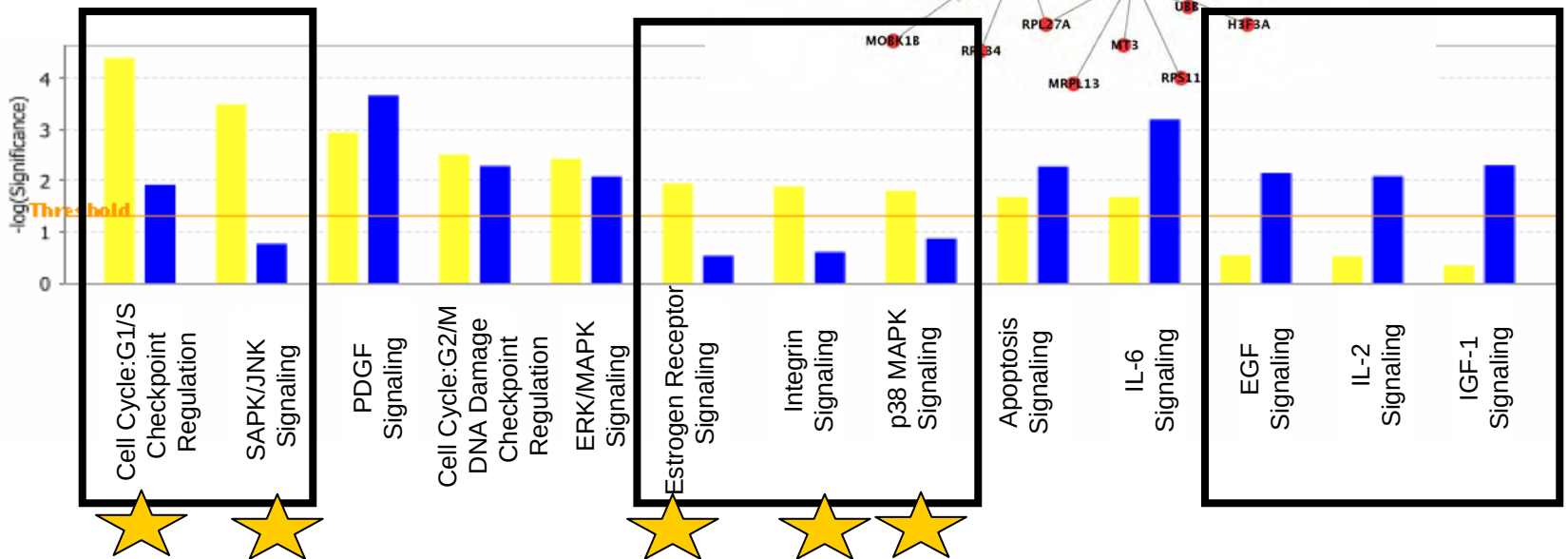


Unique High



Low

High



Genes modulated by 5cGy whole body: Six tissues show major variations in numbers of affected genes

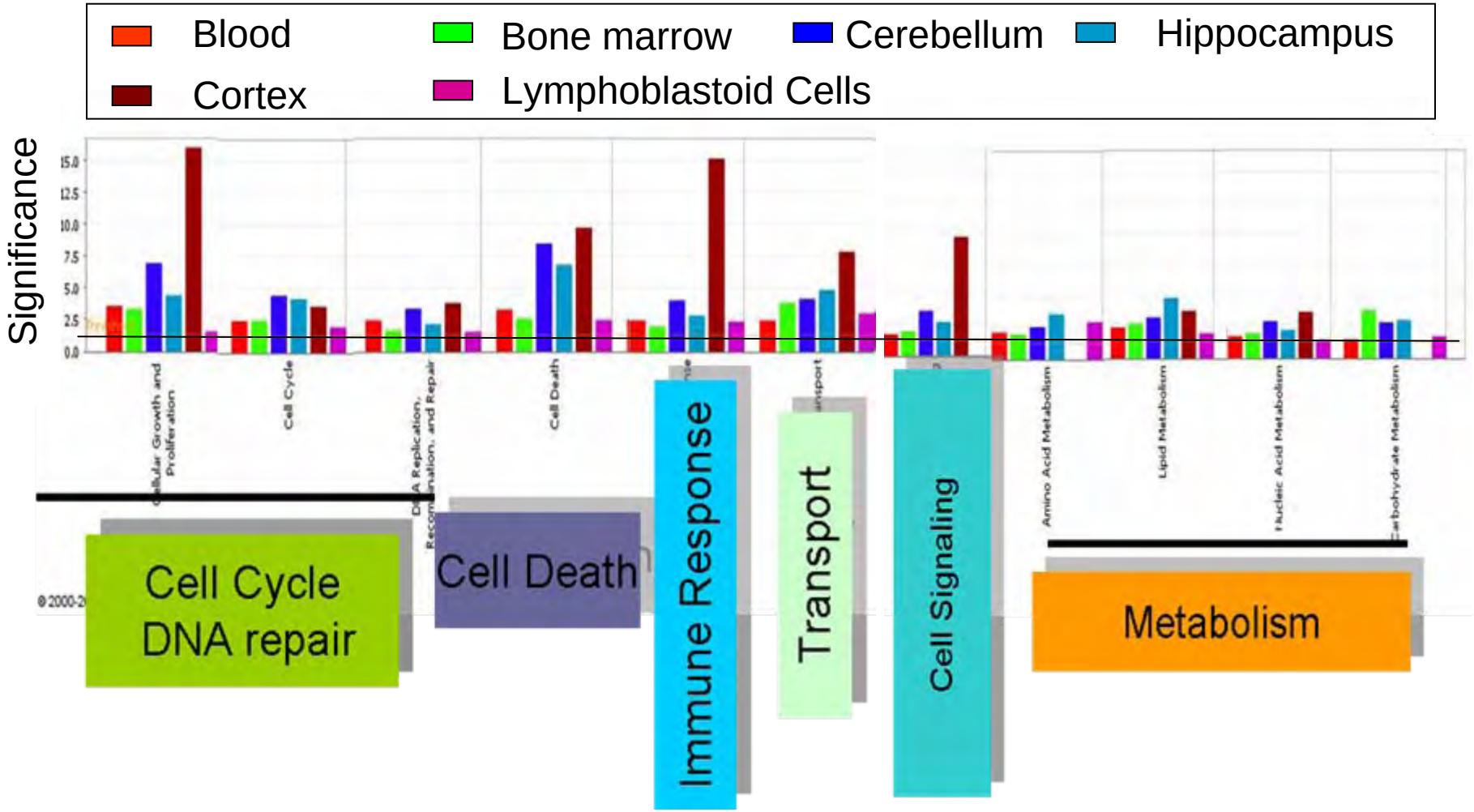
5 cGy vs 0 Gy

	Blood	Bone Marrow	BRAIN			Testis
			Cerebellum	Hippocampus	Cortex	
No. differentially expressed genes	1431	51	155	268	462	18
Upregulated genes	1065	35	14	144	226	
Downregulated genes	365	15	141	123	236	

C57BL/6J male mice; all tissues collected 10 hrs after exposure from the same animals

Cross-Tissue and Species Comparisons of Low-dose Functional Responses (1-10cGy) show similar functions

Murine tissues after whole-body exposures
Human Lymphoblastoid cells after in vitro exposures



MOUSE BRAIN: Tissue-specific Low-dose Gene Expression Phenotypes

Up and down regulated pathways associated with memory and neural plasticity

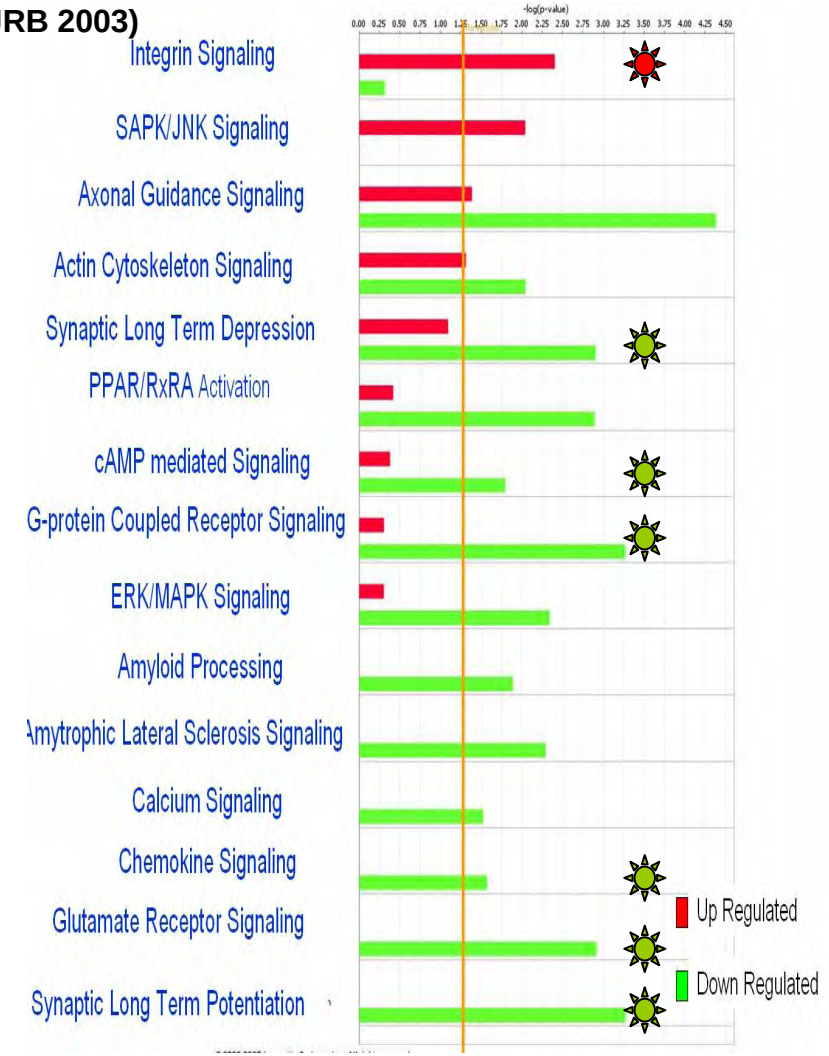
Associations with the aging brain

Associations with neurological diseases

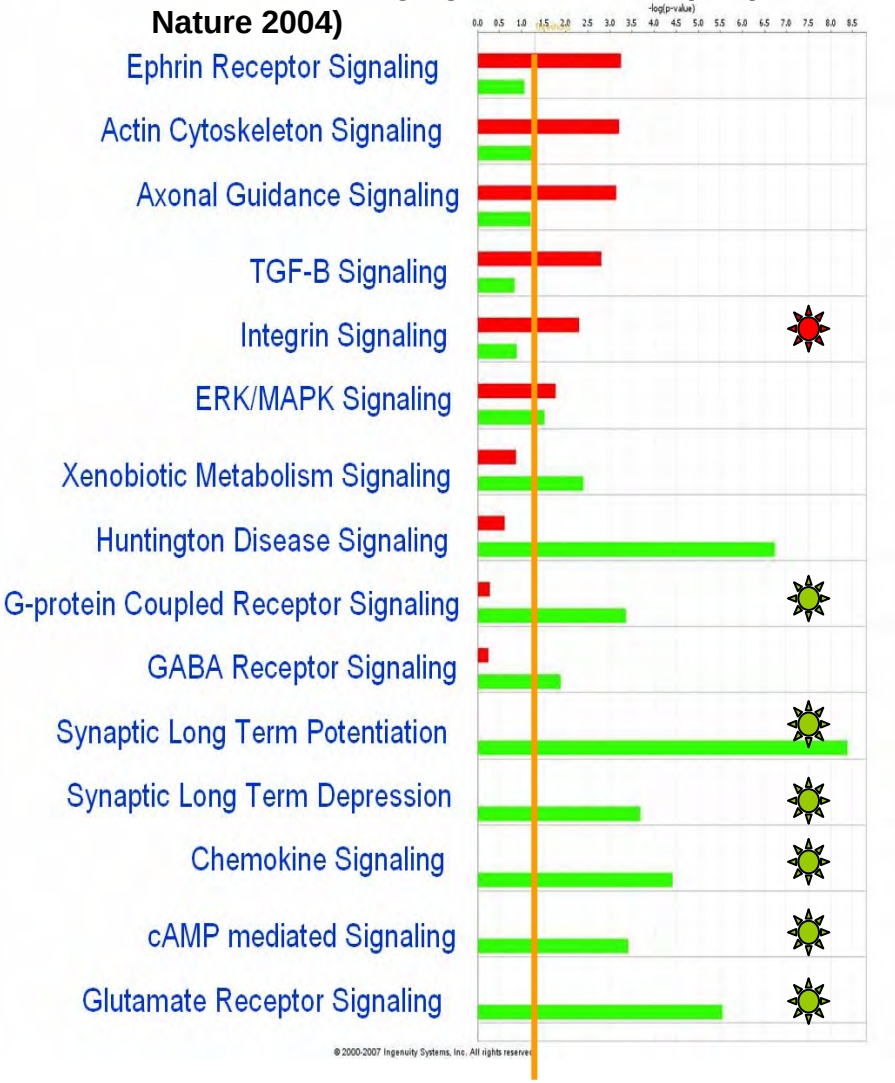
GENE EXPRESSION after LOW-DOSE RADIATION and WITH AGING

Low-dose irradiation of the brain down regulates pathways associated with cognitive function. Similar pathways are down regulated with normal human aging.

Mouse Brain: Low Dose Unique Transcripts (Yin et al., IJRB 2003)



Human Brain: Aging Brain Transcripts (Lu et al, Nature 2004)

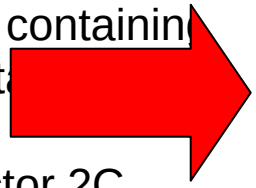


Starred pathways are significantly upregulated (red) or downregulated (green) in both irradiated brain (mouse) and aging brain (human)

BRAIN: Gene expression phenotypes after low-dose radiation in mice and in patients with neurodegenerative diseases

Low dose down-regulated genes in mice

DUSP6	dual specificty phosphatase 6
LRPPRC	leucine-rich PPR -motof containin
PRKCB1	protein kinase C, bet
SYT5	synaptotagmin V
MEF2C	myocyte enhancer factor 2C
C6ORF32	
GNAO1	guanine nucleotide binding proteir
SLC1A1	solute carrier family I
PRKAR1B	protein kinase C, cAMP- dependent, regul
NELL2	NEL-like 2
MAPRE3	microtubule associated protein, RP/El
KCNQ2	potassium voltage-gated channel, KQT -like
DYNC1I1	dynein, cytoplasmic 1, intermediate c
HERC2	hect domain and RLD2
GRIA3	glutamate receptor, ionotrophic, AM
GFRA2	GDNF2 family receptor



Alzheimers Disease down regulated dataset- Human $p<0.003$

Low dose exposed brains and brain tissue from Alzheimer's patients have statistically significant overlapping down-regulated gene expression phenotypes.

Outline

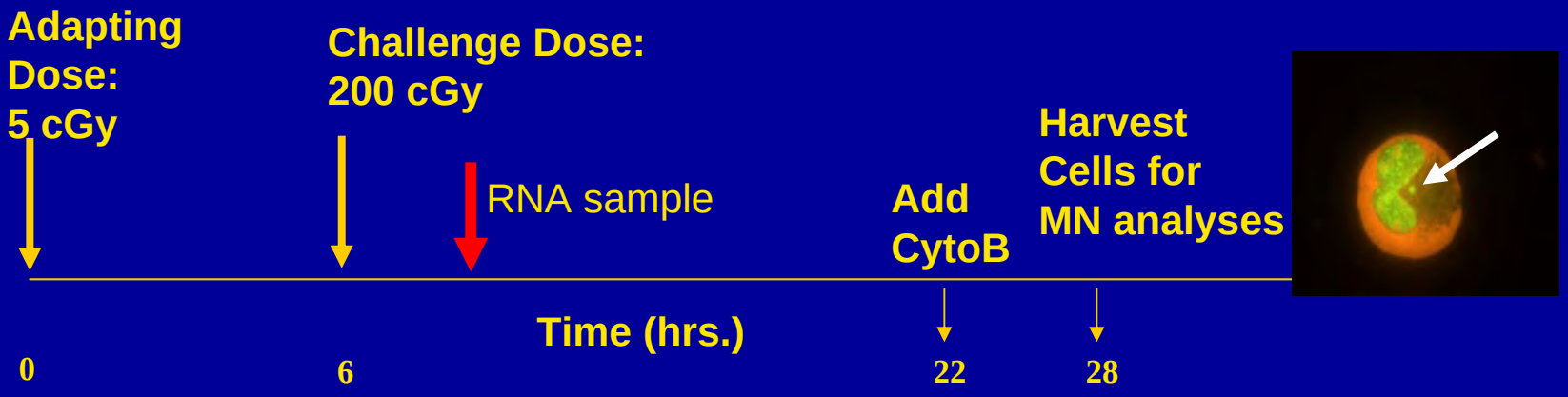
Low-dose “gene expression phenotyping”

- robust responses across human cell types
- tissue variation in responses in mice

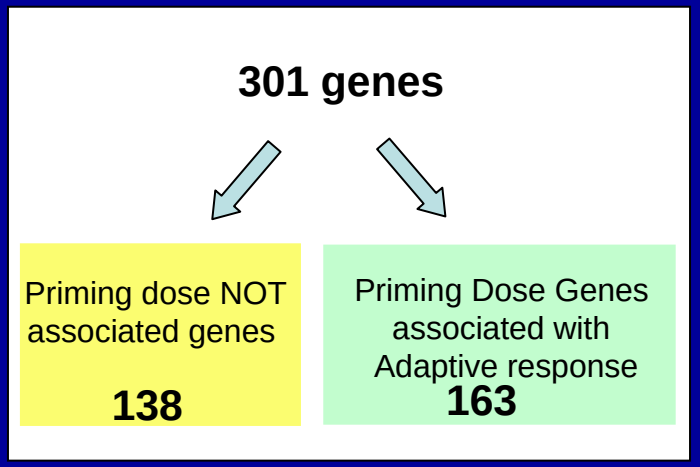
Adaptive response networks and pathways

- human cells in vitro
- mouse model - tissue variation in adaptive responses for chromosomal damage and cancers

Modeling the expression controls of the cytogenetic radioadaptive in human lymphoblastoid cell lines

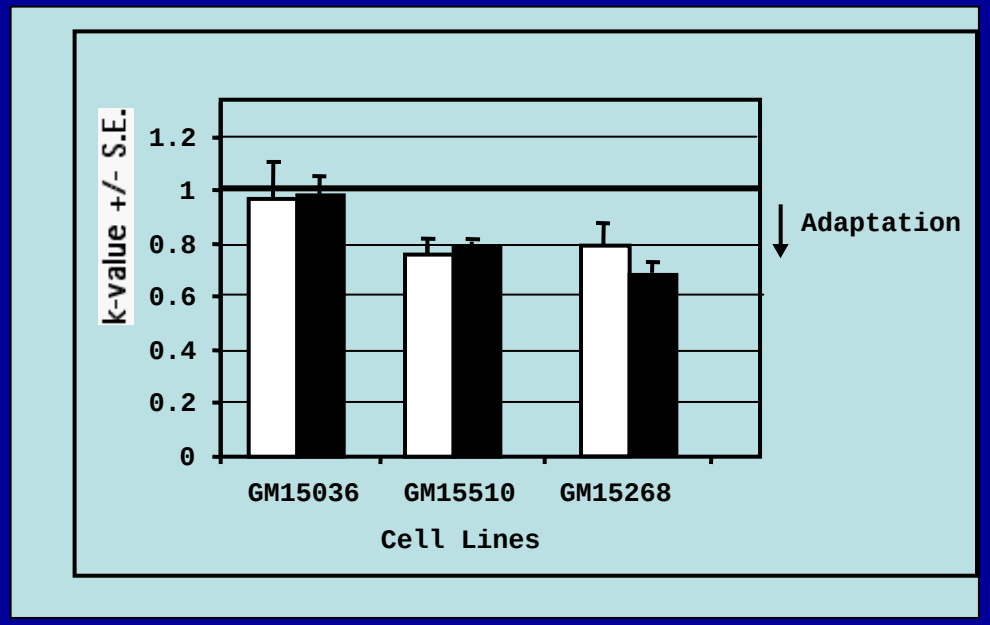


Gene expression phenotypes

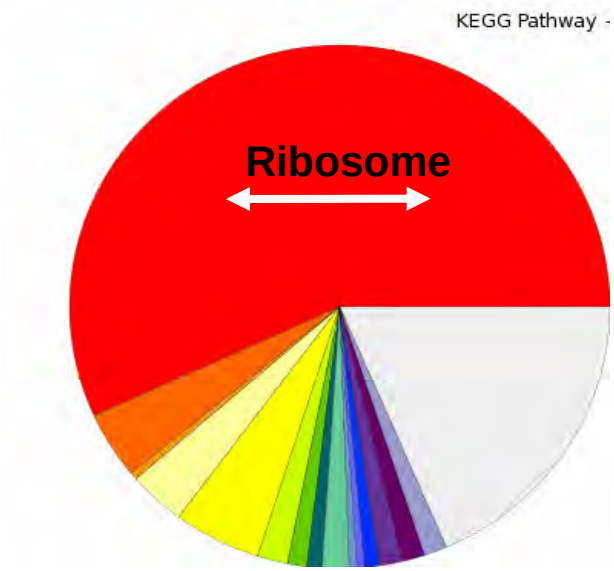


Coleman et al 2005

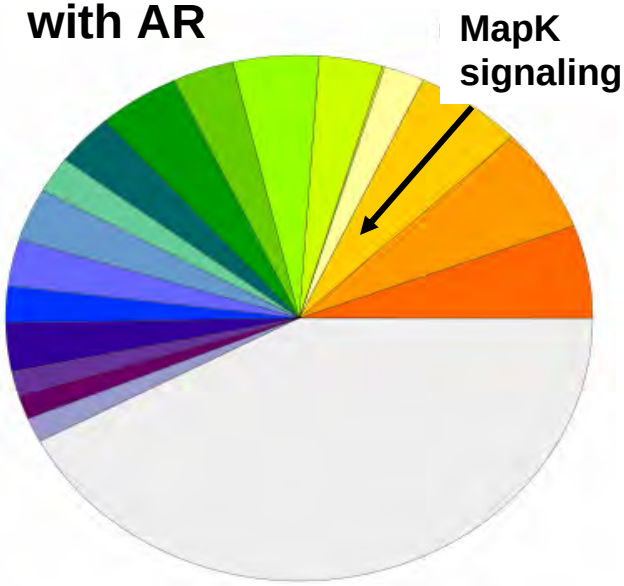
Reduced cytogenetic damage (MN)



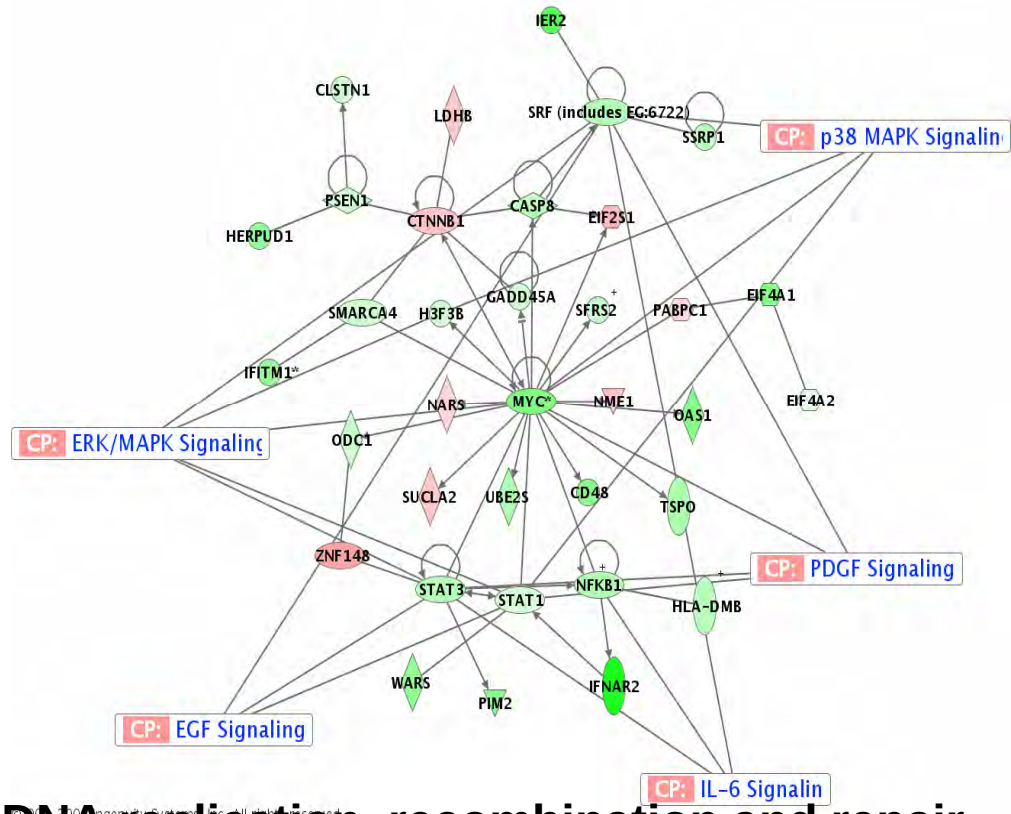
Pathways associated with priming dose, but not with AR



Pathways associated with AR



AR network containing the MYC node with mainly down-regulated genes ($p \sim 10^{-60}$)

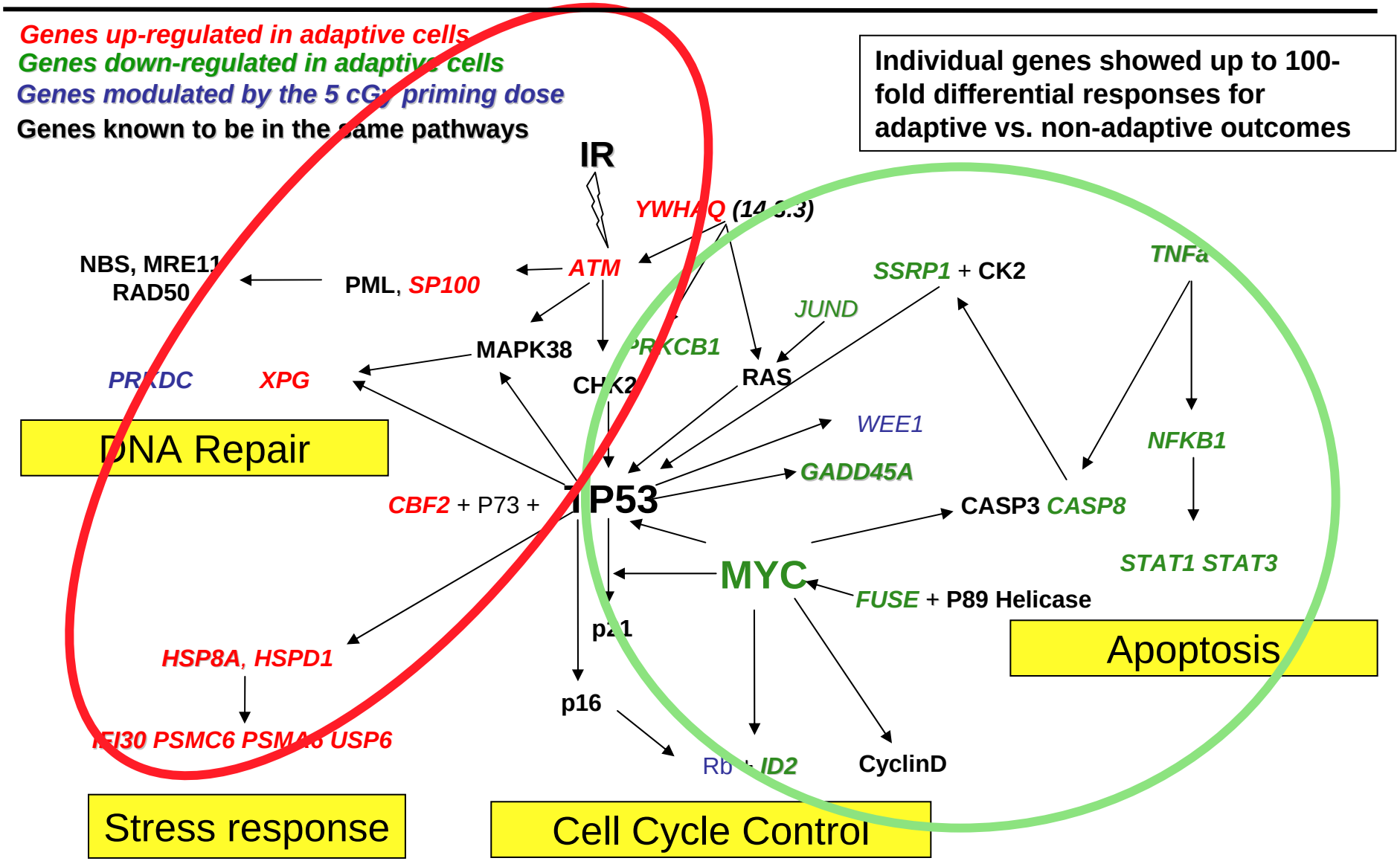


DNA replication, recombination and repair genes associated with AR

ATM	EDD1	XPG
MYC	NME1	BUB3
GADD45A	TNF	ADA
C1B1	SSRP1	POLE3
SMARCA2		

Demonstrated Protein-Protein Interactions

Hypothesis: A group of TP53 and MYC associated genes acts as a "switch" for adaptation vs non-adaptation: *the position of the switch when cells show adaptation*



Coleman et al 2005

Modeling the Expression Controls of the Radio-adaptive response and its health consequences in mice

Mouse model: gene expression phenotypes associated with adaptive responses across tissues

Priming Dose

0Gy or 5cGy

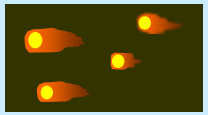
Challenge Dose

2Gy

Early DNA Damage

Blood
Brain

COMET



Tissue Transcript Profiling

Brain – Cortex
Brain – Cerebellum
Brain - Hippocampus

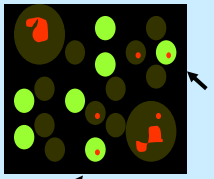
Bone Marrow
Blood

MICROARRAY

Chromosomal Damage

Micronuclei in Bone Marrow

FLOW CYTOMETRY



Time →

-6 hr **0** **+15 min** **+4 hr** **+24** **+48** **+72 hr**

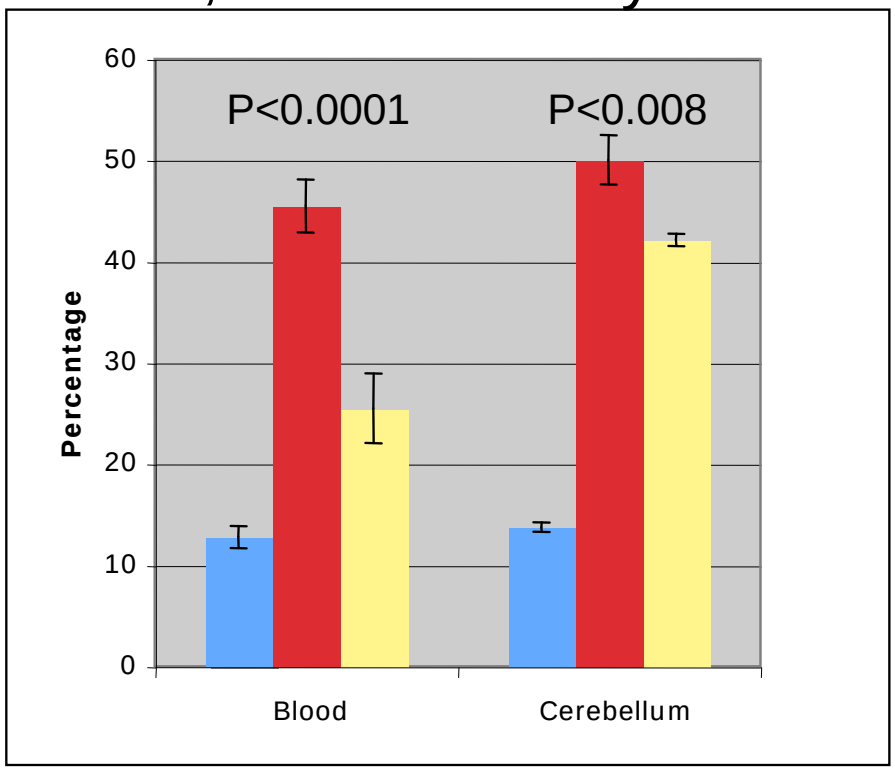
5+200 cGy

versus

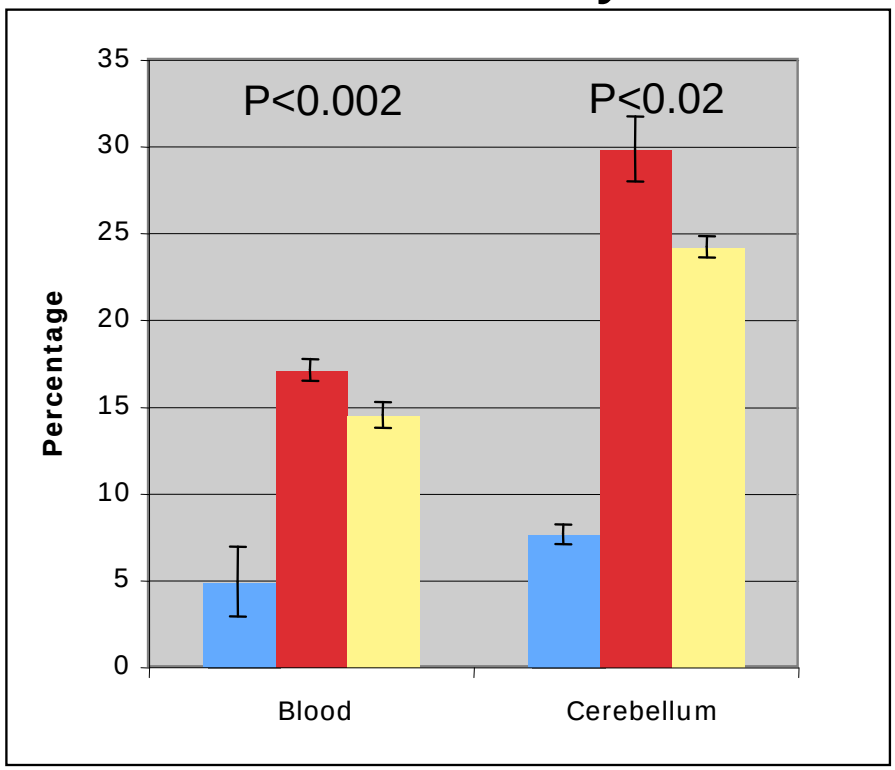
200cGy

Mouse Model: radio-adaptive response in blood and brain tissue in young adult males

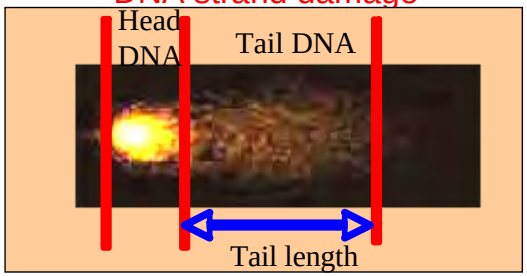
Comet, Alkaline Assay



Comet, Neutral Assay



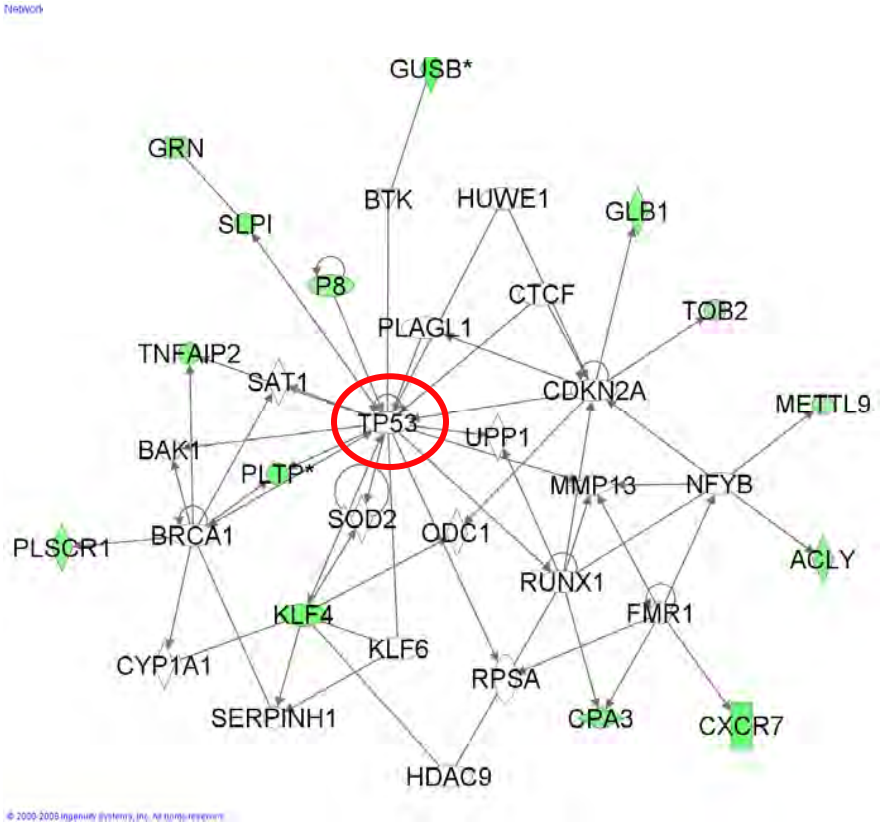
Comet assays for the detection of DNA strand damage

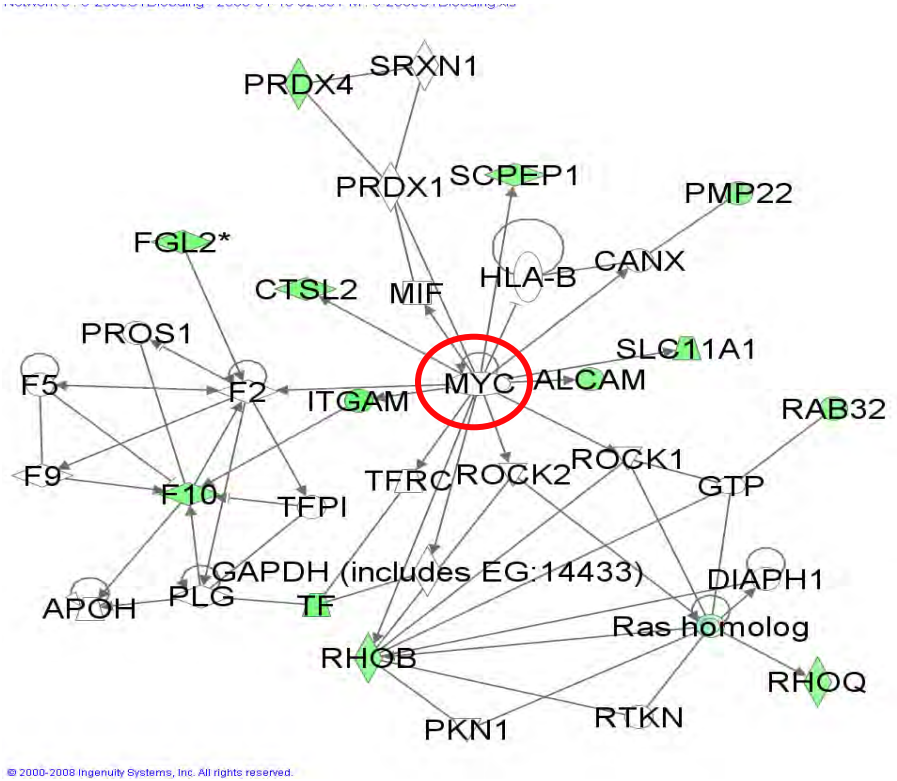


sham 200 cGy 5 + 200 cGy

- 3 male mice per group
- analysis at 15 minute after the 2Gy challenge dose
- WBCs, Cerebellum

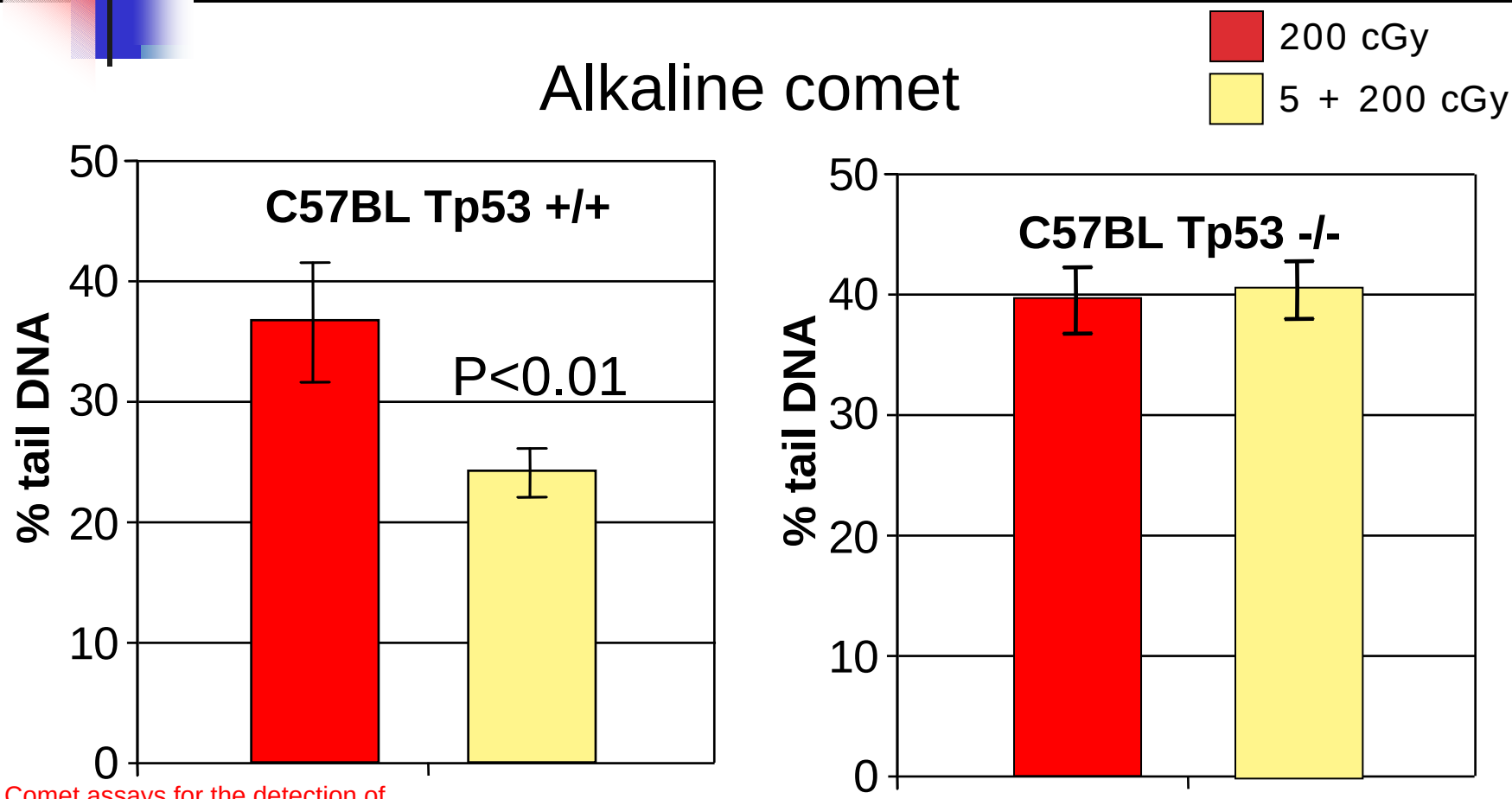
Mouse Model in blood: TP53 and MYC networks of genes that were differentially enriched after 5+200cGy when compared to the 200cGy



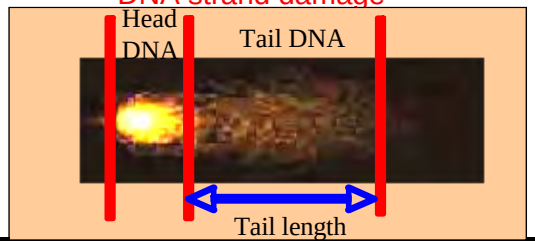


Both networks contain predominantly down-regulated genes (green), as seen in the adaptive response for human lymphoblastoid cells.

Lack of Tp53 function abrogates the AR in mouse peripheral blood cells



Comet assays for the detection of DNA strand damage

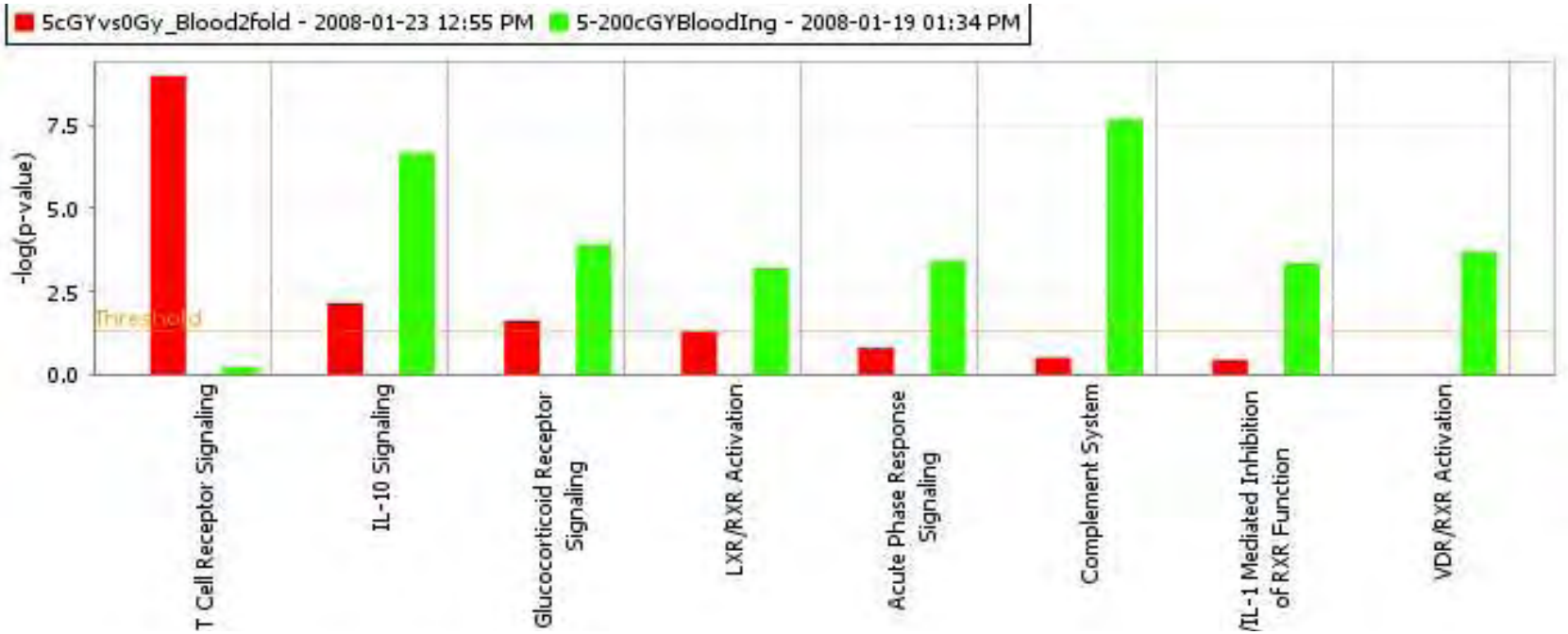


Alkaline analysis at 15 minute after the 2Gy challenge dose

Relative Pathway Enrichment between 5cGy and (5+200 vs 200cGy) in Blood

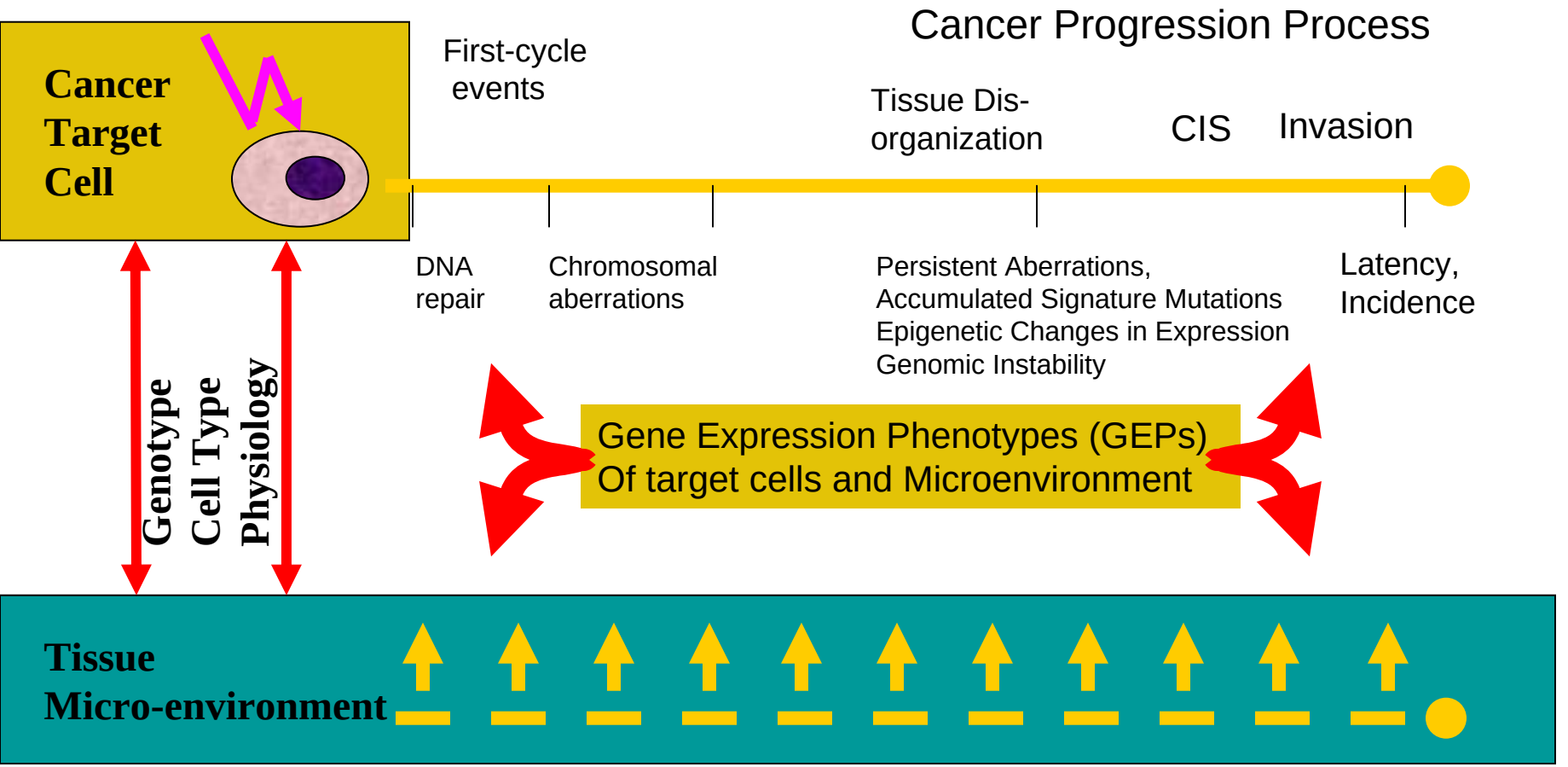
5cGY

5+200 versus 200cGY



- **Il-10 signaling** involved in inflammation
- **Glucocorticoid receptor** controls metabolism and immune response
- **LXR/RXR activation** regulates cholesterol absorption
- **VDR/RXR activation** involved in growth plate development
- **Acute phase response**, involved in infection, physical trauma and malignancy

Tissue system biology approach to understanding the low dose and adaptive responses of cancer target cells in their tissue microenvironments during cancer progression



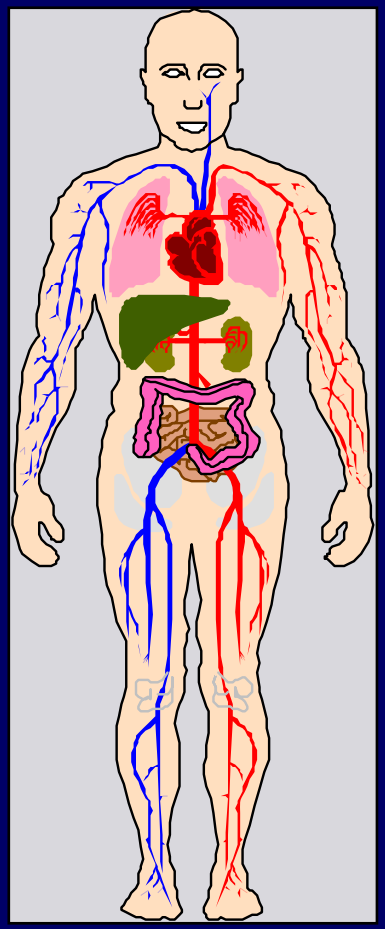
- What are the low-dose and adaptive-response GEPs:
  - in radiation-sensitive and cancer target cells over time?
  - in the tissue microenvironment over time?
- What gene pathways are predictive of adaptive response protection for chromosome damage and cancer risks?

The Radio-adaptive Response

An approach for understanding the tissue-specific risks low-dose radiation for genomic damage and health risks

Questions for human health studies

- **does the AR occur in all tissues and cell types of the human body**
- **molecular nature of the AR switch in tissues**
- **effects of gender and genotype**
- **relevance to low-dose chemical exposures**
- **role of physiological stress**
- **effects of age, diet, micronutrients, and environmental exposures on AR protection**
- **spectrum of health effects affected: cancer, brain function, other diseases**



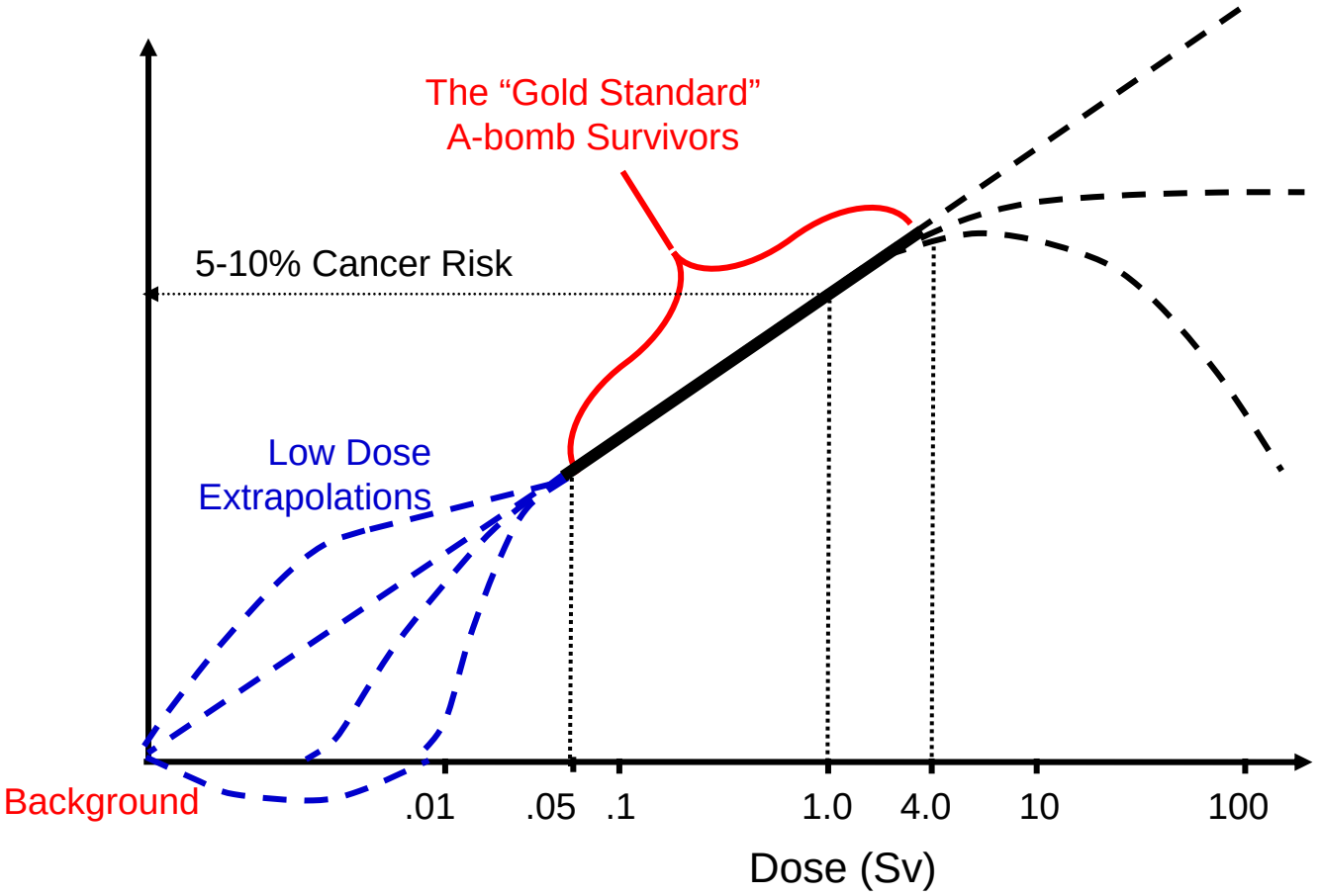
Low Dose & Non-Targeted Effects of Ionizing Radiation:
Implications for Risk Assessment

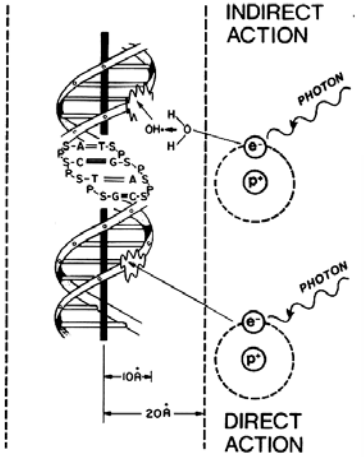
William F. Morgan. Ph.D., D.Sc.

Radiation Oncology Research Laboratory
University of Maryland, Baltimore

WFMorgan@som.umaryland.edu

The dilemma for radiation protection: what is the scientific basis for radiation standards to protect the public from exposures to low levels of ionizing radiation (<0.1 Sv) where there are considerable uncertainties in the epidemiological data.

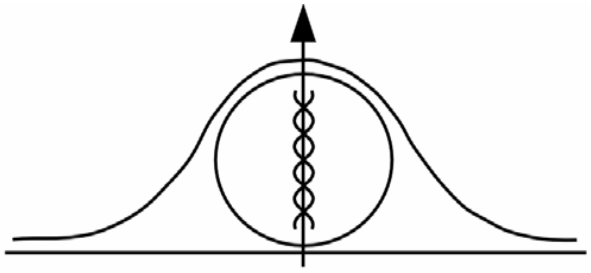




DNA damage is the result of direct and indirect effects of radiation

Damage / cGy of X-rays:

- 0.4 DSBs
- 1.5 DNA crosslinks
- 10 SSB
- 25 base damages



Radiation

High Fidelity DNA Repair

DNA Damage

Senescence

Death
- Apoptosis
- Necrosis
- Mitotic Linked

Mutation(s) and/or Chromosome Rearrangements

Somatic

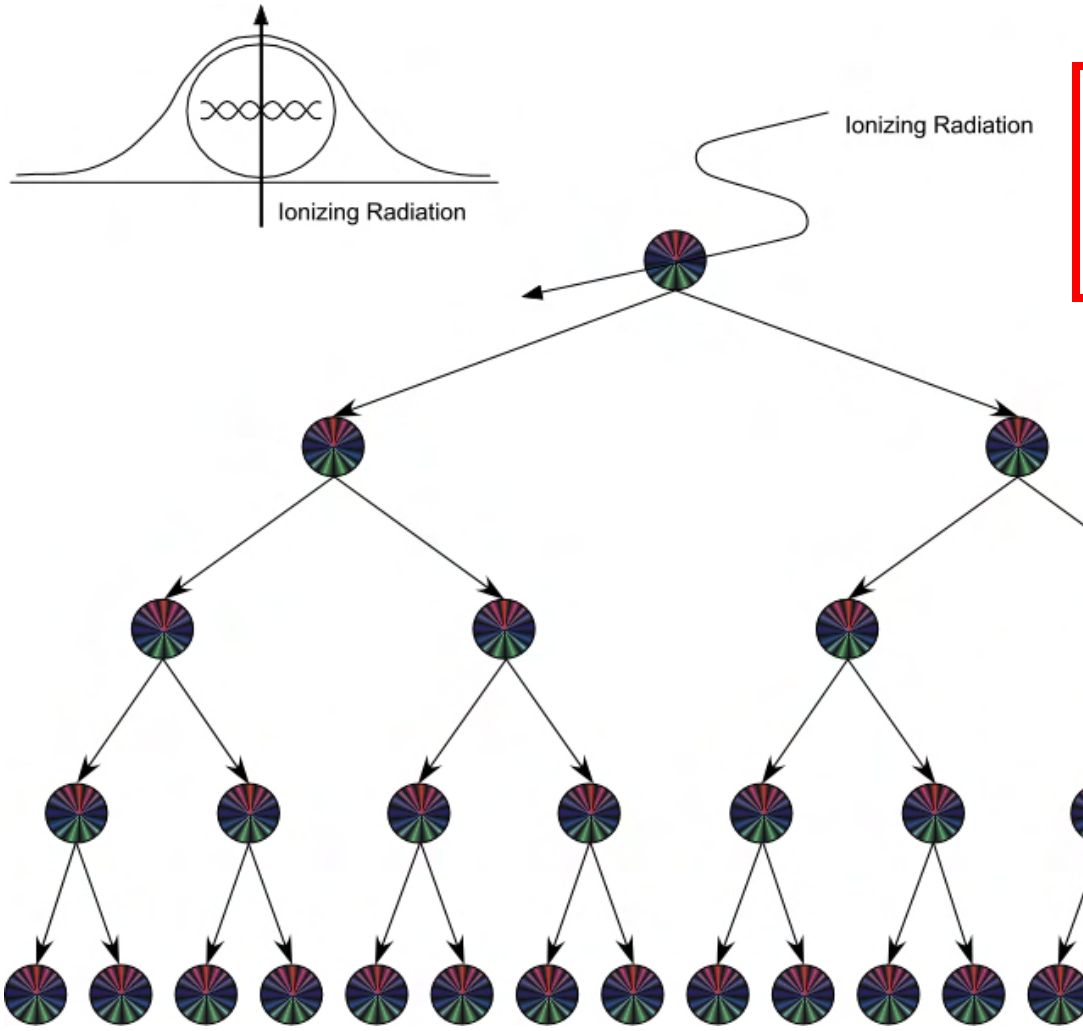
Germline

Fetal

Carcinogenesis — Heritable Genetic Effects — Developmental Effects

Genetics
Environment
Lifestyle, diet, smoking
Stress

Conventional paradigm for radiation effects: Effects occur in “hit” (targeted) cells



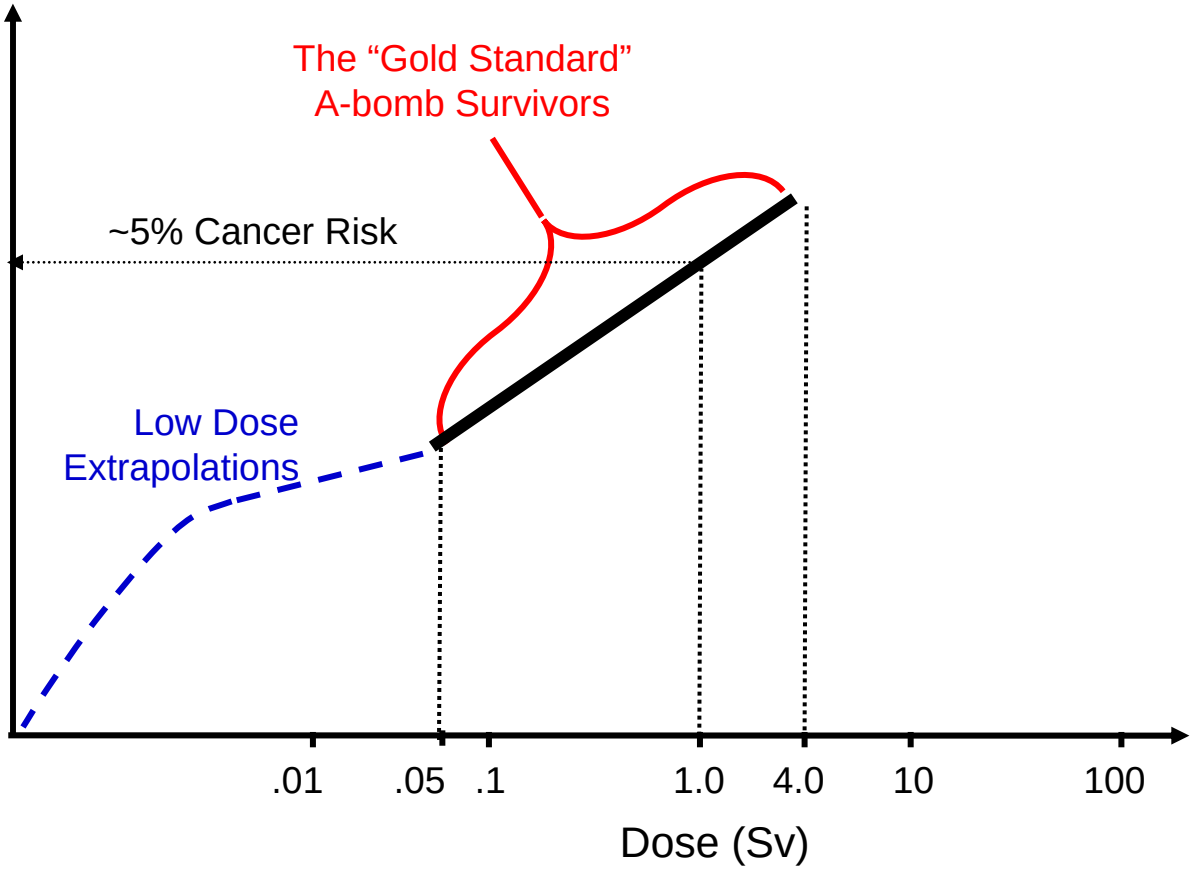
“Initiated” Cell
Mutation(s)
Chromosomal damage

Impact of the tissue micro-environment

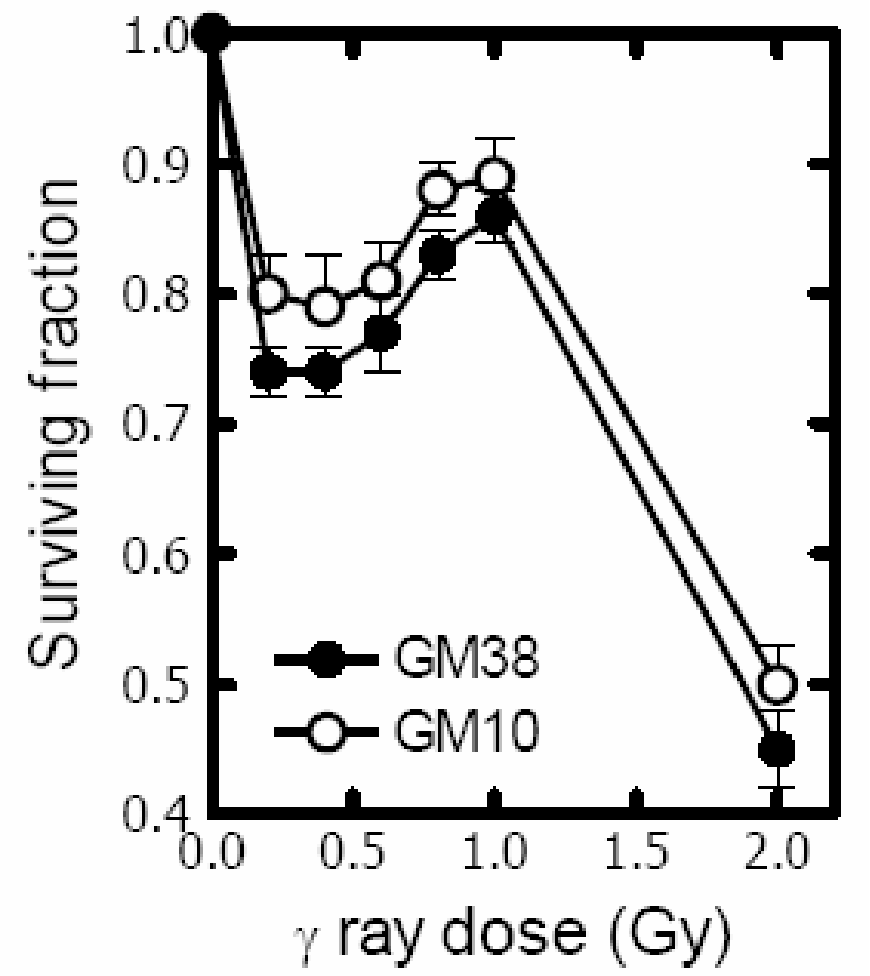
angiogenesis

Supra-linarity:

Low dose hypersensitivity
Genomic instability
Detrimental bystander effects



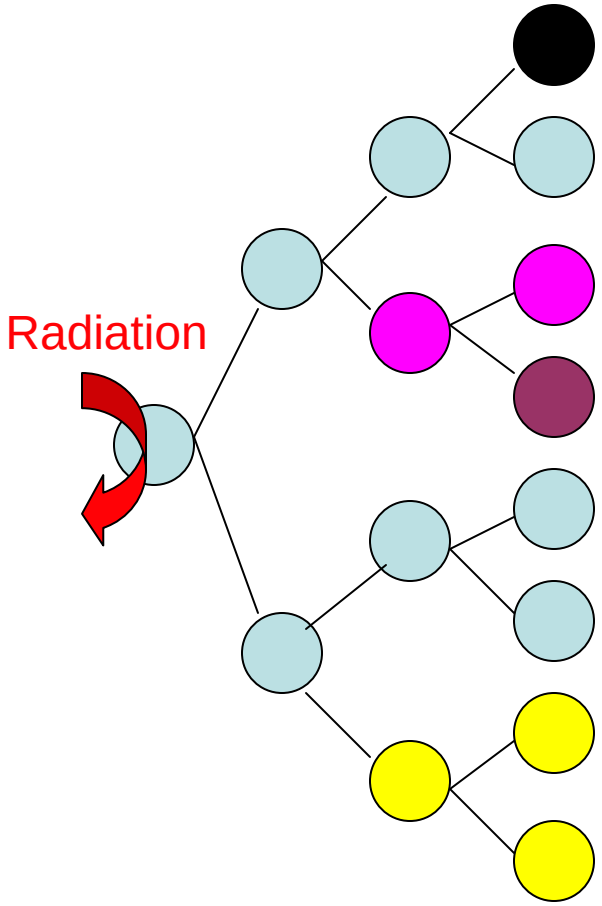
Hypersensitivity to low doses of ionizing radiation



Joiner et al. I.J.R.O.B.P. 49; 379-89 (2001)

RADIATION-INDUCED GENOMIC INSTABILITY

Increased rate of genomic alterations in the progeny of irradiated cells



Manifests as:

chromosomal rearrangements

micronuclei

aneuploidy

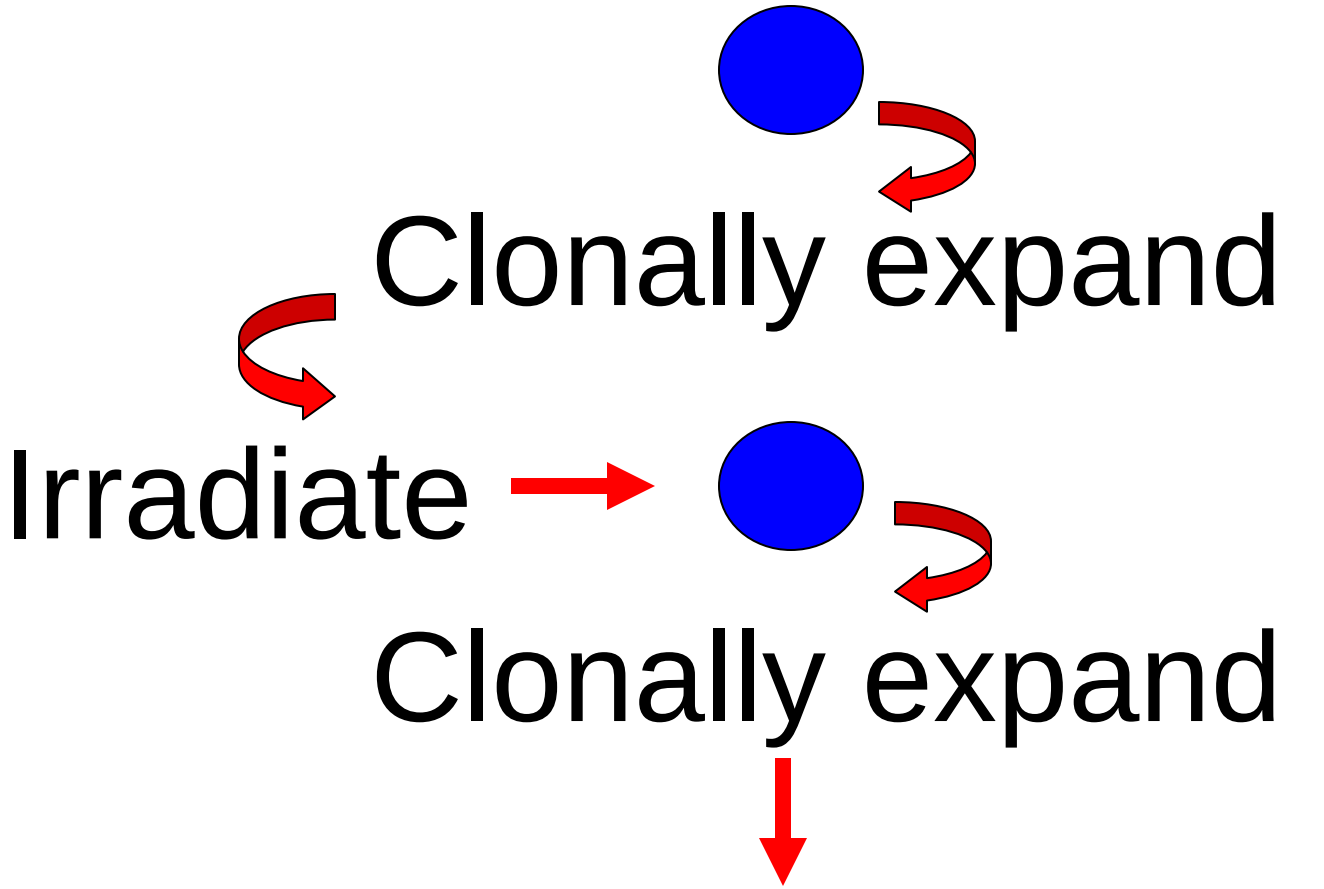
delayed mutation

(spectrum different)

gene amplification

cell killing

Non clonal - not necessarily a fixed genetic change that is passed on.


Clonally expand
Irradiate
Clonally expand
Metaphase analysis of
clonally expanded cells

Radiation-induced instability can occur in non-targeted cells:

Instability observed in cells not traversed by an alpha particle

Kadhim et al. Nature 355, 738-40 (1992)

Shielded grid experiment

Lorrimore et al. PNAS 95, 5730-3 (1998)

secreted factor?

cell to cell gap junction communication*?

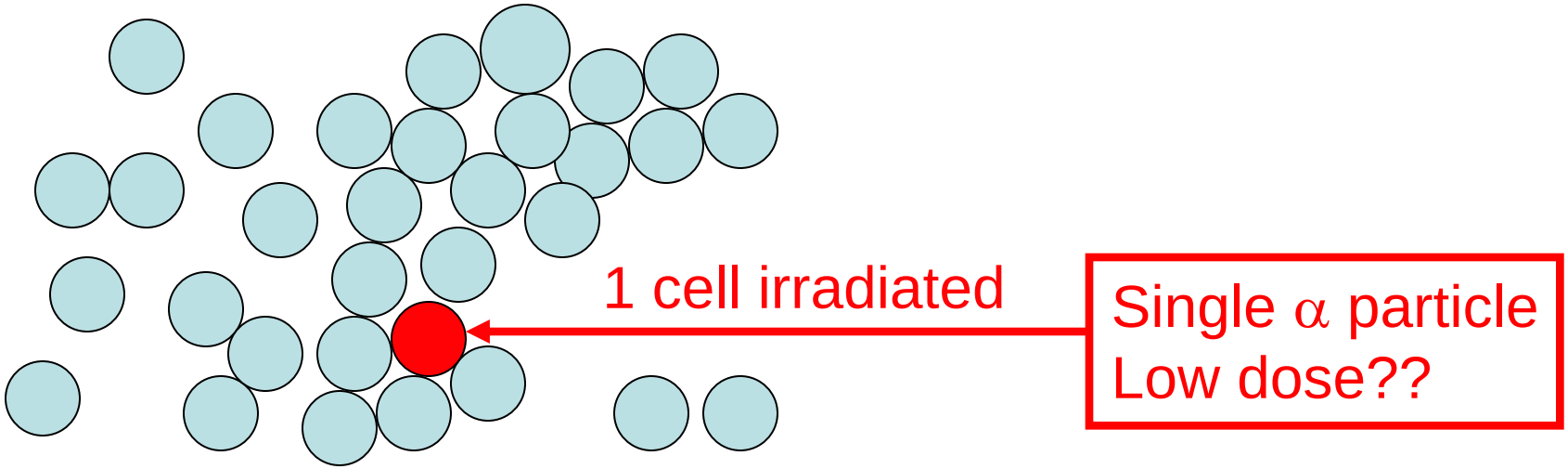
dead / dying cells*?

*Not in our cell system

Radiation induced bystander effects:

Effects observed in cells that were not irradiated but were “bystanders” at the time of irradiation

Single cell microbeam irradiation



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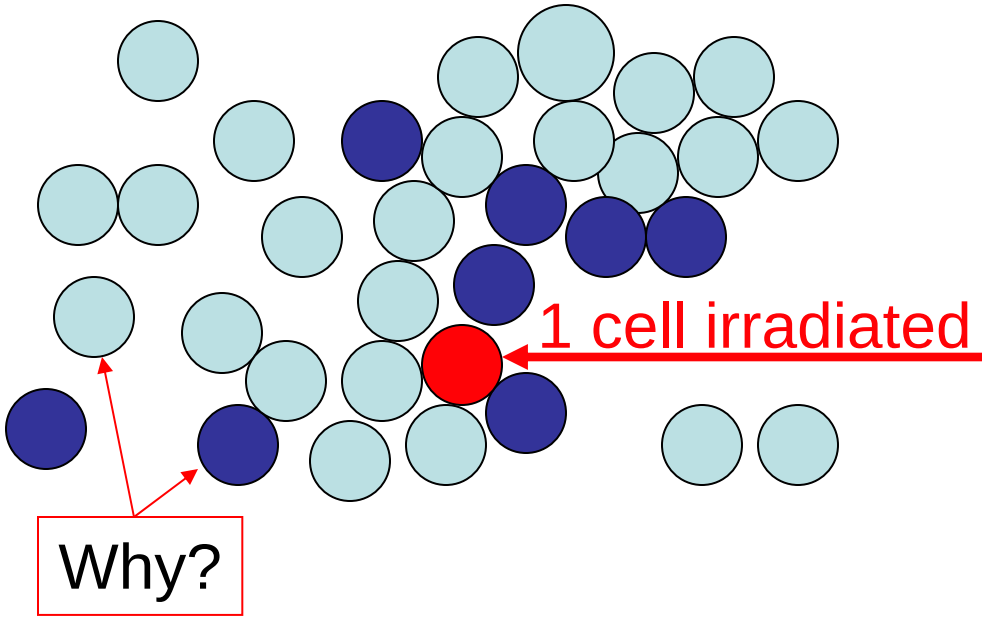
Effects observed in cells that were not irradiated but were “bystanders” at the time of irradiation

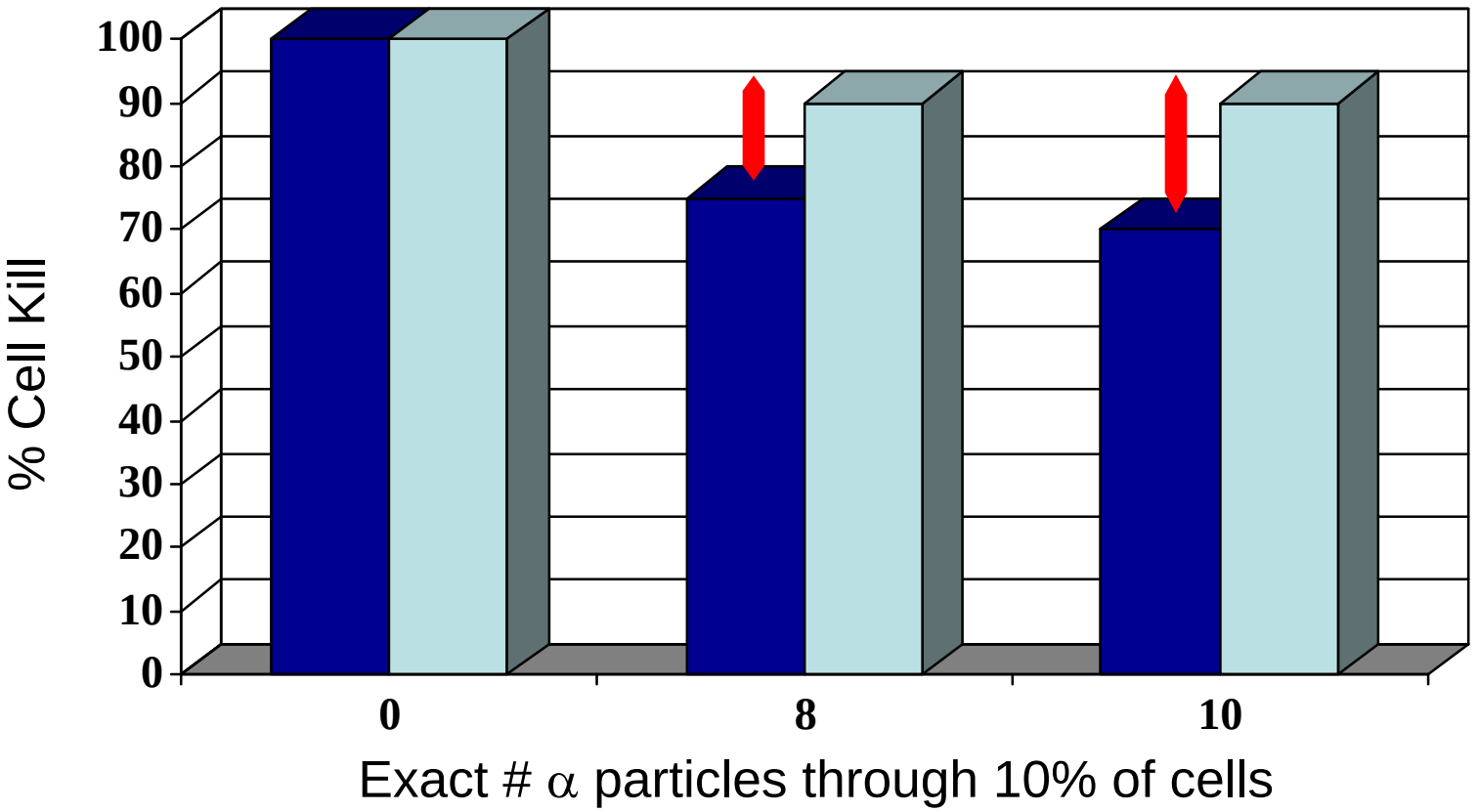
Single cell microbeam irradiation



A binary effect

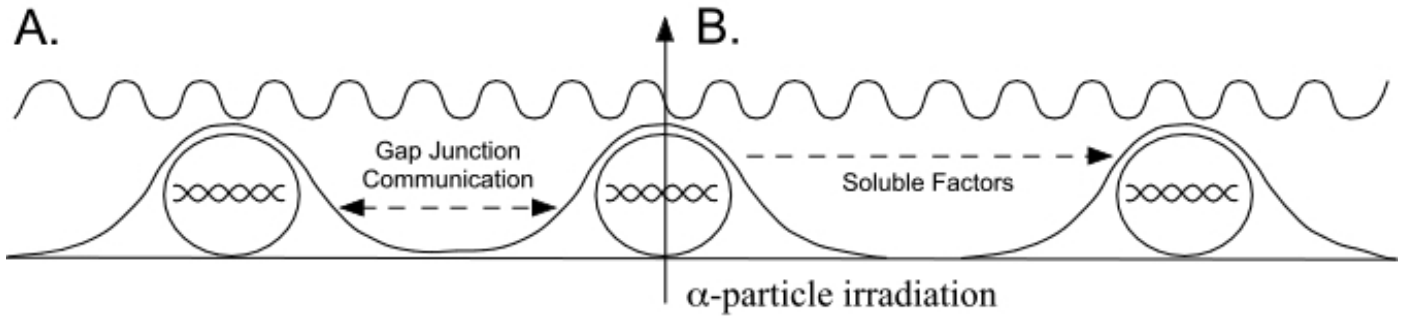
gene expression
mutation
transformation
micronuclei
cell killing

Bystander effect for cell survival



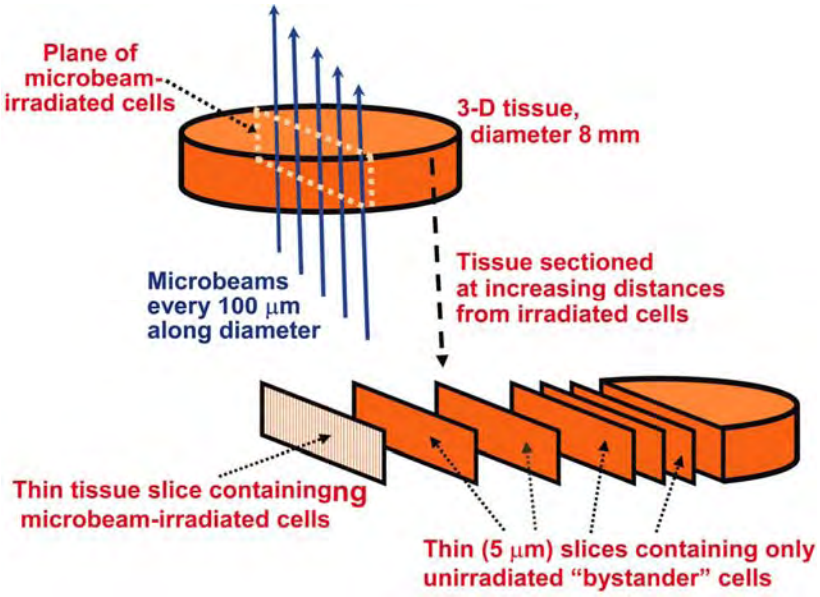
Cell kill due to bystander effect

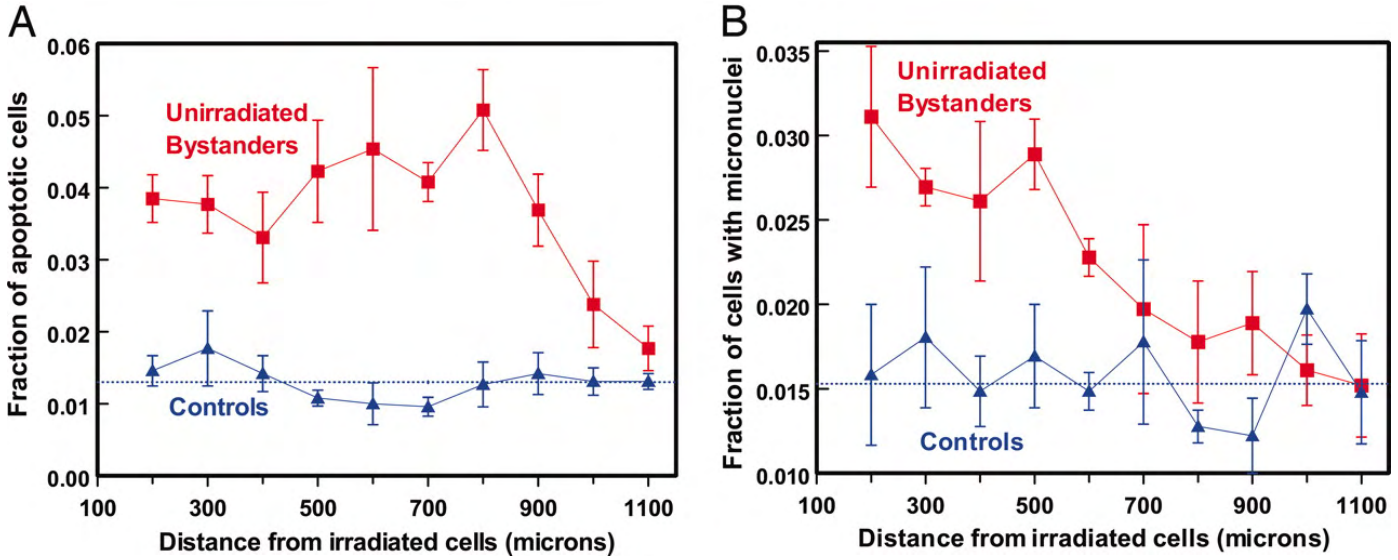
Sawant et al. Rad. Res. 156, 177-180 (2001)



Bystander effects in an *in vivo* human skin model (3D).

Belyakov et al. PNAS 102, 14203-7 (2005)

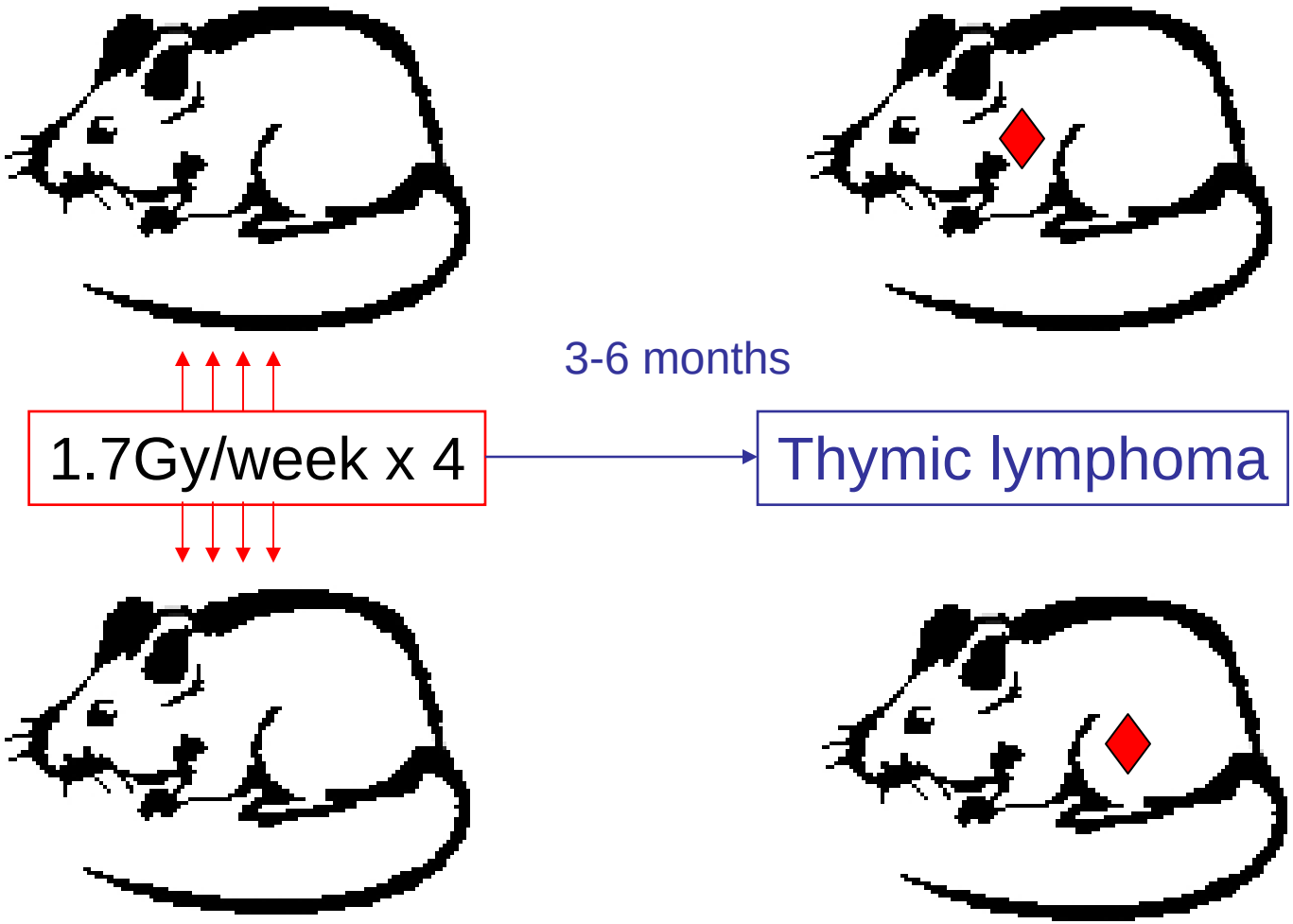




Beneficial? Eliminating damaged or initiated cells

Detrimental? Inducing damage in non-irradiated cells

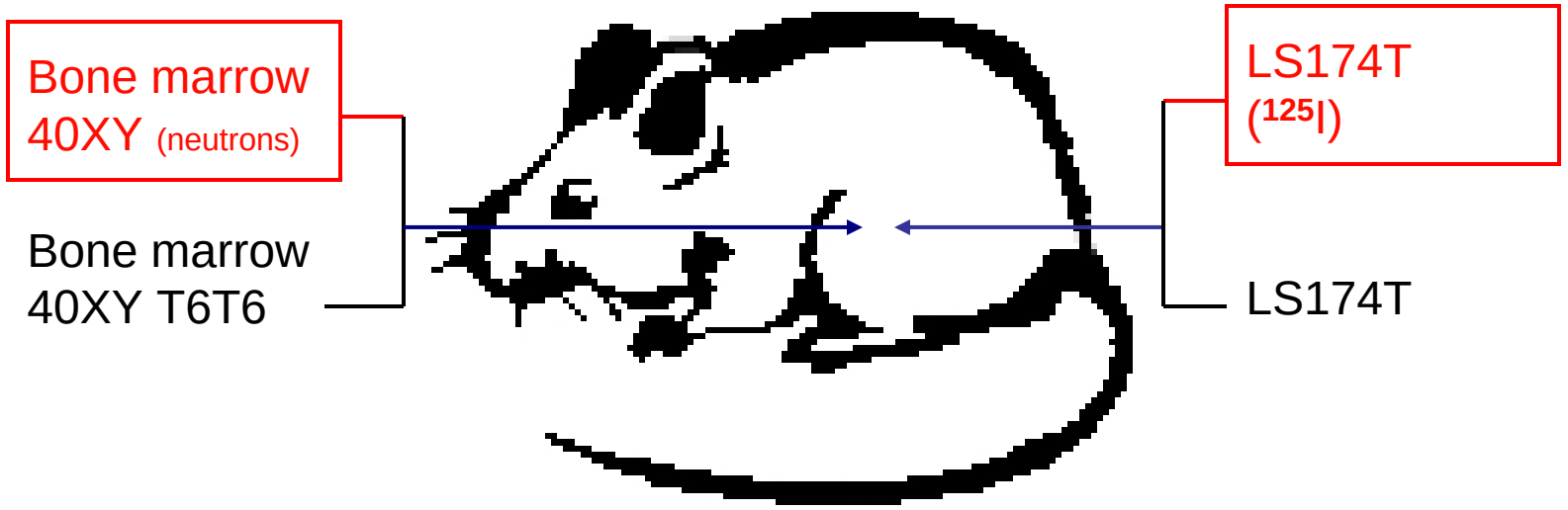
Bystander effects *in vivo*



Thymectomy
Post irradiation thymus transplant

Kaplan et al. Science 119; 439-340, 1954
Kaplan et al. Cancer Res. 16; 422-5, 1956
Kaplan et al. Cancer Res. 16; 425-8, 1956

Bystander effects *in vivo*



Chromosomal instability in progeny of non-irradiated hemopoietic stem cells

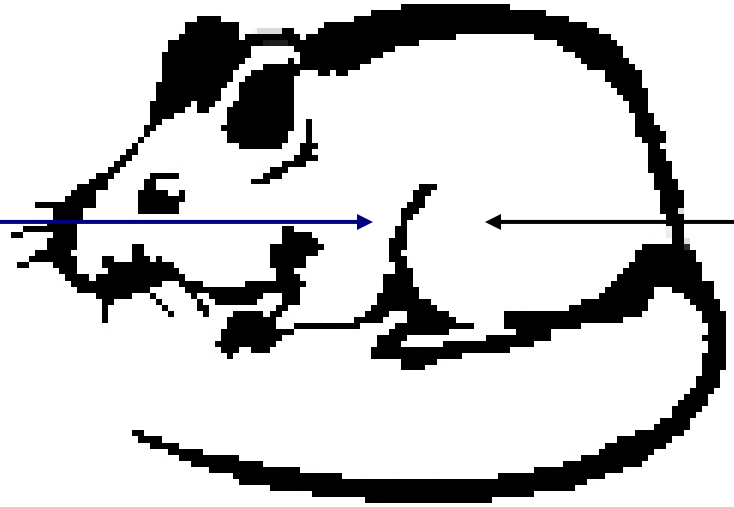
Watson et al., Cancer Res. 60, 5608 - 5611 (2000)

Inhibitory effect on tumor growth

Xue et al., PNAS 99, 13765-70 (2002)

Abscopal “anti-tumor” effects *in vivo*

Implanted LLC cells



5 x 10Gy
12 x 2Gy
fractionated

Significant delay in LLC cell growth.

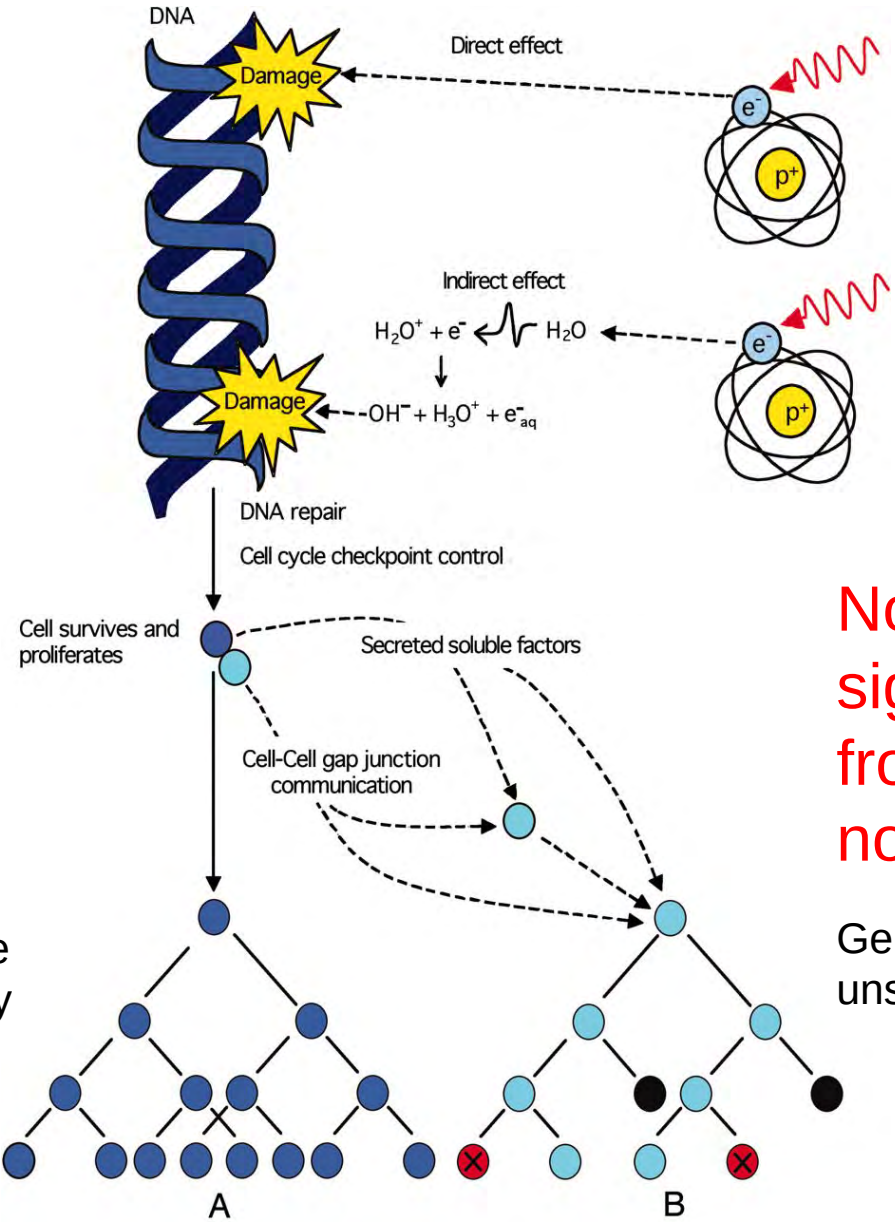
Camphausen et al. Cancer Res. 63, 1990-1993 (2003)

Further focused studies required

What is the factor?

Mechanism of transmission?

Organ specific or whole body at risk?



Targeted

+

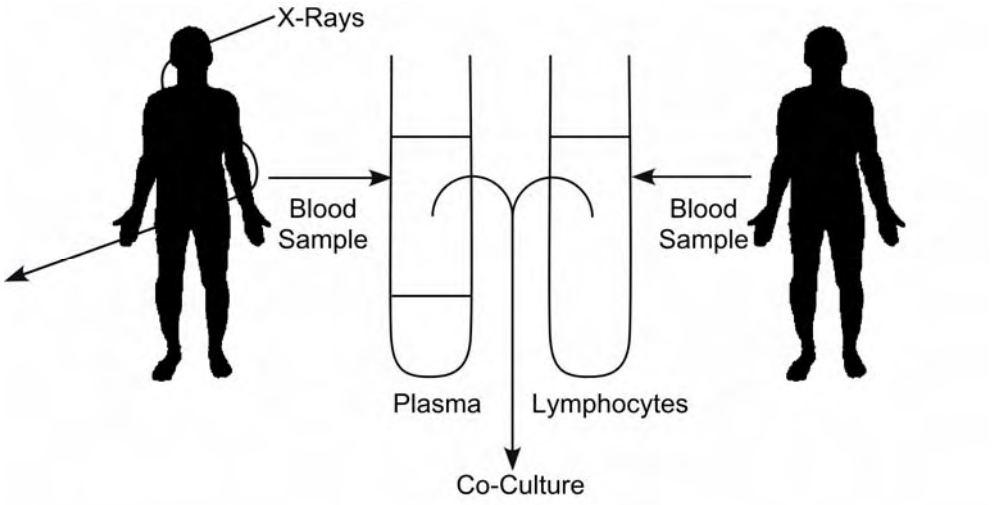
Non-Targeted - signaling messages from irradiated to non-irradiated cell(s)

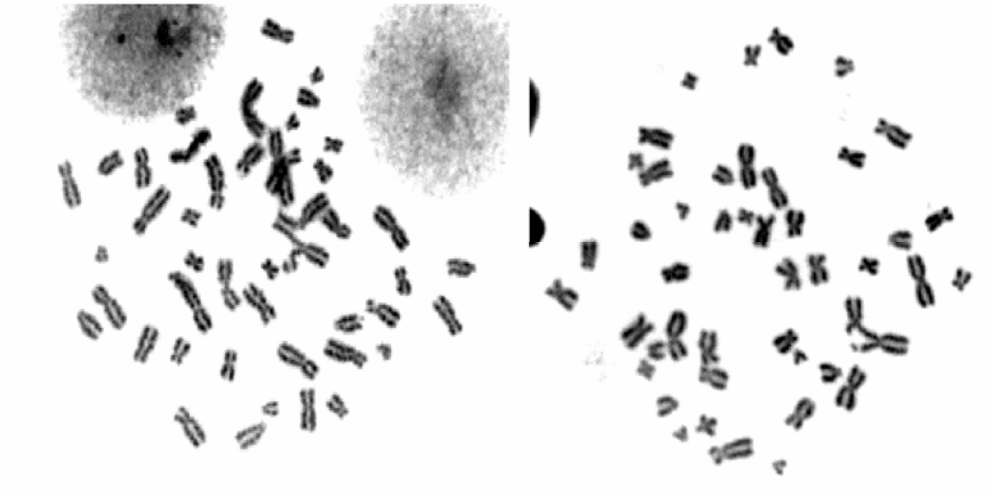
Genomically unstable colony

Morgan & Sowa, PNAS 102, 14127-8 (2005)

Role for the “instability” signal in non-cancer effects?

Precedent for secreted factor(s) in humans - clastogenic factors





Clastogenic factors in plasma from:

Accidentally irradiated individuals

Goh & Sumner, Radiation Res. 35, 171-181 (1968)

Therapeutically irradiated individuals

Hollowell & Littlefield, PSEBM. 129, 240-244 (1968)

A-bomb survivors

Pant & Kamada, Hiroshima J. Med. Sci. 26, 149-154 (1977)

Chernobyl clean up workers

Emerit et al., J. Cancer Res. Clin. Oncol. 120, 558-561 (1994)

Children exposed after Chernobyl

Emerit et al., Mutation Res. 373, 47-54 (1997)

Human blood irradiated *in vitro*

Scott, Cell Tissue Kinet. 2, 295-305 (1969)

CF-Nelson rats

Fagnet et al., Cancer Genet. Cytogenet. 12, 73-83 (1984)

Patients with chromosome fragility syndromes

Bloom syndrome, Fanconi anemia, xeroderma pigmentosum

What is the nature of the signal generating bystander effects?

Reactive oxygen/nitrogen species; cytokine signaling, inflammatory responses

What is the interaction of that signal with the bystander cell?

DNA double strand breaks

γ-H2AX foci, chromosomal aberrations micronuclei, apoptosis

Biological significance - good or bad?

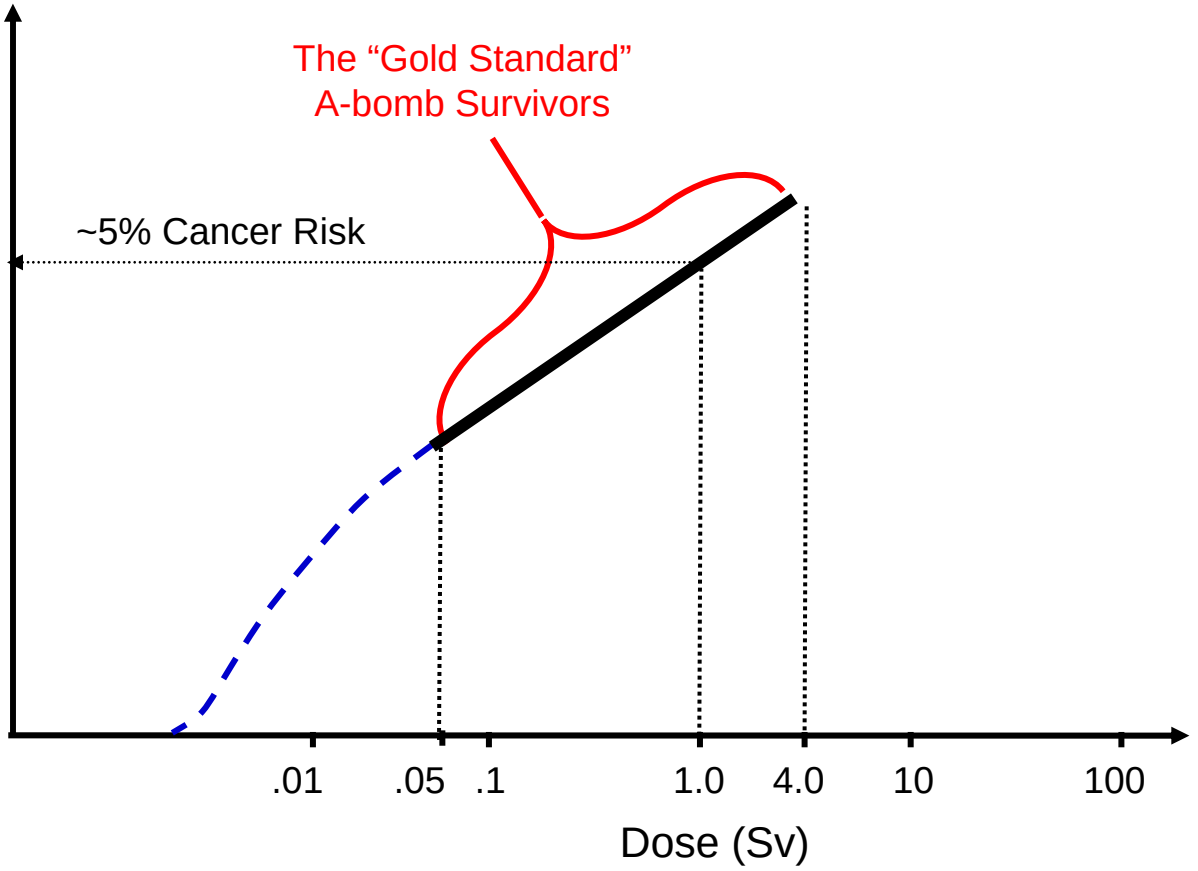
Target > volume irradiated

Role in non-cancer effects?

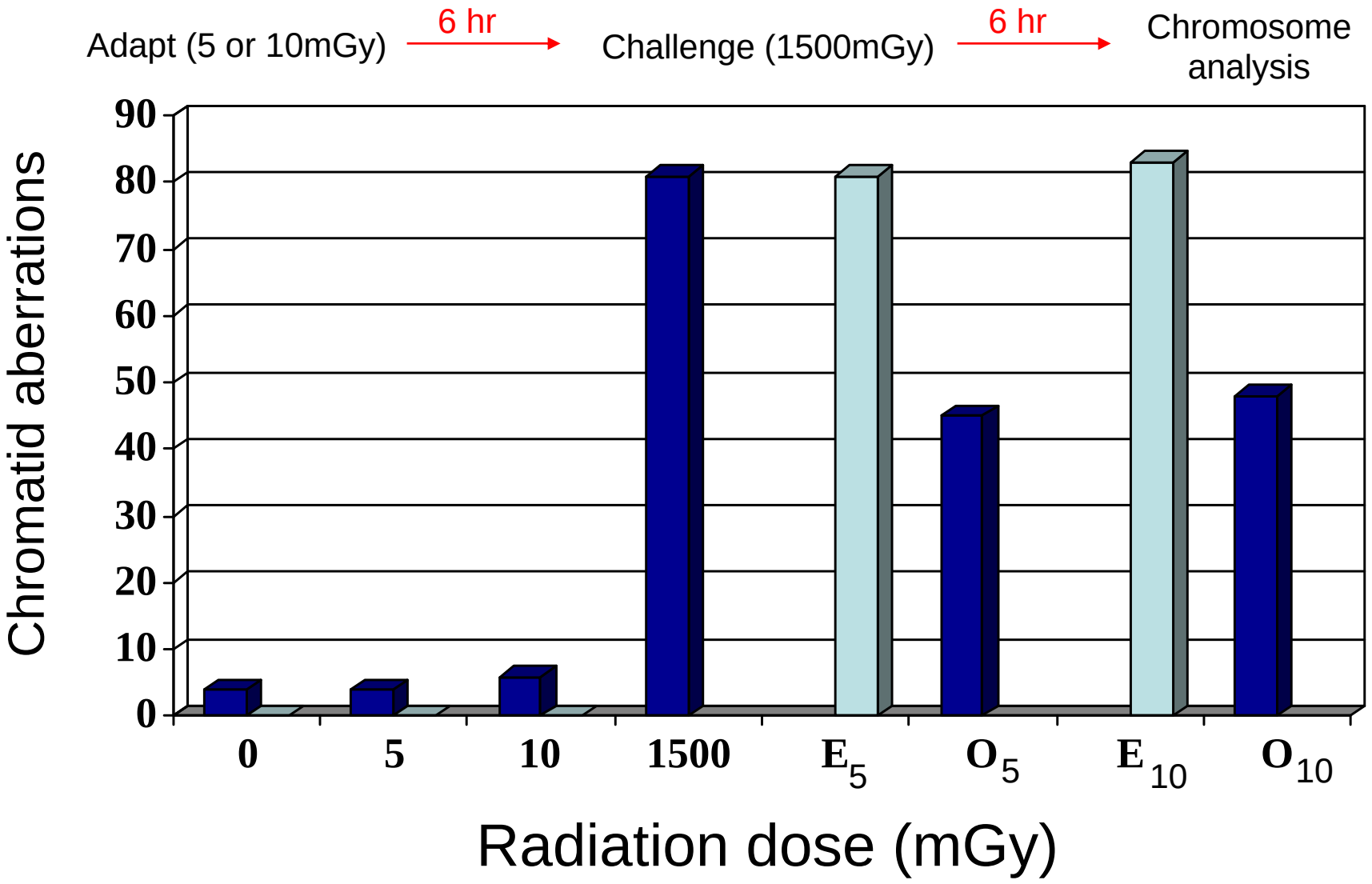
Less than linearity:

Beneficial bystander effects

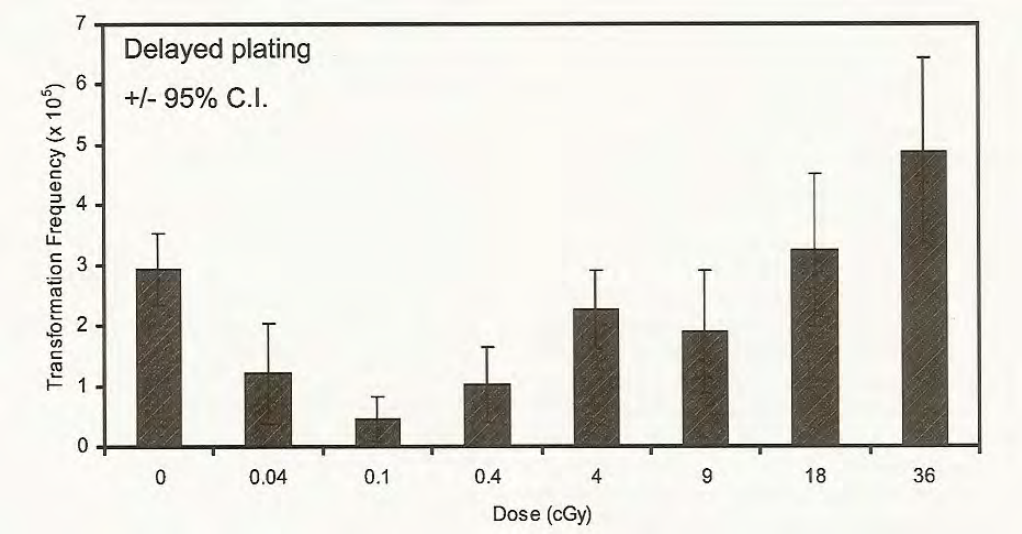
Adaptive responses



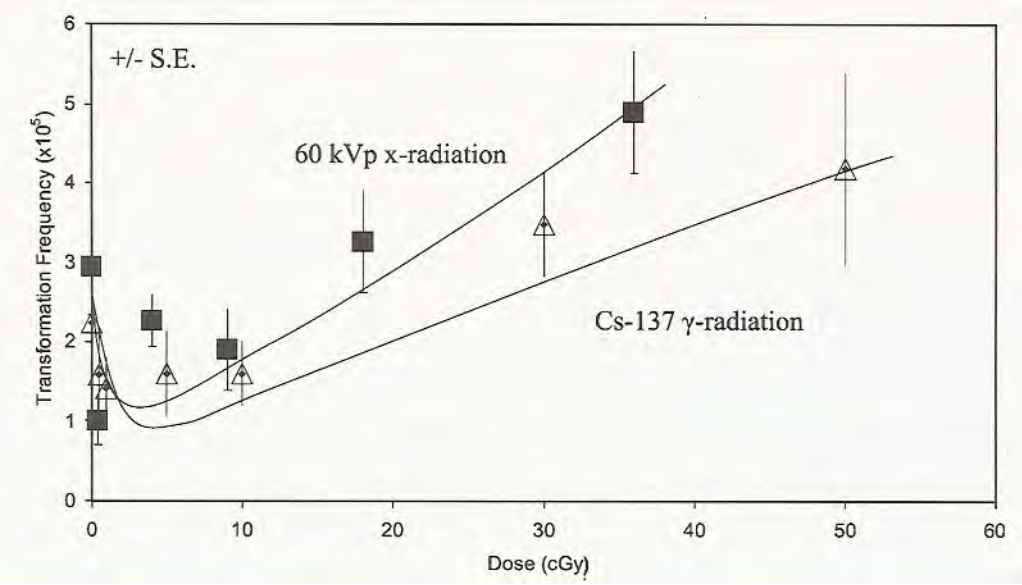
Adaptive Responses: Wolff Adaptation



Adaptive Responses: Low adapting doses reduce the background (spontaneous) levels of DNA damage



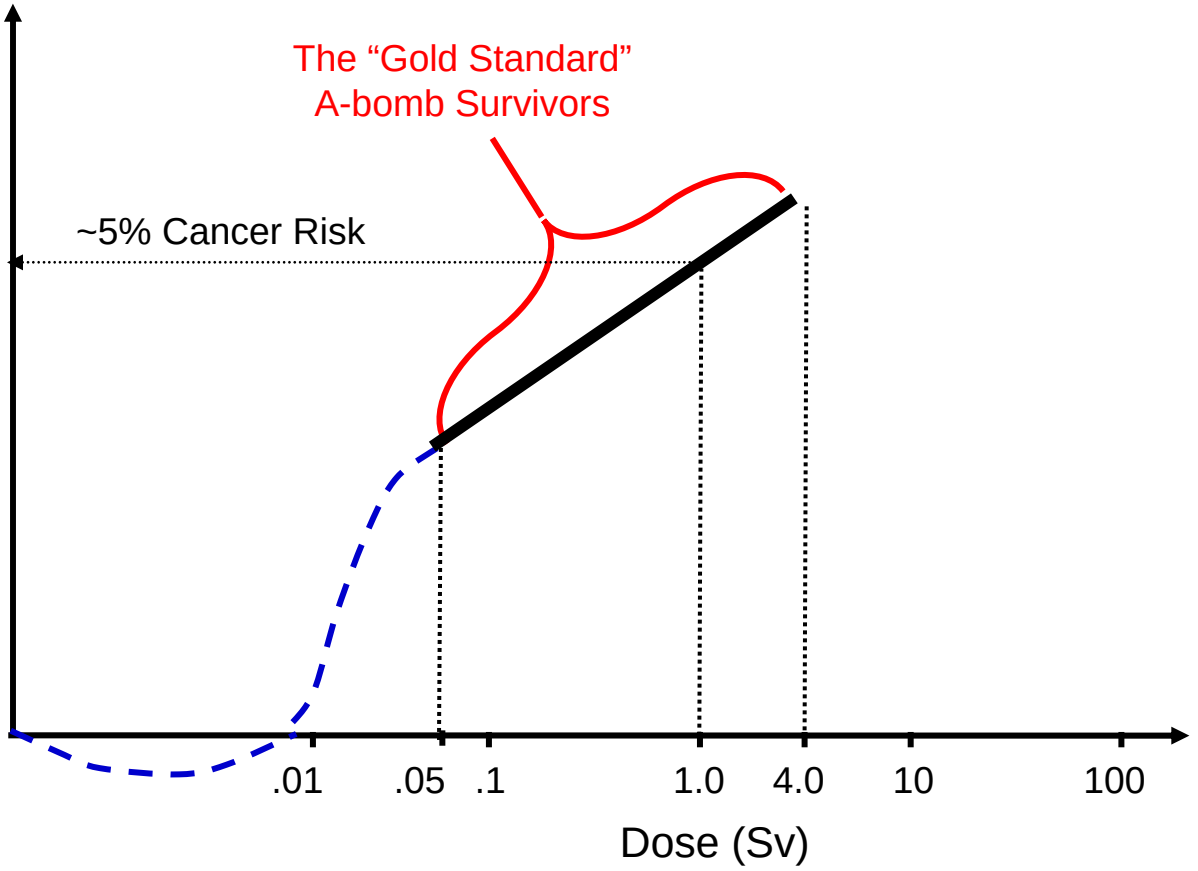
Dose dependence for neoplastic transformation by 60kVp x-rays

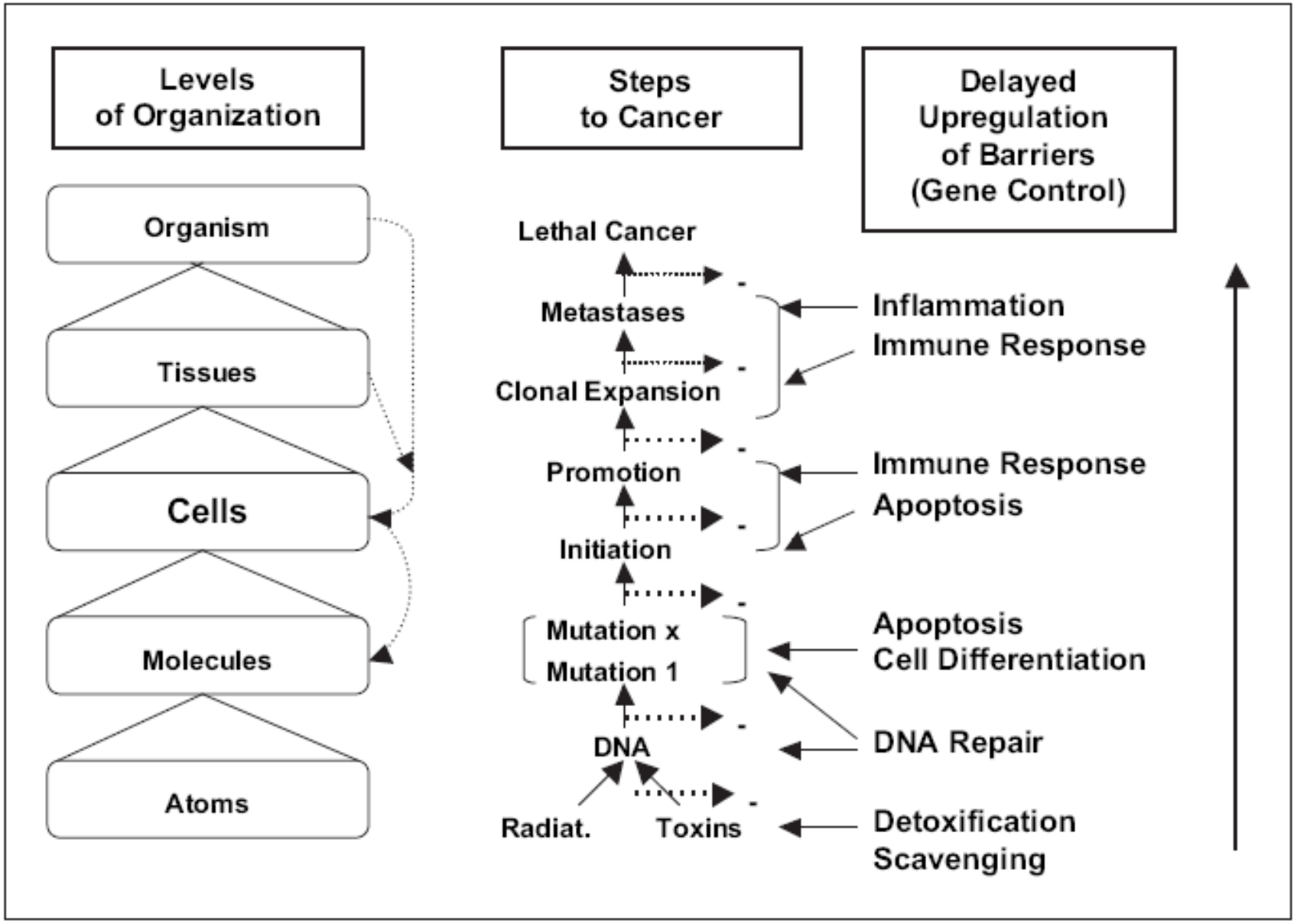


Comparison of the dose dependence for neoplastic transformation by 60kVp x-rays and Cs-137 gamma-rays

Redpath et al., I.J.☐R.B. 79, 235-40 (2003)

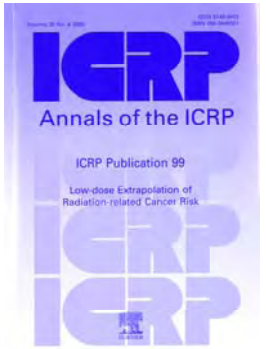
Hormesis (the “H” word): complex biological systems have physiological barriers against damage and disease. Primary damage linear with dose, secondary damage not. Cellular processes block damage propagation to clinical disease.





Feinendegen et al., Exp. Hem. 35, 37-46 (2007)

ICRP Publication 99, (2005) Conclusions, page 112



(264) When considered as a whole, the emerging results with regard to a radiation-related adaptive response, genomic instability, and bystander effects suggest that the risk of low-level exposure to IR is uncertain, and a simple extrapolation from high-dose effects may not be wholly justified in all instances. However, a better understanding of the mechanisms for these phenomena, the extent to which they are active in vivo, and how they are inter-related is needed before they can be evaluated as factors to be included in the estimation of potential risk to the human population of exposure to low levels of IR. It should be recognised that information from direct epidemiological measure of cancer risk will, by definition, include any potential contribution from these mechanistic processes, and may therefore provide insights about them, subject to the constraints of low statistical power at low doses.

Challenges For The Future:

Mechanistic studies essential

- Do “hit” and non-targeted cells respond differently?
- Nature of bystander signal and response
- Low dose effects and the cell survival curve
- Differences between high and low LET radiation

Biological significance of non-targeted effects?

- Cells / tissues communicate
- Impact on non-cancer diseases?
  - Inflammatory responses and cardiovascular
- Are effects BENEFICIAL or DETRIMENTAL?
- Higher doses - built into cancer risk estimation
  - What if not limited to a specific organ?
- Individual sensitivity / susceptibility
- Now science immature, no impact on protection

Factors that Modify Radiation-Induced Carcinogenesis

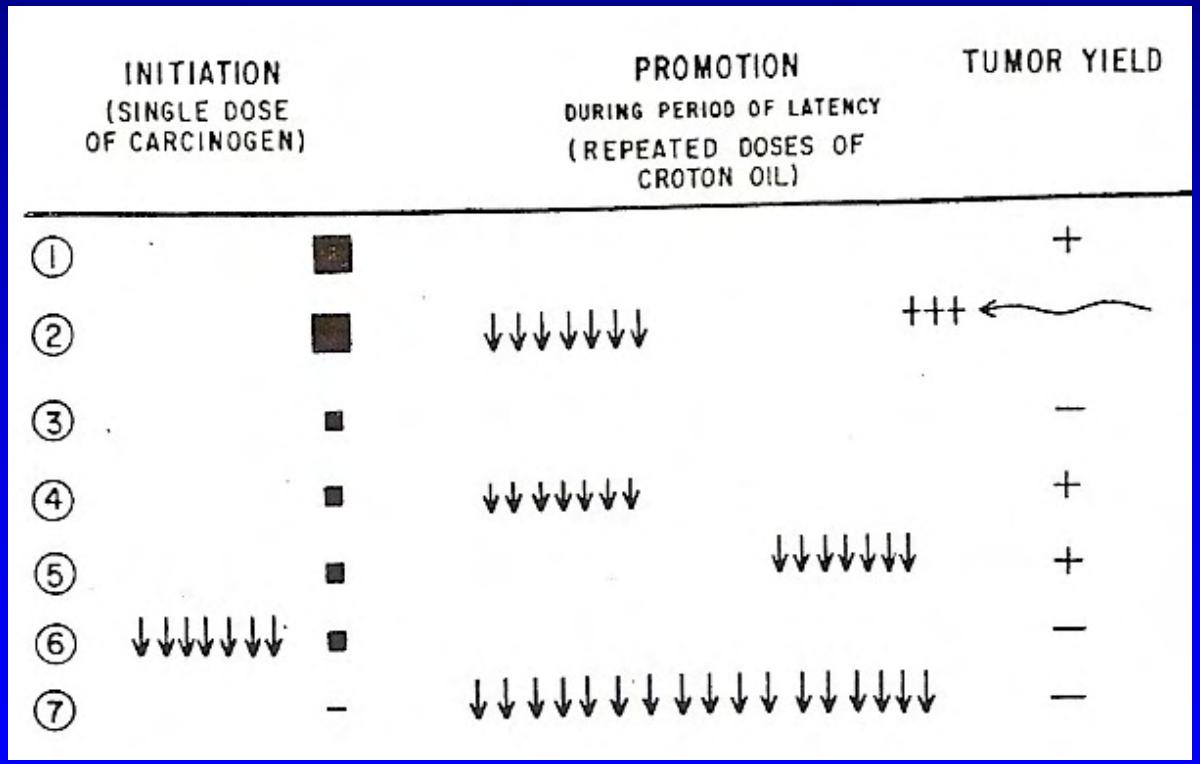
Ann R. Kennedy

University of Pennsylvania
School of Medicine,
Philadelphia, PA

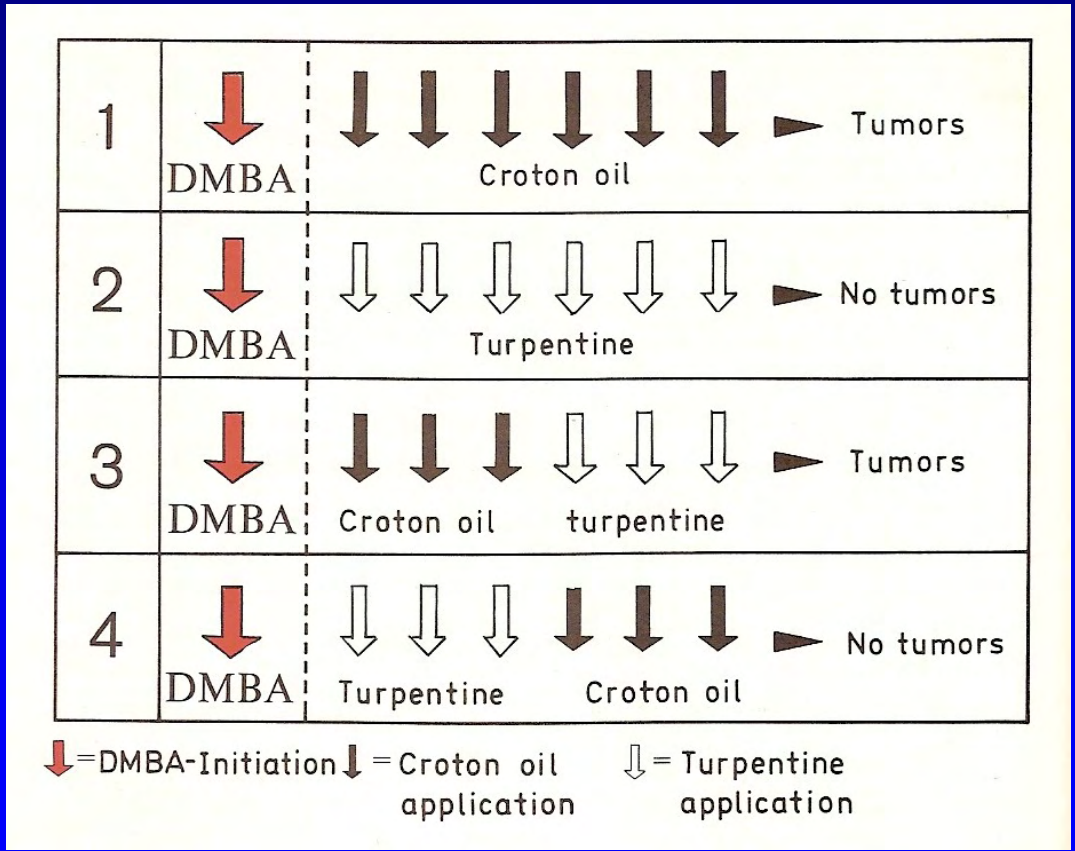
Some Examples of Modifying Factors for Radiation Carcinogenesis

- Specific characteristics of the radiation (e.g., radiation type and dose, dose-rate, dose fractionation, dose distribution, etc.)
- Genetic characteristics
- Life style and environmental factors, including diet
- Specific modifying factors for radiation carcinogenesis (e.g., cocarcinogens, promoting factors, suppressing factors)

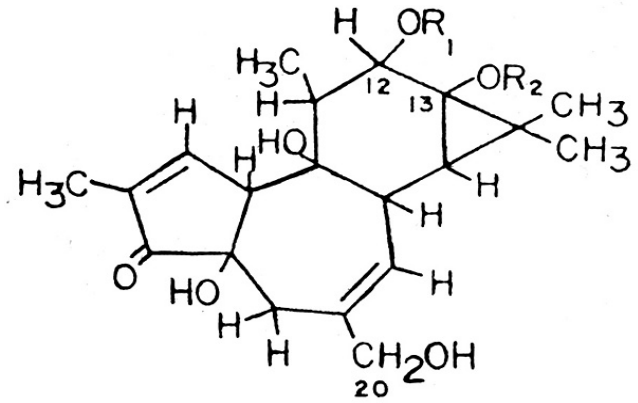
Carcinogenesis Occurs in Stages (e.g., Initiation, Promotion and Progression)- Slide from Ryser, New Engl. J. Med. 285: 721-734, 1971)



Promoting Agents Can Have Different Effects at Different Stages of Carcinogenesis (slide from Suss, Kinzel and Scribner, 1973)



12-O-Tetradecanoyl-phorbol-13- acetate (TPA), the most active promoting agent in croton oil



COMPOUND	R_1	R_2	ACTIVITY
Tetradecanoyl-phorbol-acetate	Tetradecanoate	Acetate	++++
Phorbol-didecanoate	Decanoate	Decanoate	++
Phorbol-dibenzoate	Benzoate	Benzoate	+
Phorbol-diacetate	Acetate	Acetate	0
Phorbol	H	H	0

Characteristics of Initiating and Promoting Agents (from Weinstein, 1978)

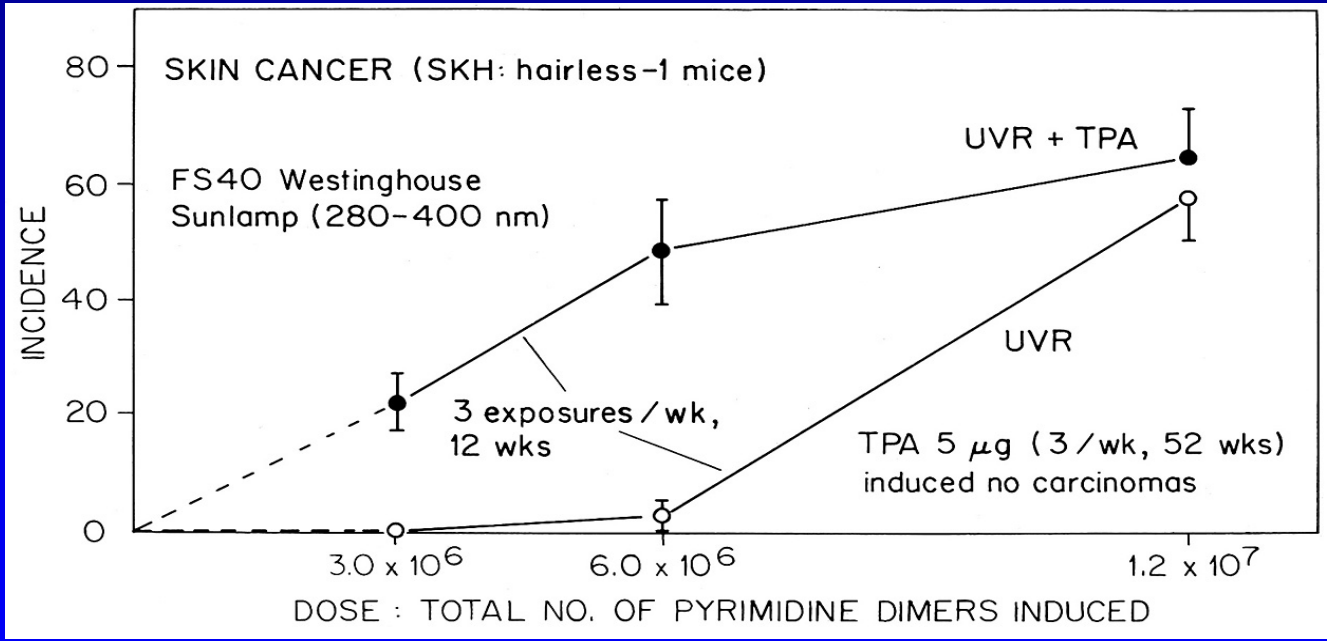
TABLE 7
BIOLOGIC PROPERTIES OF INITIATING AND PROMOTING AGENTS[36,47]

Initiating Agents	Promoting Agents
1. Carcinogenic by themselves—"solitary carcinogens"	1. Not carcinogenic alone
2. Must be given before promoting agent	2. Must be given after the initiating agent
3. Single exposure sufficient	3. Require prolonged exposure
4. Action "irreversible" and additive	4. Action reversible (at early stage) and not additive
5. No apparent threshold	5. Probable threshold
6. Yield electrophiles—bind covalently to cell macromolecules	6. No evidence of covalent binding
7. Mutagenic	7. Not mutagenic

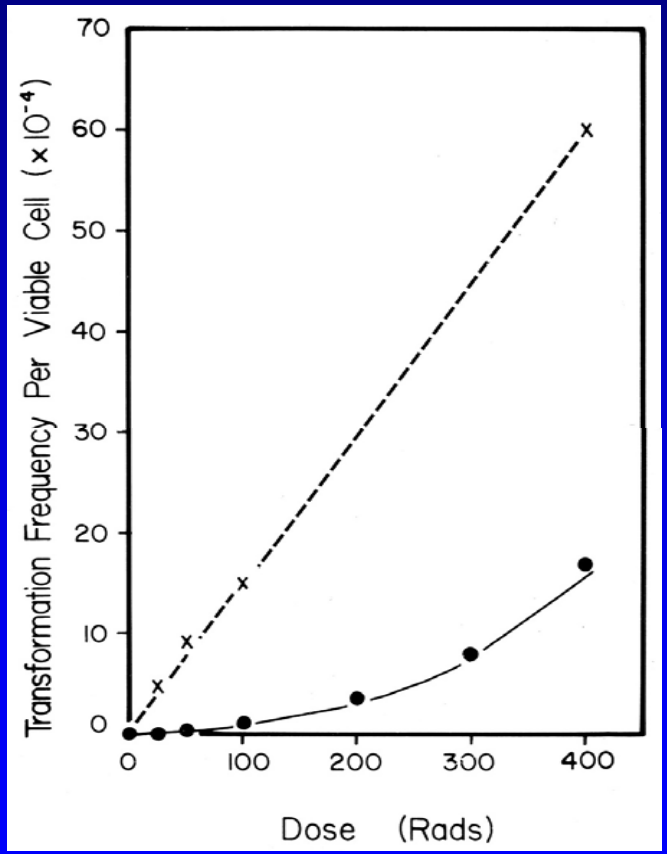
First Observation (?) of Promotion of Radiation Carcinogenesis Induced by Thallium-204 (Shubik, Goldfarb, Ritchie, and Lisco. Latent Carcinogenic Action of Beta-Irradiation on Mouse Epidermis, Nature, 1953)

Group	No. of animals	Irradiation (rep.)	Croton oil	Animals with tumours	Total No. of tumours	Survivors (8 months)
I	26	800	0	0	0	21
II	30	800	twice weekly	6	13	17
III	30	0	twice weekly	0	0	20

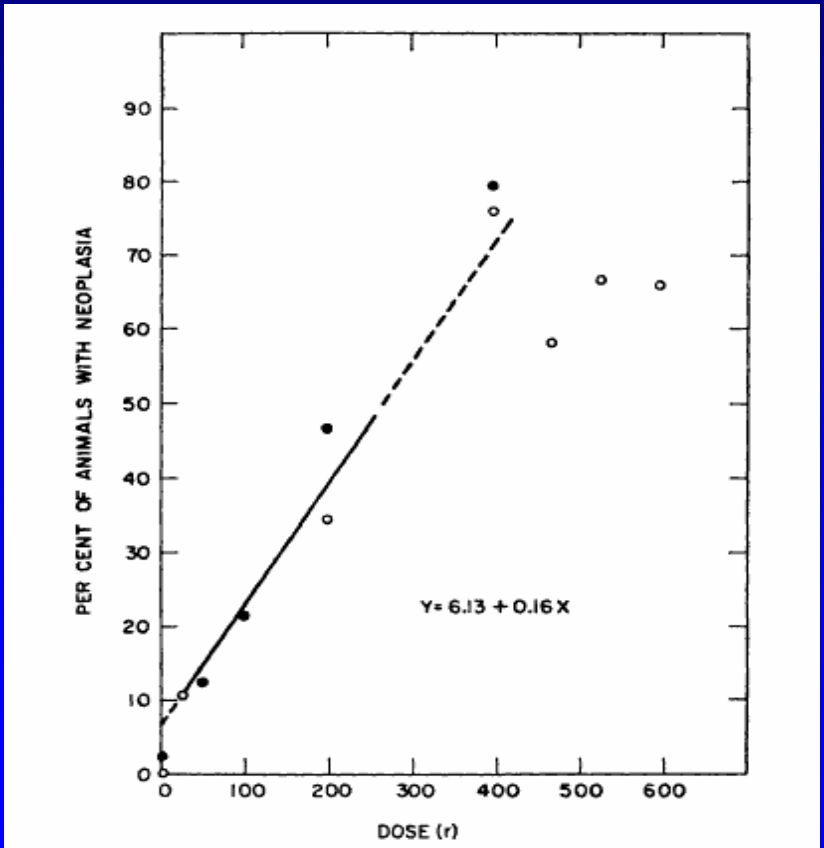
Initiation and Promotion of Mouse Skin Carcinogenesis by Ultraviolet Light and TPA (Slide from Fry and Ley, 1978)



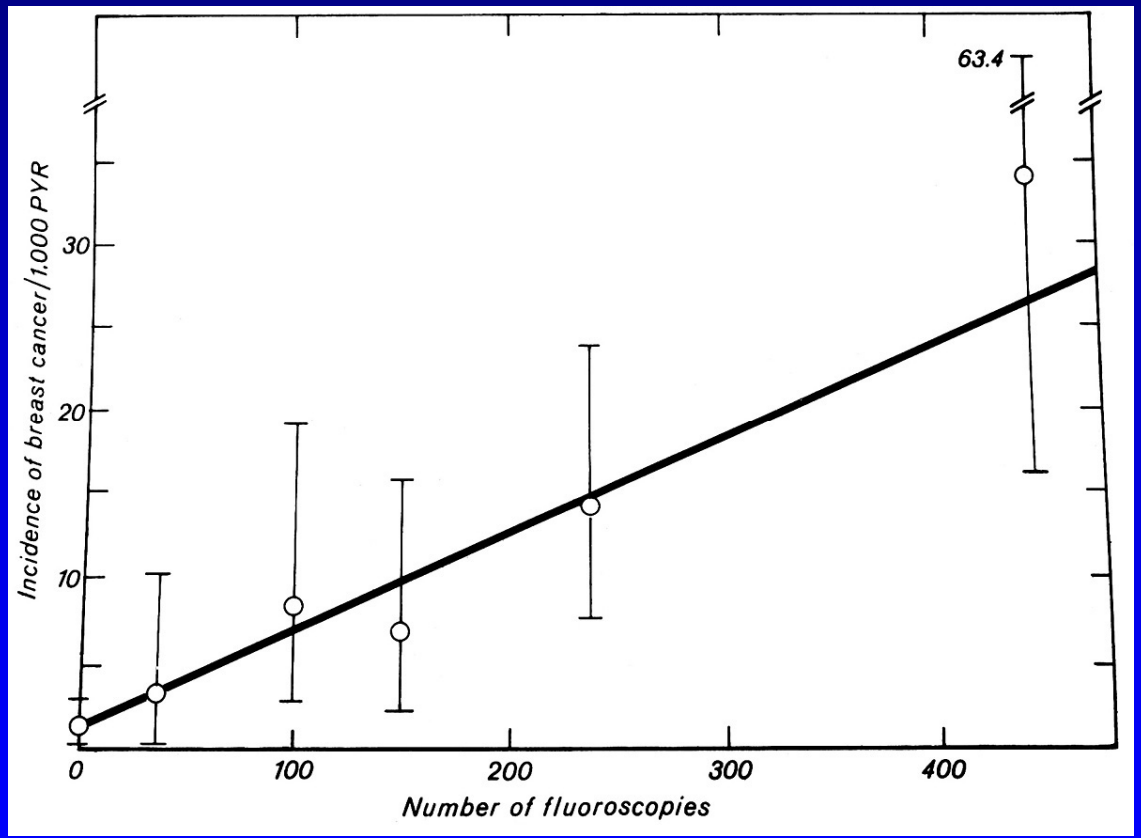
Initiation and Promotion of Radiation Transformation *in vitro* (Lower curve-Radiation alone, Upper curve: Radiation + TPA); slide from Little and Kennedy, 1982)



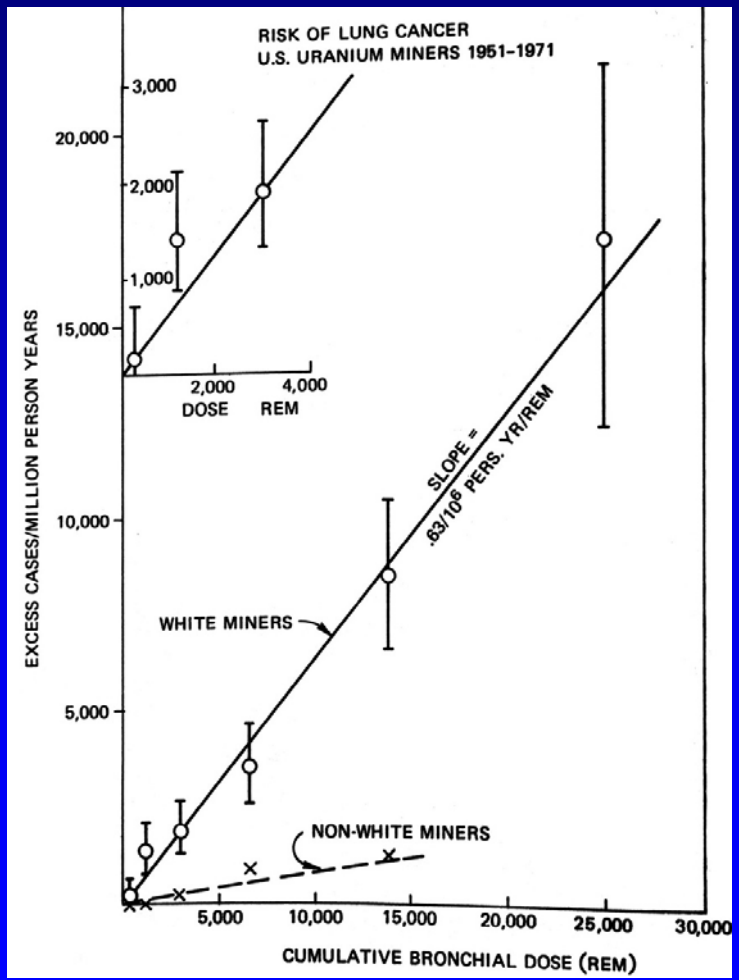
Linear-Dose Response Relationship for Radiation Induced Breast Cancer in Animals (From: Bond et al., 1960).



Example of Linear Dose-Response Curve for Human Radiation Induced Carcinogenesis - Breast



Potential Example of Promotion of Radiation Carcinogenesis - in Smoking Miners



Promotion of Radiation Induced Lung Carcinogenesis by Instillations of Saline (from Little et al., 1978 and Shami et al. 1982)

EFFECT OF SUBSEQUENT DOSES OF SALINE ON LUNG CANCER INDUCED BY A SINGLE DOSE OF ^{210}Po

Treatment	Experiment No.	No. of Hamsters with Lung Cancer / Total No. of Hamsters (%)
^{210}Po – Single instillation (75 rads)	1	2/47=4%
	2	0/29=0%
^{210}Po – Followed 5 months later by 7 instillations of saline	1	18/82=22%
	2	12/27=44%

Prevention of Radiation-Induced Carcinogenesis

- Dietary Restriction (Caloric)
- Cancer “Chemoprevention” (i.e., the retardation, blockade or reversal of the process involved in carcinogenesis (which leads to malignancy) by natural or synthetic agents (includes drugs, dietary supplements, etc.)
- Examples of cancer chemopreventive agents that have been shown to prevent radiation induced carcinogenesis: hormones (e.g., cortisone), retinoids (vitamin A analogues), antioxidants, the soybean derived protease inhibitor known as the Bowman-Birk Inhibitor, etc.

Caloric Restriction Suppresses Radiation Induced Myeloid Leukemia in C3H/He Mice (Yoshida et al., PNAS, 1997) (all animals received 3 Gy total body radiation; diets: 3C-control; 3RA and 3RB – restricted diet groups)

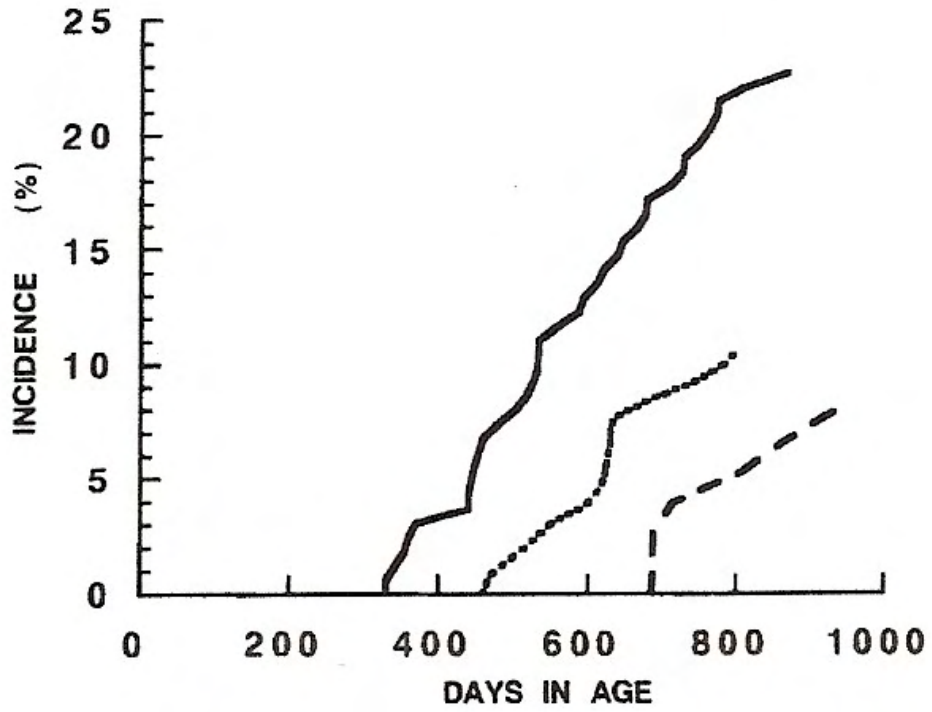
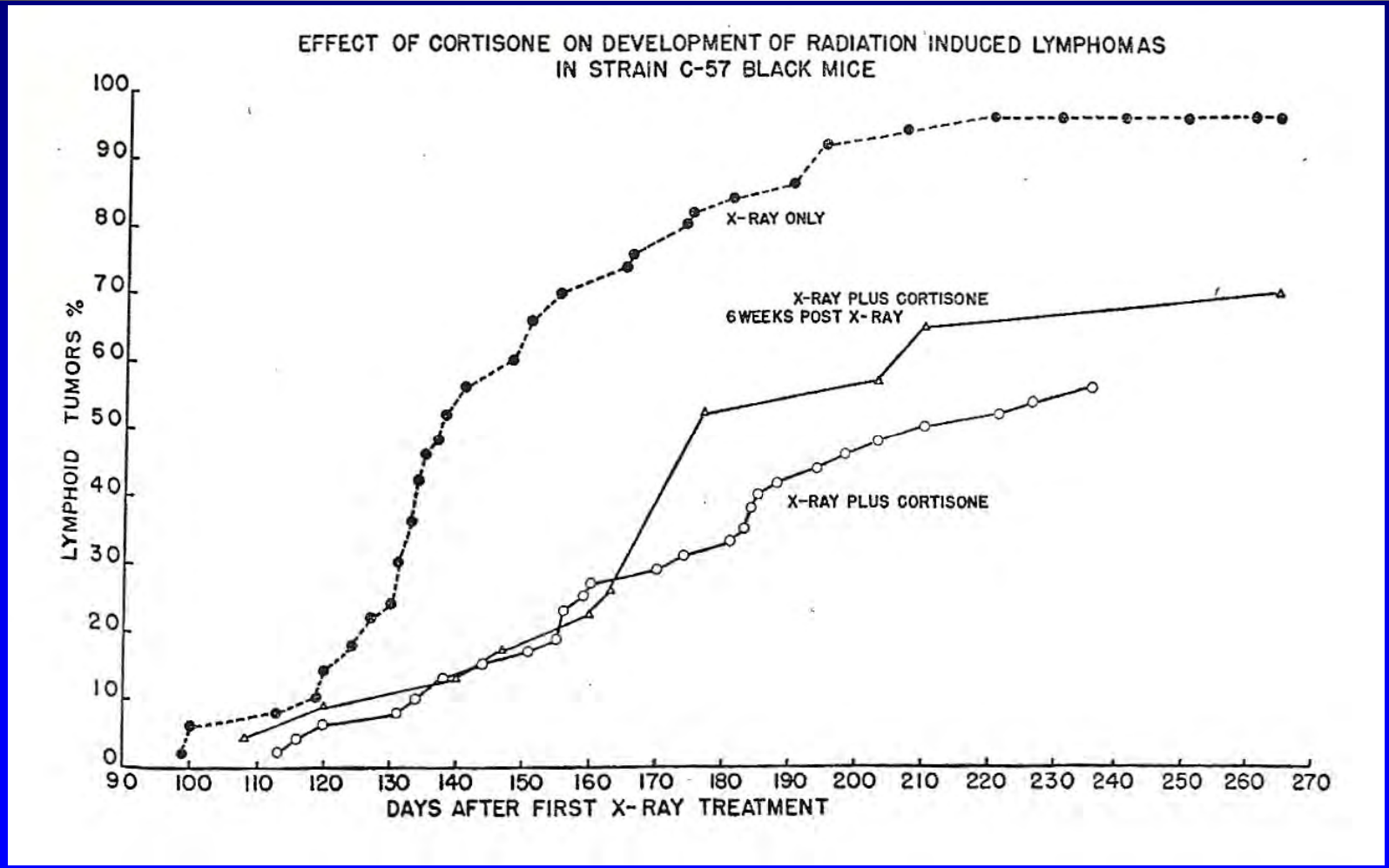
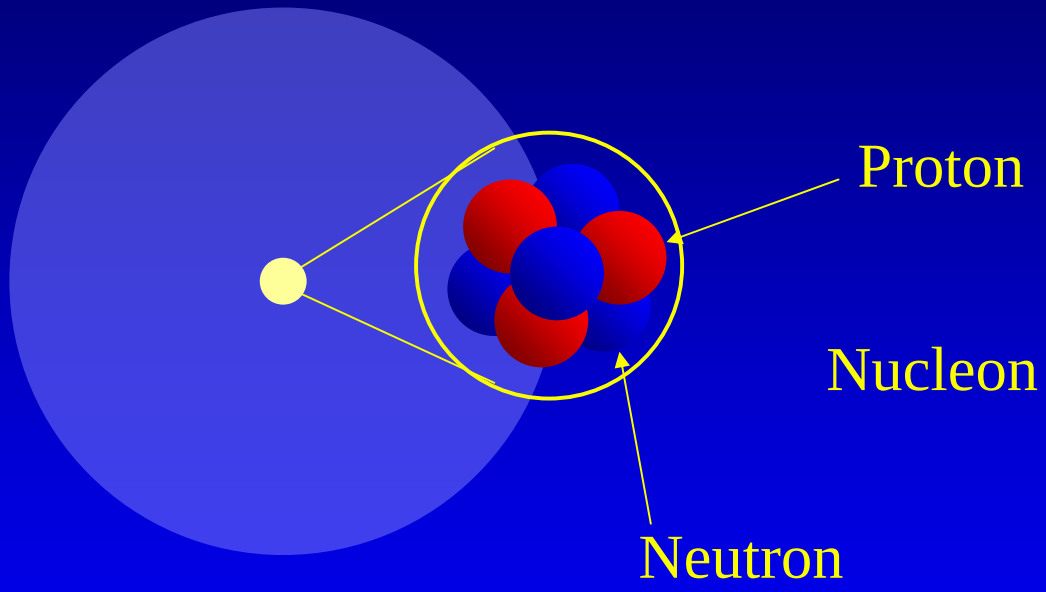


FIG. 5. Cumulative incidence of myeloid leukemia. The latent period of the myeloid leukemia in 3RA (·····) and 3RB (– – –) was prolonged as compared with 3C (——).

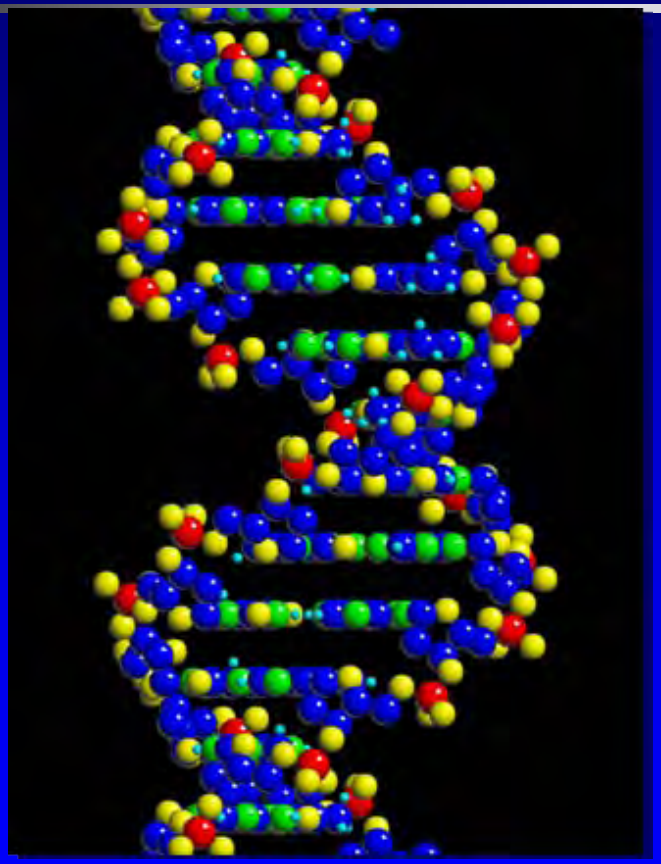
Cortisone Suppresses Radiation Induced Lymphomas in Mice (Kaplan, Marder and Brown, Cancer Res., 1951

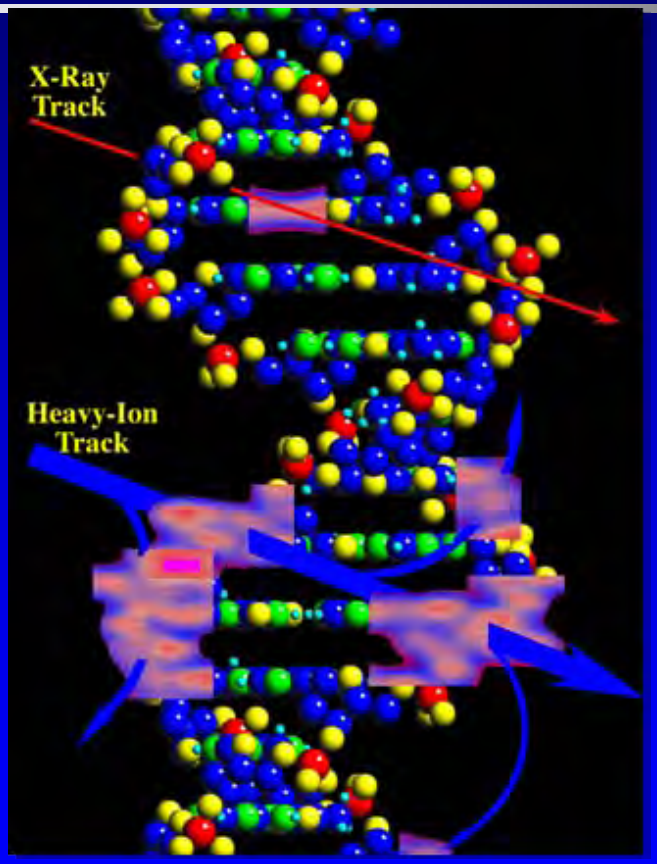


Several recent studies on the suppression of radiation carcinogenesis have been performed with heavy ions from the Brookhaven National Laboratory (NSRL)



DNA Damage –X-rays vs. Heavy Ions (slide from Brookhaven National Laboratory – NSRL)

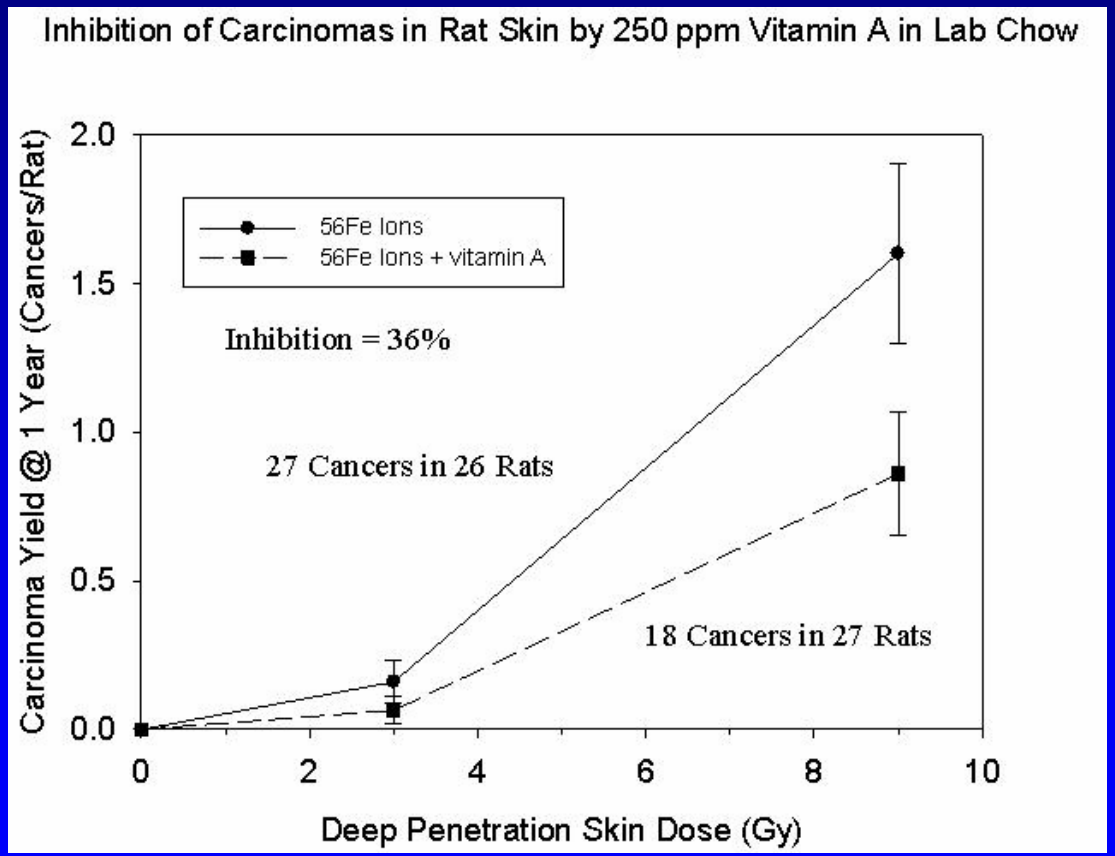




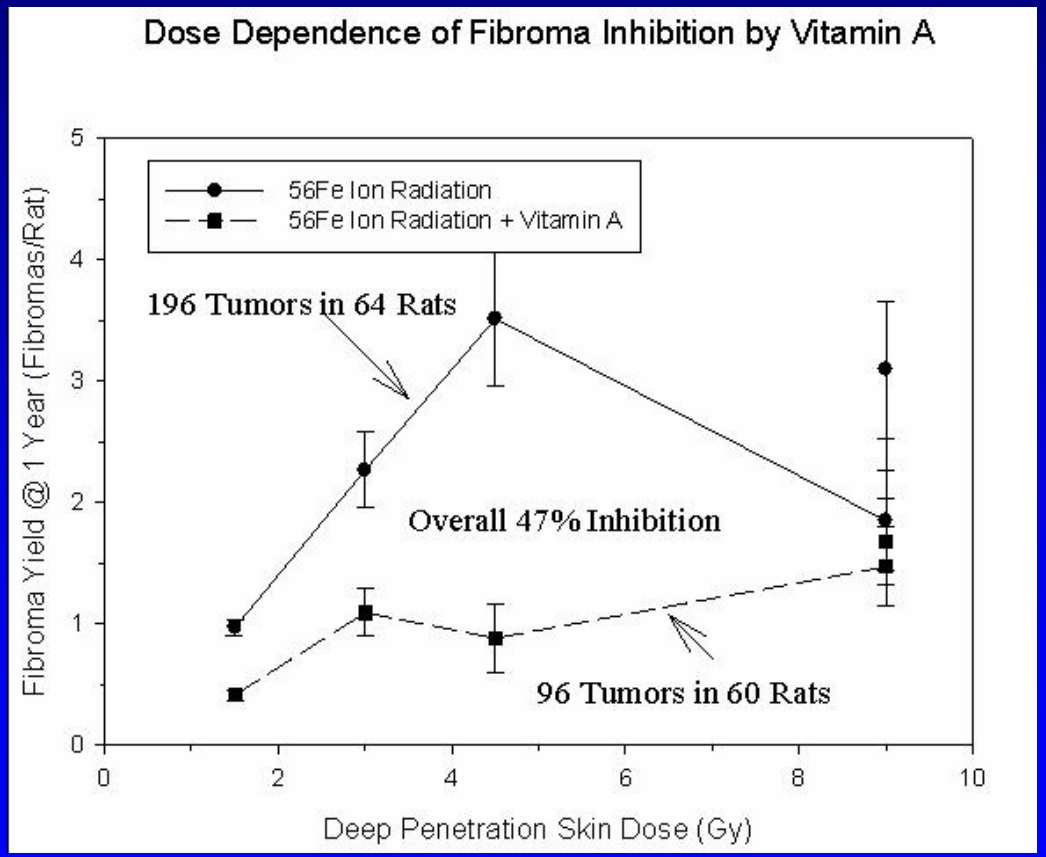
P. Saganti

BROOKHAVEN NATIONAL LABORATORY NSRL

Suppression of High LET Radiation (Iron Ion-) Induced Skin Cancer in Rats by a Retinoid (From: Burns et al., 2007)



Suppression of High LET Radiation (Iron Ion-) Induced Fibromas in Rats by a Retinoid (From: Burns et al., 2007)

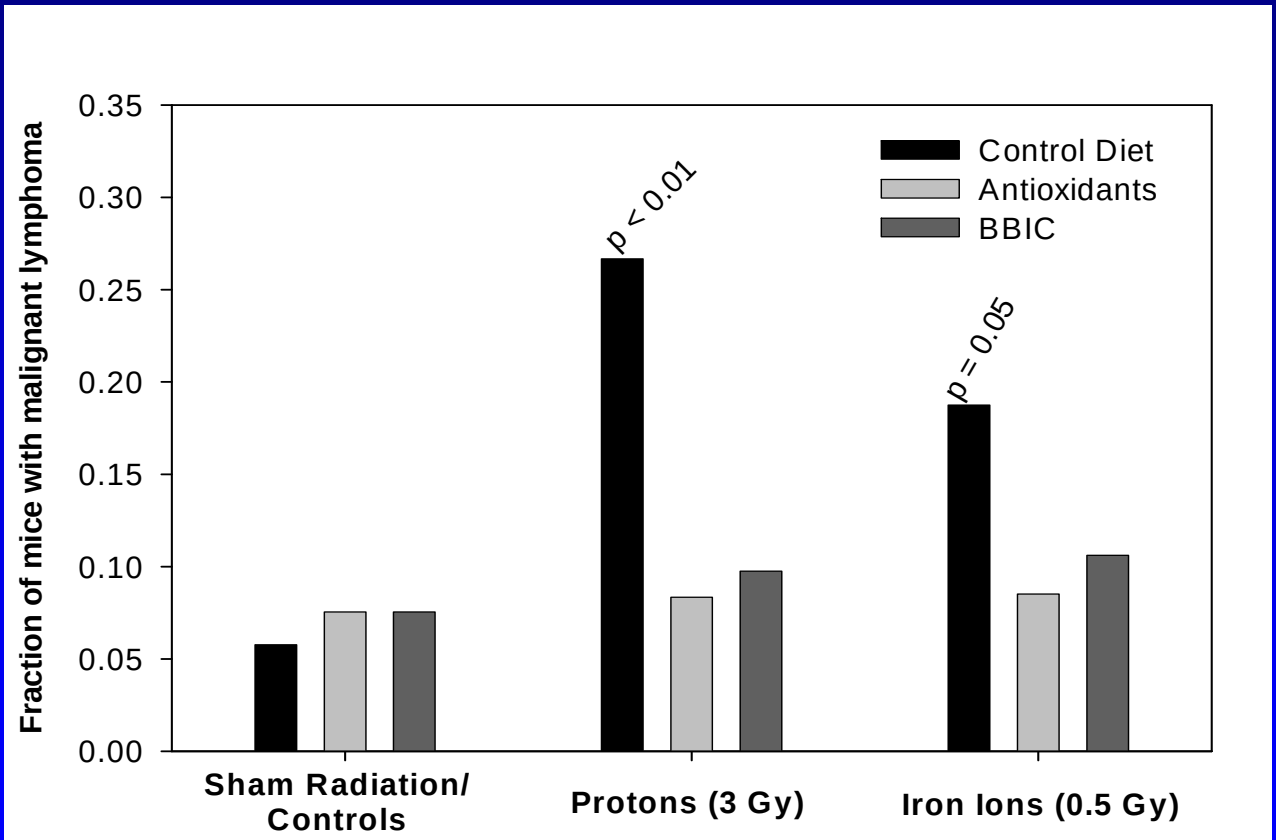


Oxidative Stress

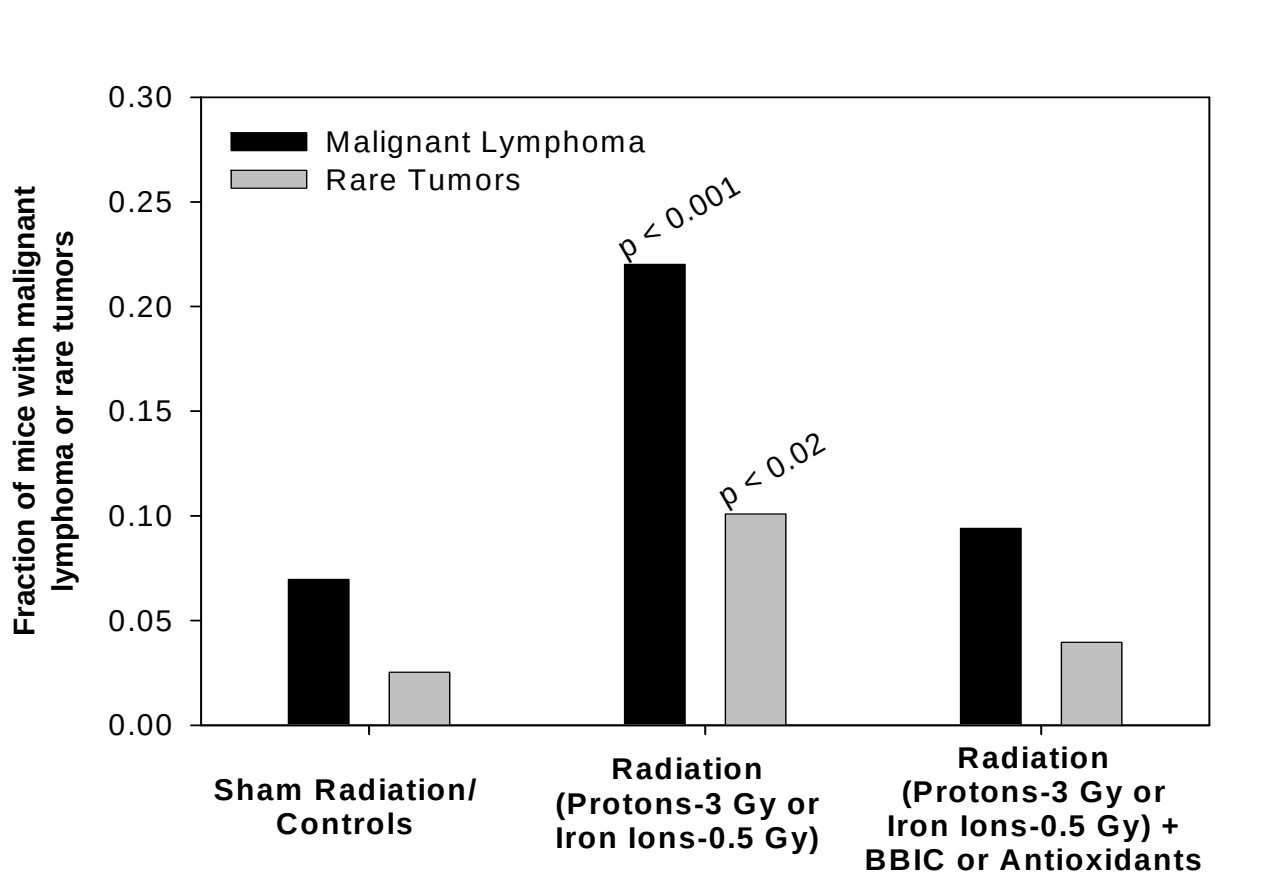
Oxidative Stress results whenever there is an imbalance between the pro-oxidants and antioxidants, favoring the pro-oxidants. By definition, all types of ionizing radiation generate ions. These ions can lead to the formation of oxygen reactive free radicals; thus, ionizing radiation is a pro-oxidant.

Agents with the ability to prevent radiation induced oxidative stress in both *in vivo* and *in vitro* systems: vitamin C, vitamin E succinate, L-selenomethionine, coenzyme Q10, α-lipoic acid, and N-acetyl cysteine. The ability of these agents to affect downstream effects of radiation induced oxidative stress, such as the induction of cancer, has been determined.

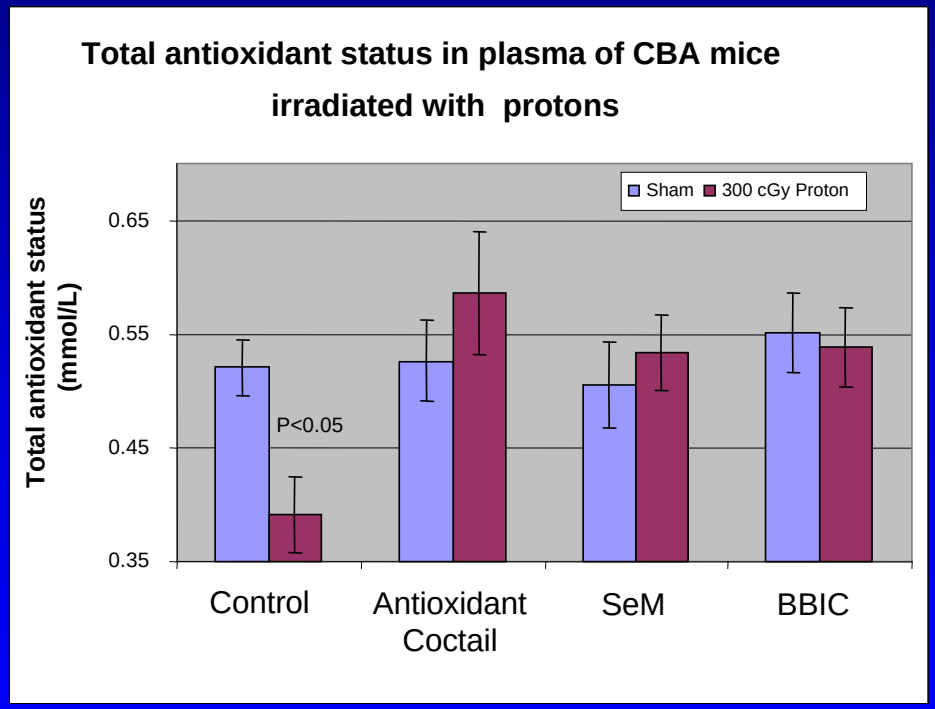
Suppression of Iron Ion or Proton Induced Malignant Lymphoma in Mice By Antioxidants or Bowman-Birk Inhibitor Concentrate (From: Kennedy et al., 2008) (Antioxidants: L-selenomethionine, vitamin C, vitamin E succinate, N-acetyl cysteine, coenzyme Q10 and α-lipoic acid)



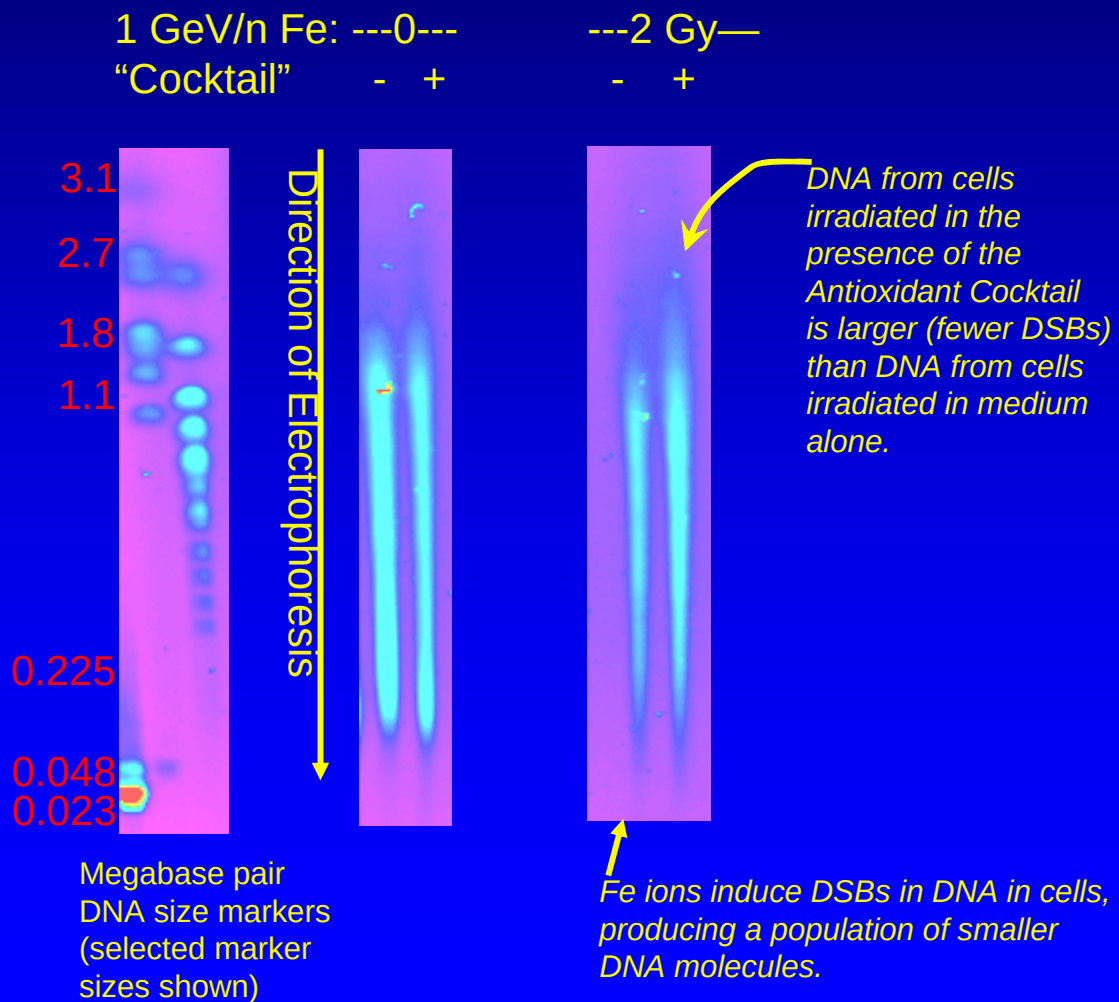
Suppression of Iron Ion or Proton Induced Malignant Lymphoma or Rare Tumors in Mice (From: Kennedy et al., 2008) (BBIC – Bowman-Birk Inhibitor Concentrate; Antioxidants: L-selenomethionine, vitamin C, vitamin E succinate, N-acetyl cysteine, coenzyme Q10 and α-lipoic acid)

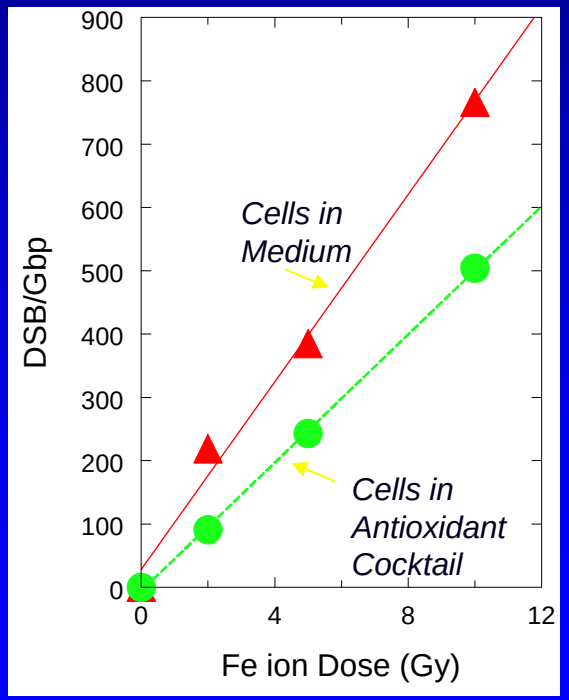


Mixture of Antioxidants, L-selenomethionine or BBIC suppress radiation induced oxidative stress in animals (From: Guan et al., 2006)



Antioxidant Cocktail Reduces DSB Levels Produced by Fe ions (1 GeV/n) in Human Hematopoietic Cells (Sutherland, B., Kennedy, A.R. and Gewirtz, A., unpublished data)





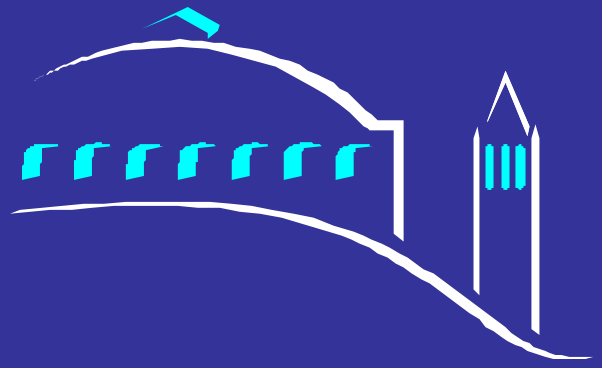
Factors that Modify Carcinogenesis

- Epidemiological evidence suggests that lifestyle factors, such as nutrition, could account for approximately 70% of cancer risk (Doll and Peto, J. Natl Cancer Inst. 66: 1191-1308, 1981).
- Factors other than the random distribution of energy from radiation may be extremely important as determinants of radiation induced cancer incidence and mortality rates.

Concluding Remarks – Kennedy Hypothesis

In Japan, the intake of soybean products is very high and the incidence of western cancers (breast, prostate, colon, etc.) is very low. The offspring of Asian immigrants to the U.S. have approximately the same incidence and mortality rates of the "western" cancers as do Americans. Thus, the very low rates of "western cancers" for the Japanese population consuming the traditional Japanese diet is not likely to be a genetic difference in the population.

Kennedy hypothesis: the low rates of radiation induced cancer in the Japanese population from the atom bombs is due to their consumption of the traditional Japanese diet containing high levels of soybean products (and soybean products have at least 5 reasonably well-characterized anticarcinogenic agents in them).



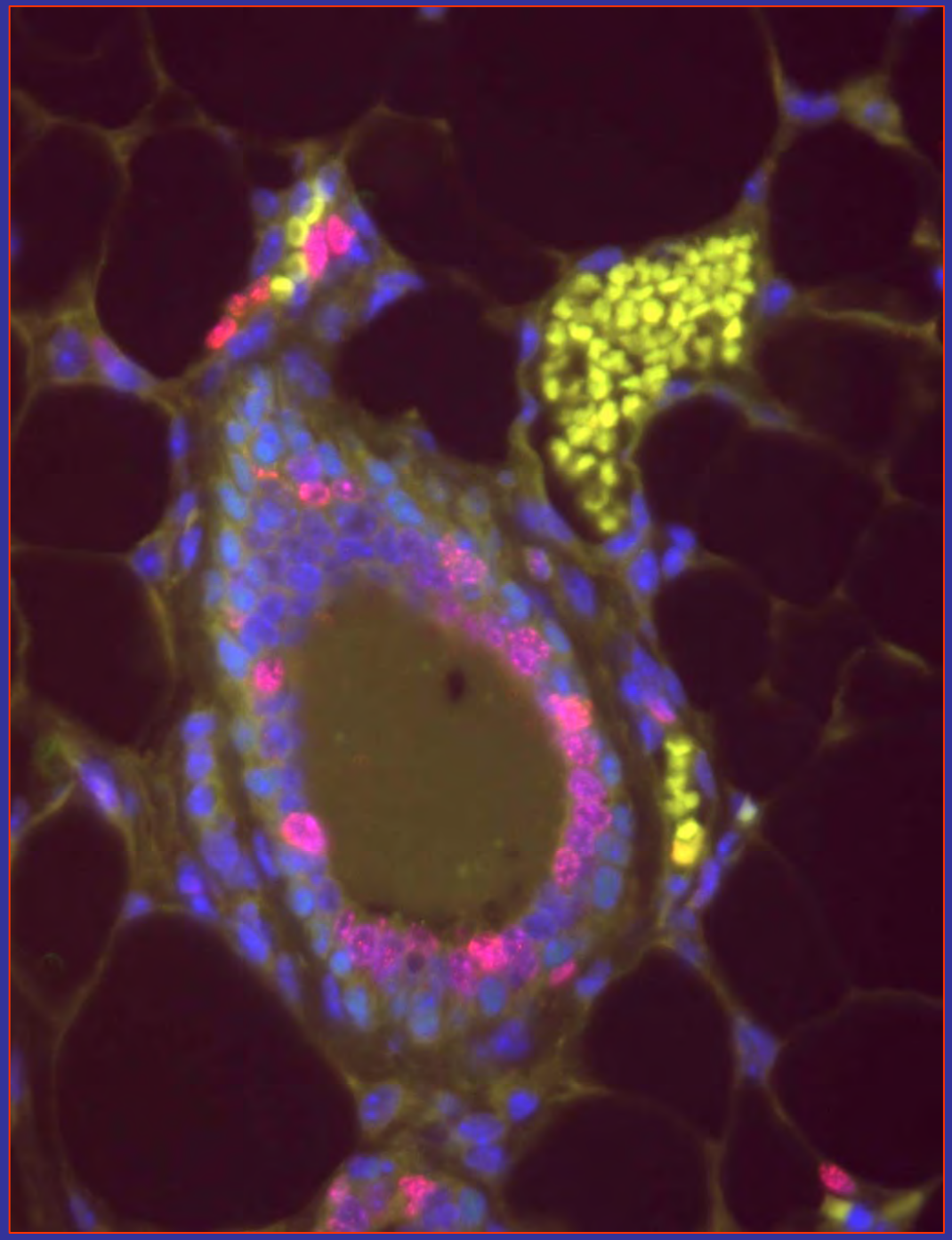
ERNEST ORLANDO LAWRENCE
BERKELEY NATIONAL LABORATORY

Role of Tissue in Radiation Effects

Mary Helen Barcellos-Hoff

Life Sciences Division
Lawrence Berkeley National Laboratory

It takes a tissue to make a tumor.



Health risks from radiation are system, rather than component, driven.

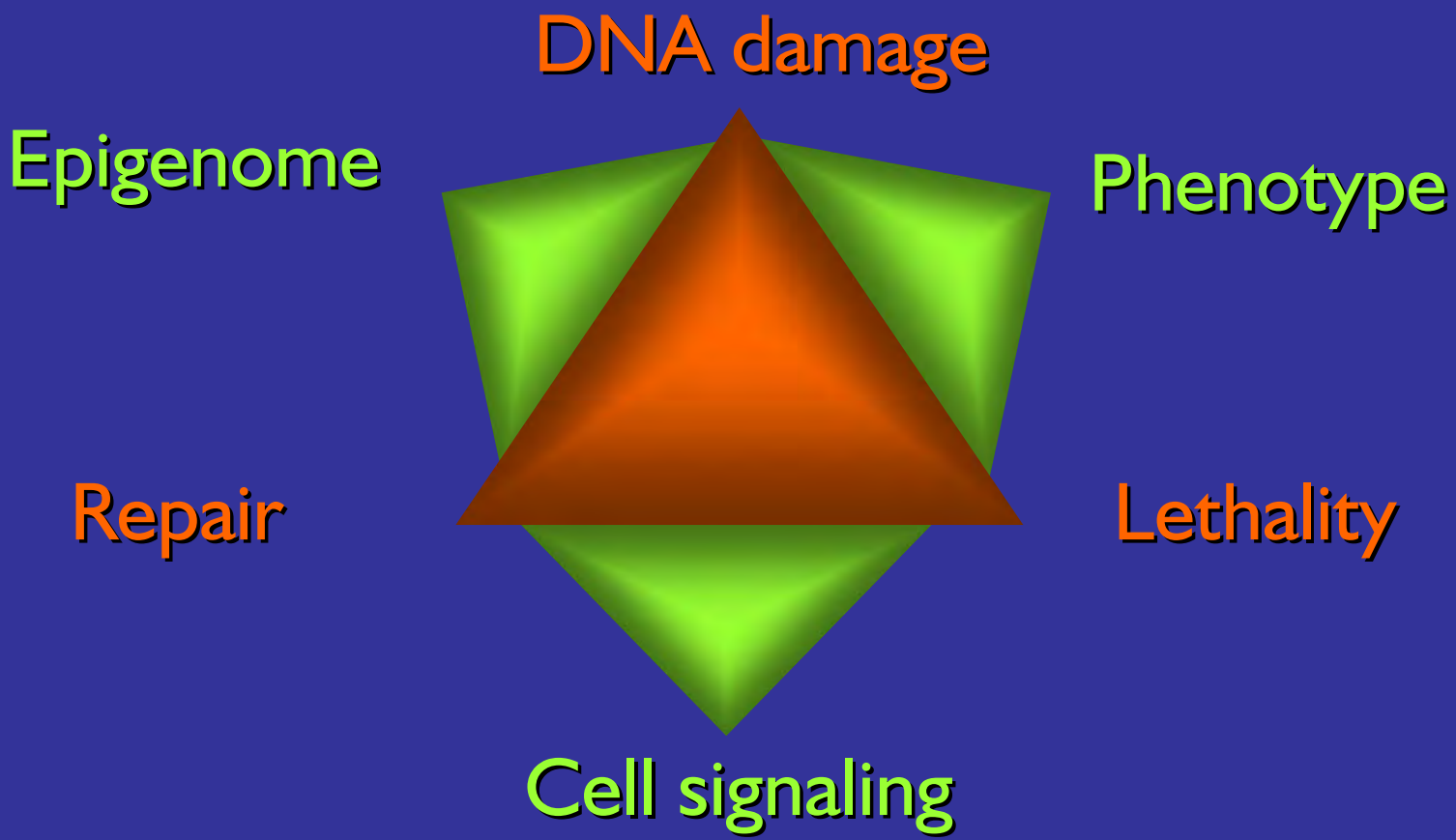
Systems Biology

What distinguishes a **complex** system from a merely complicated one is that some behaviors emerge as a result of altered relationships between the elements.

http://www.biologydaily.com/biology/Systems_thinking

Reconstructing health effects in a biological systems requires understanding the relationships between radiation effects and consequences.

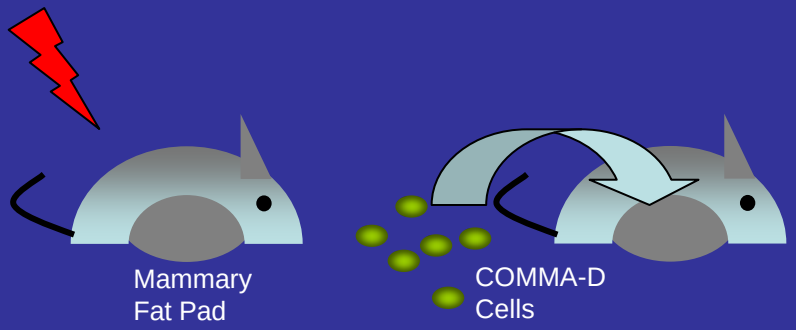
Diverse Radiation Effects



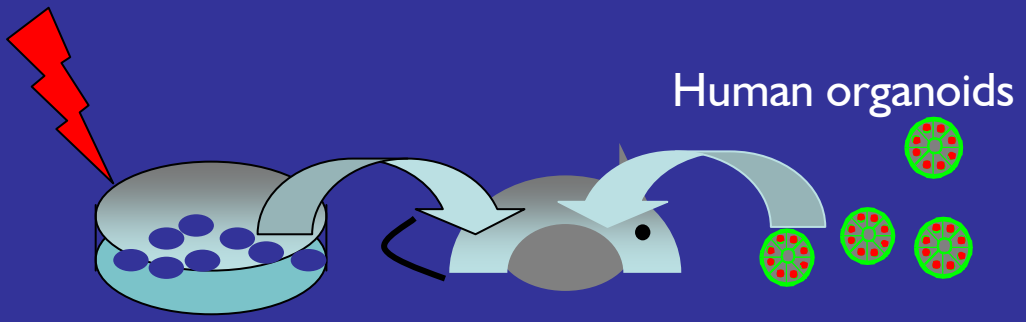
Does radiation induce *emergent phenomenon,* i.e. behaviors that result from altered interactions?

Radiation Chimera Models

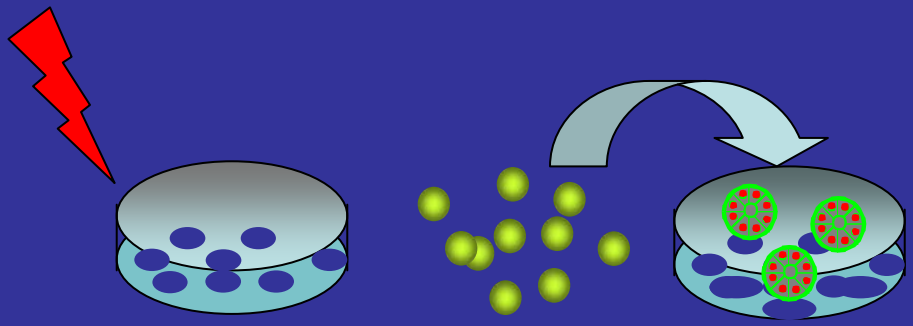
Barcellos-Hoff & Ravani, 2000
Mammary epithelial transplanted to irradiated hosts form tumors



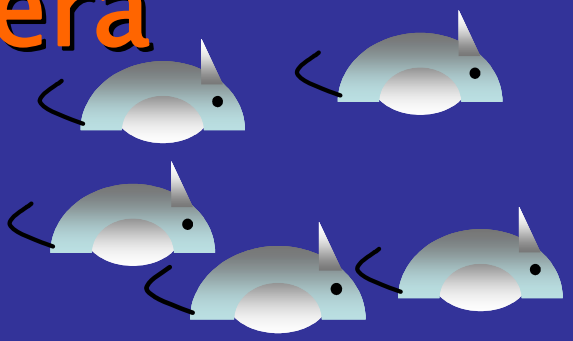
Kupperwasser, 2004
Irradiated fibroblasts humanize stroma to permit transplantation of human epithelium



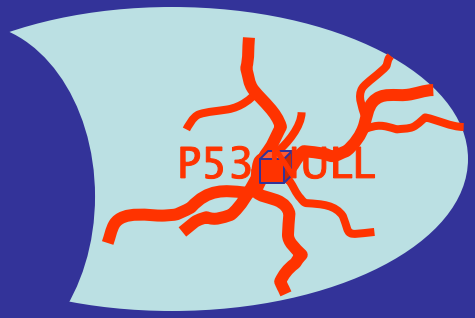
Tsai, 2005
Co-culture of irradiated fibroblasts stimulate malignant progression of non-irradiated cells

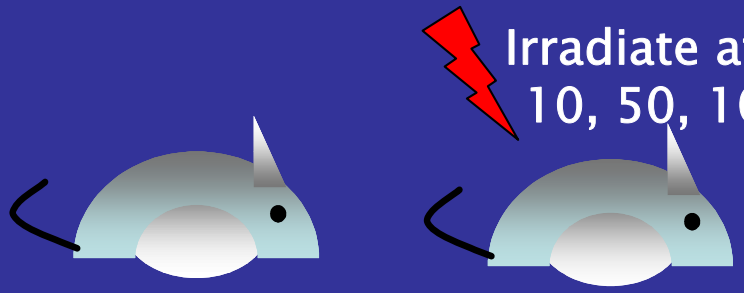


Stromal-Epithelial Radiation Chimera



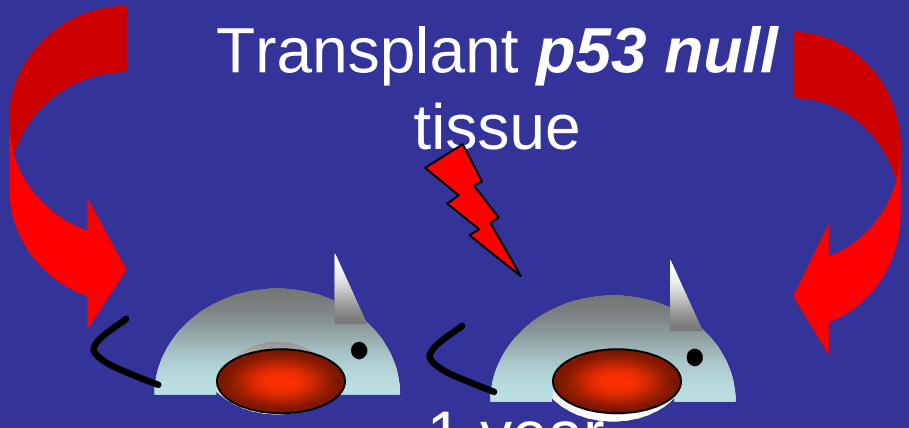
Remove epithelium





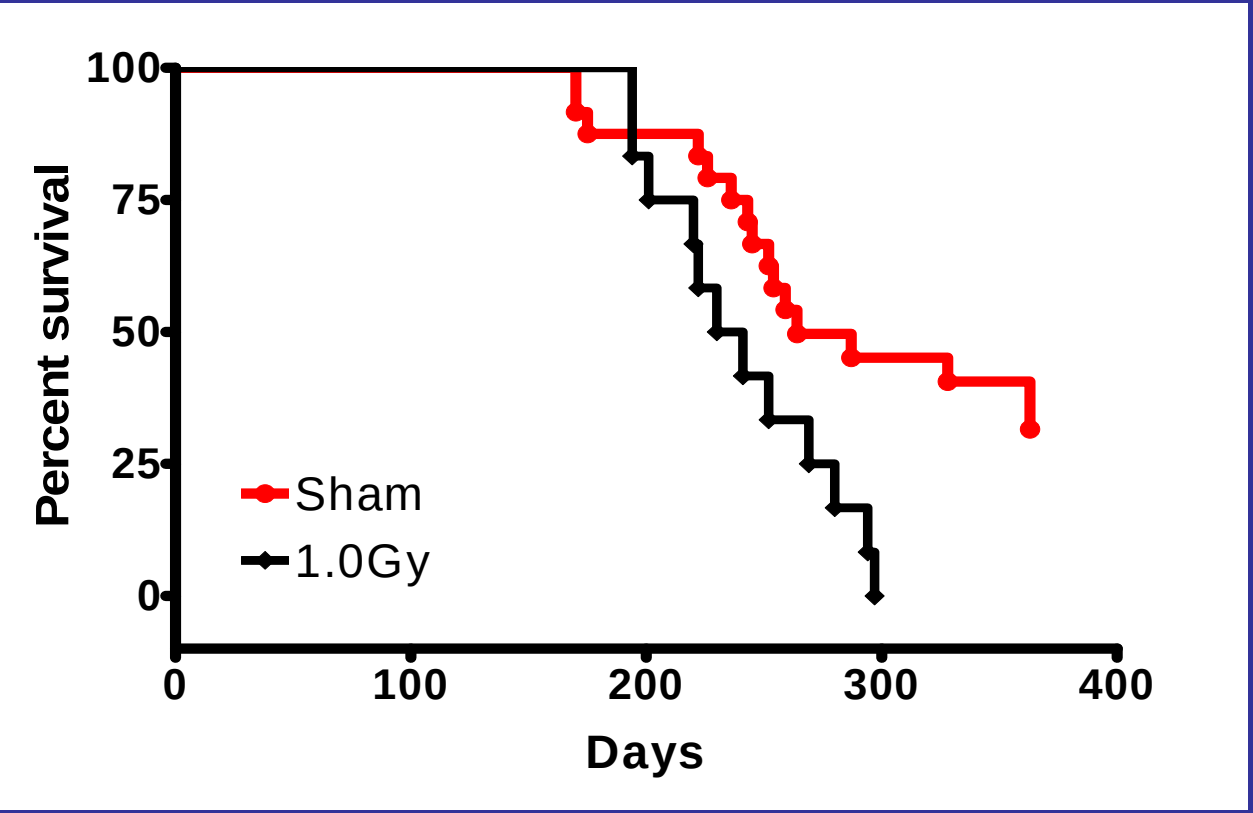
Irradiate at 10 wk
10, 50, 100 cGy

Transplant ***p53 null*** tissue



~1 year

Stromal-Epithelial Chimera Model

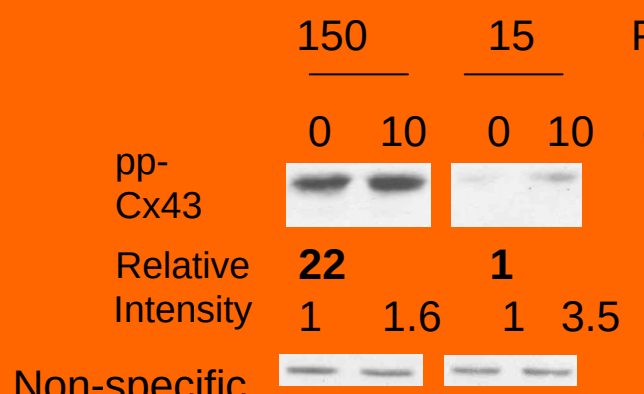


- *p53* null epithelium formed more tumors in the irradiated host (98% vs 68%)
- Host irradiation significantly decreased tumor latency (328 vs 235, p=0.009).

Putting Effects into Context

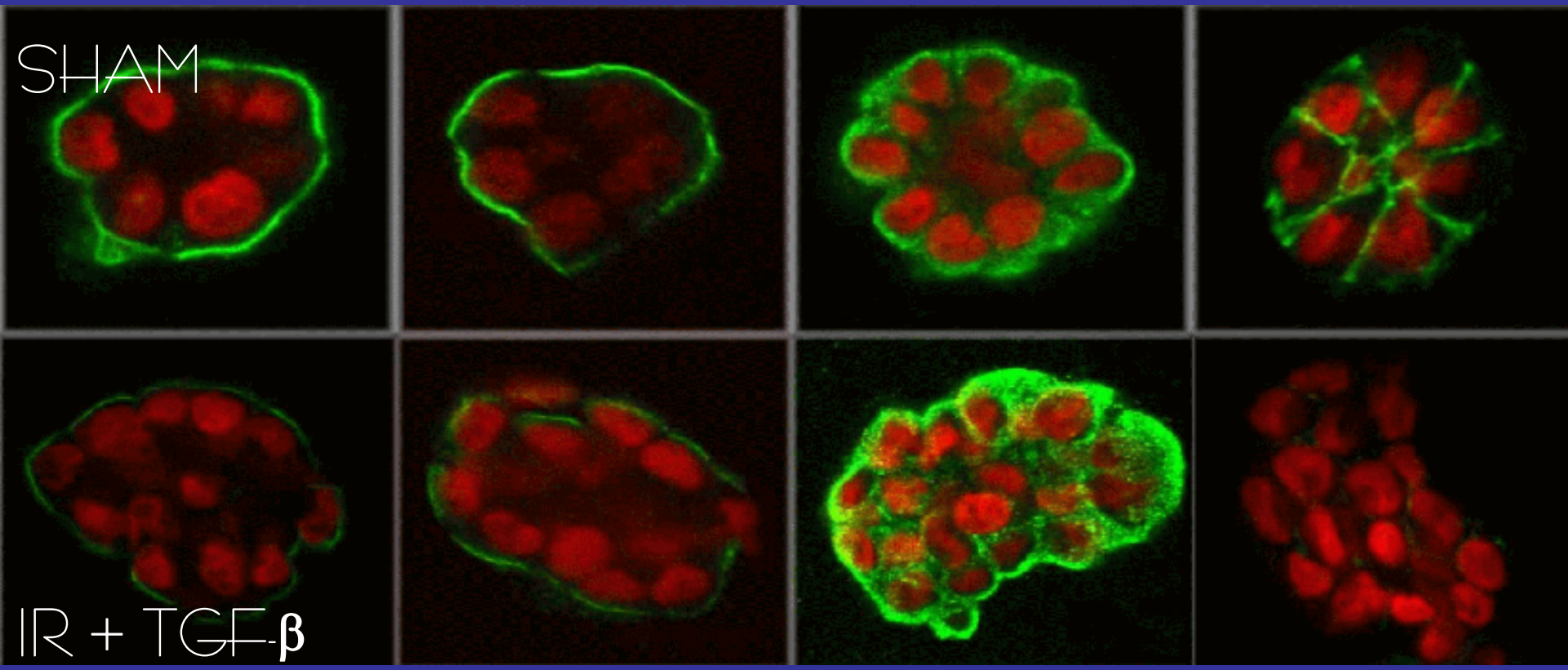
- Radiobiology in single cells need to be put into context
  - Physiology
  - Multicellular
  - Tissue specific

Po_2 effect on gene expression in irradiated human cells



Azzam et al.

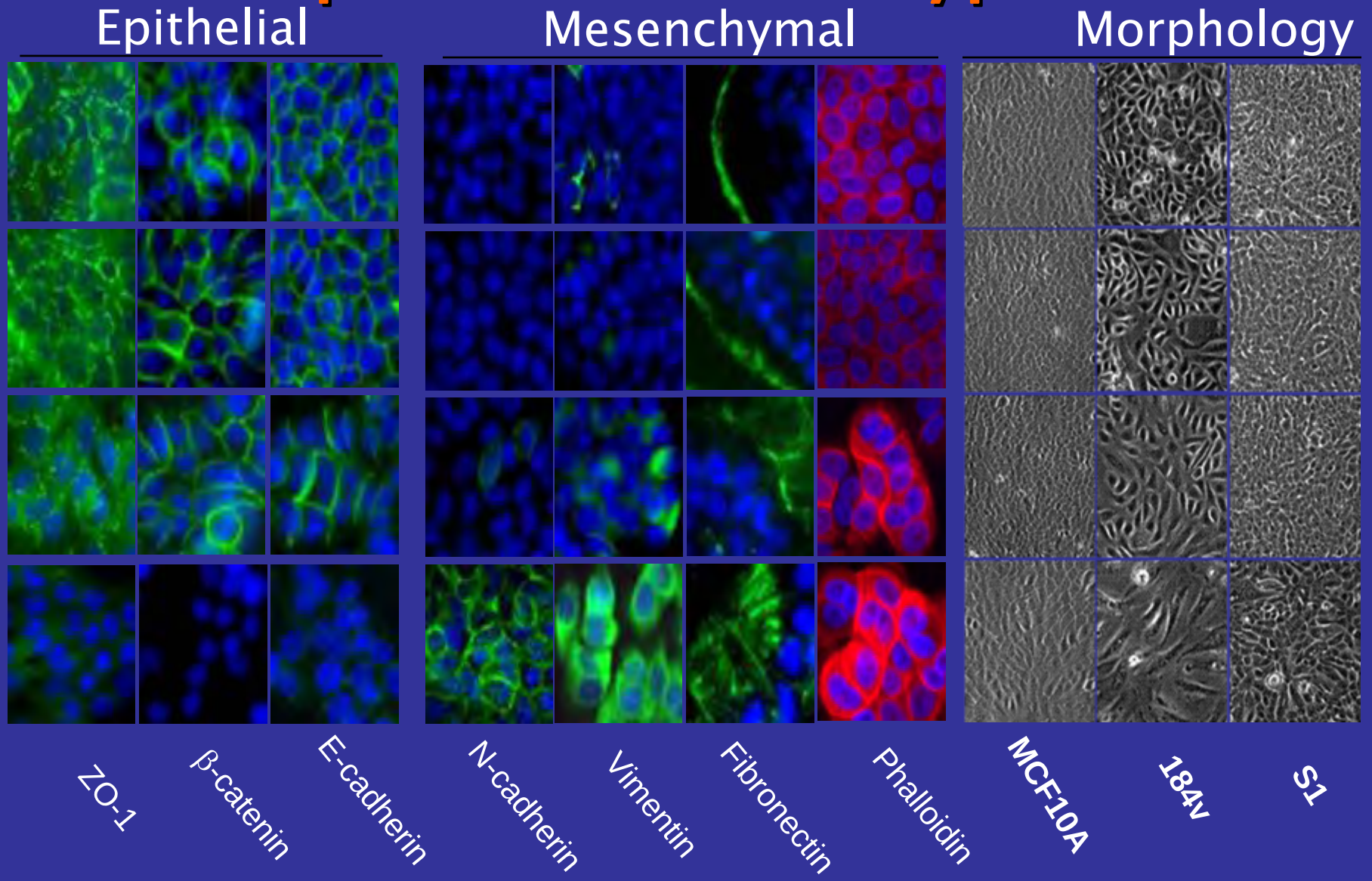
TGFβ induces a heritable phenotype in irradiated cells



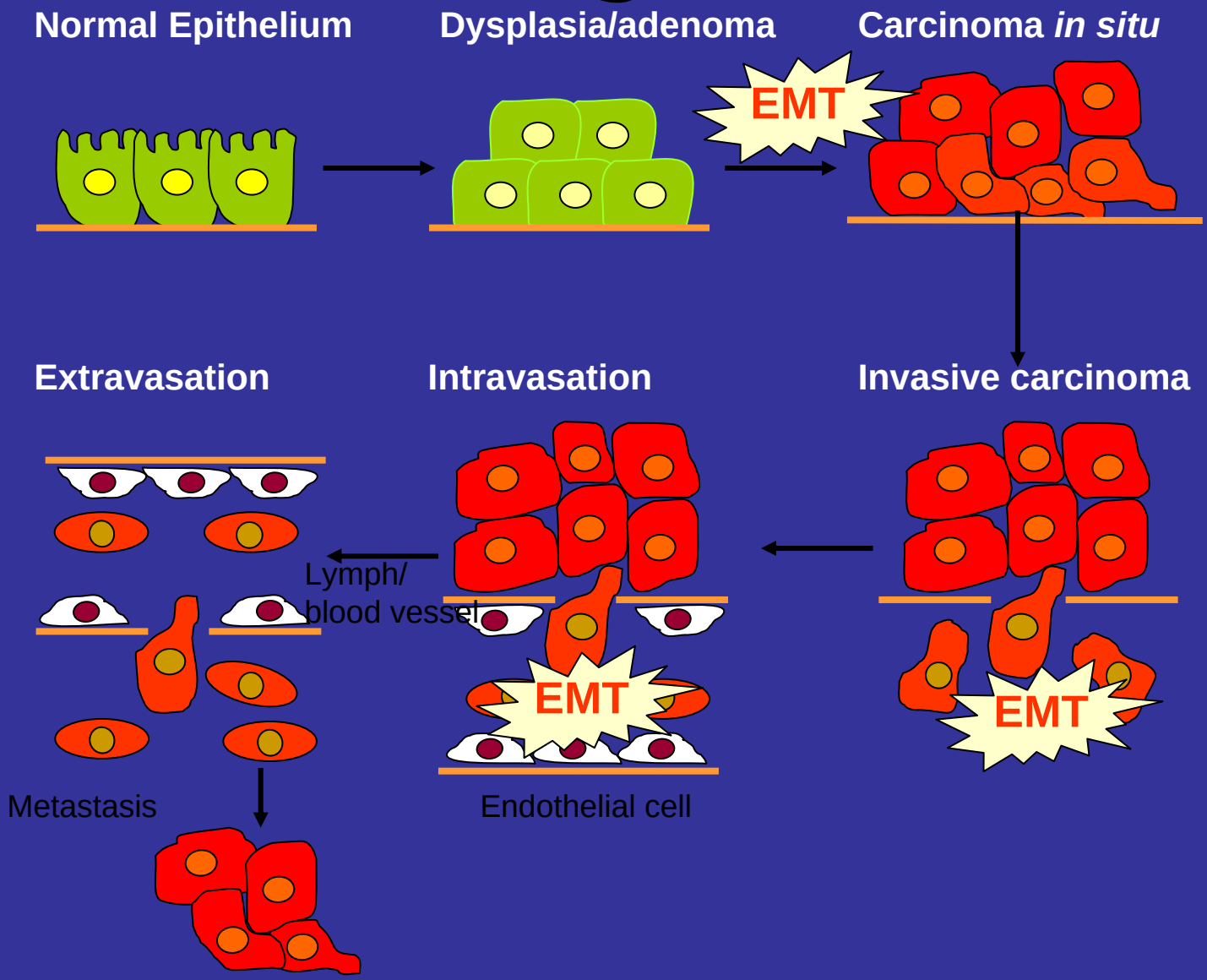
α6 integrin *α3 integrin* *β1 integrin* *E-cadherin*

Park et al. PNAS 2003

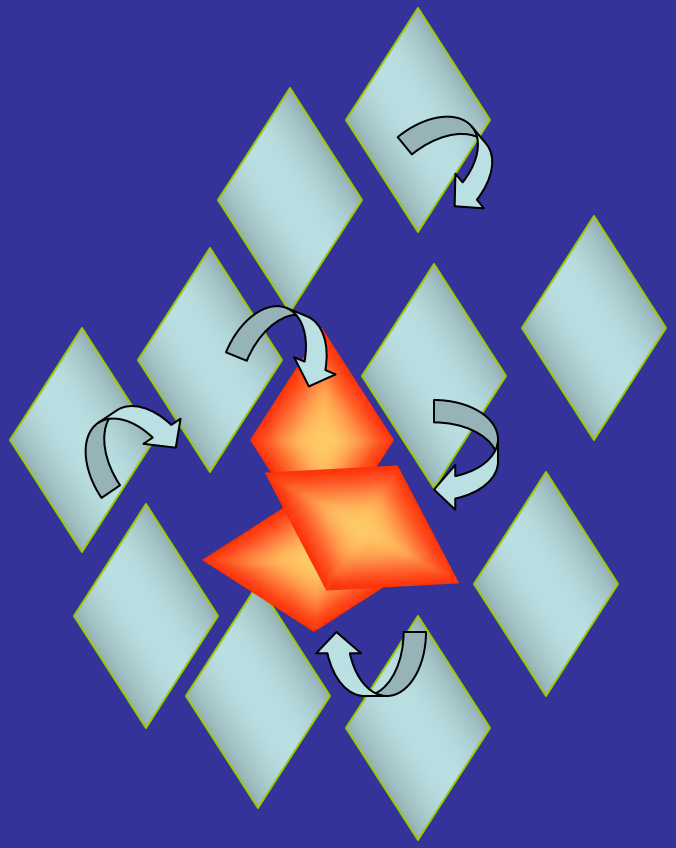
Radiation + TGF-β Induced Epithelial Phenotypes



EMT in Epithelial Carcinogenesis

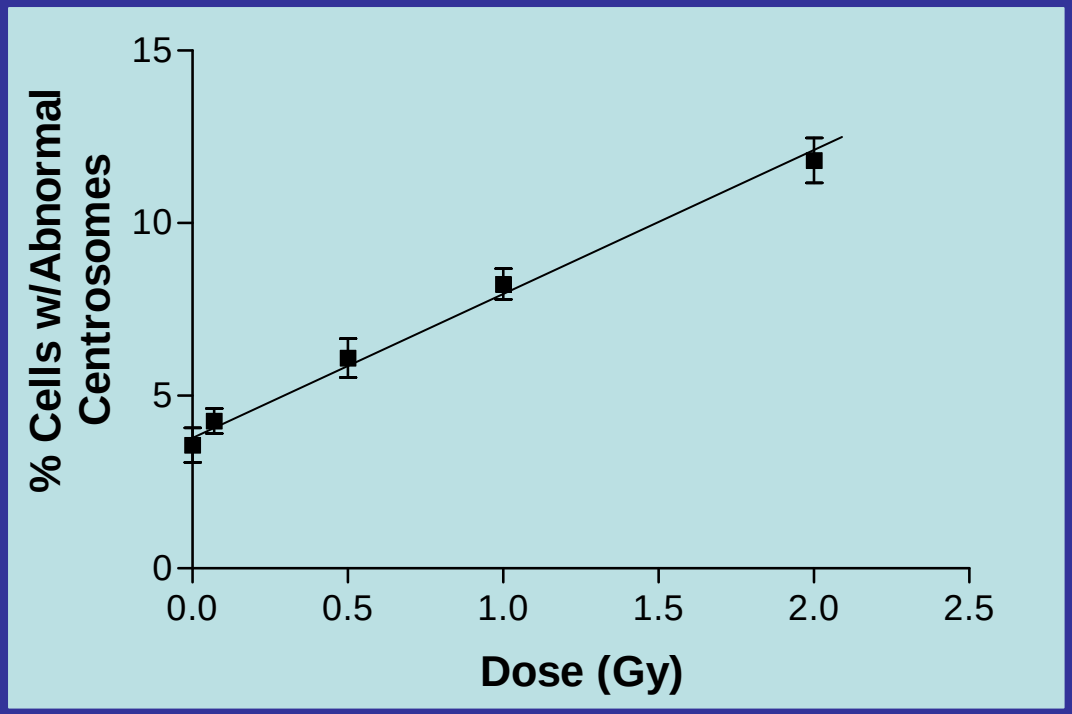


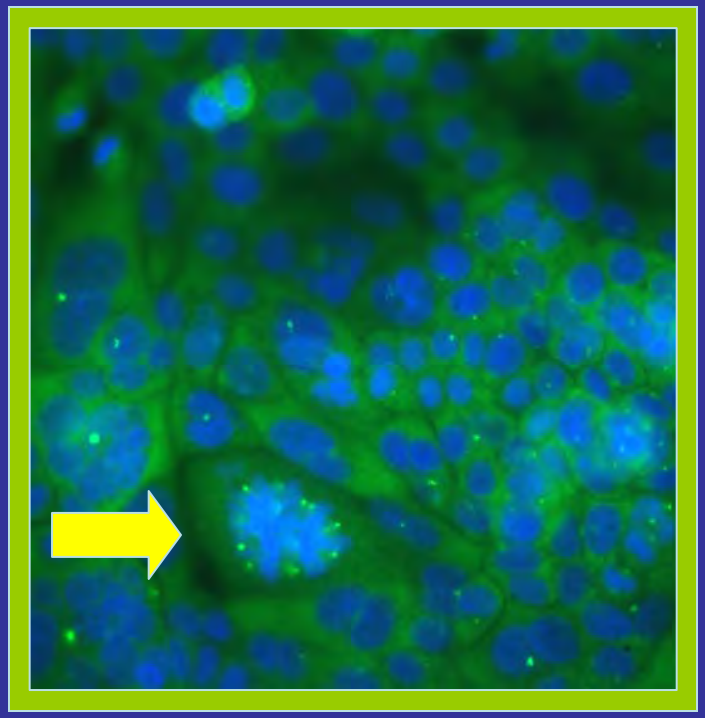
Protection by Selective Deletion



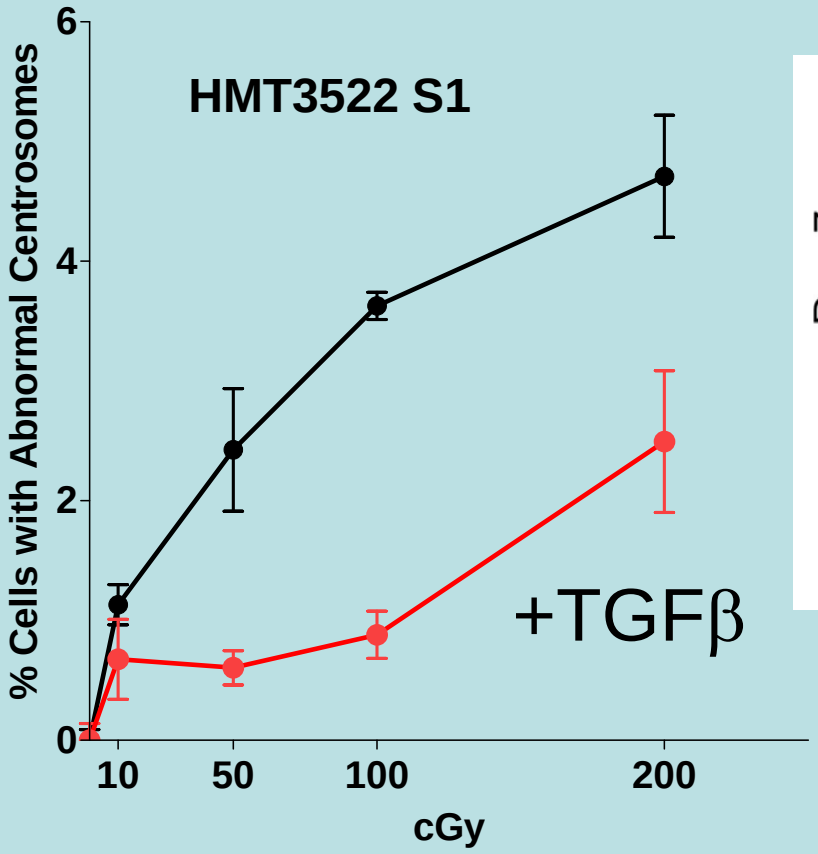
- Transformed cells are susceptible to elimination by normal cells (Bauer, many)
- Irradiation may augment the efficacy of normal cells (Portess et al. 2007)
- Surveillance of genomically unstable cells? (Maxwell, B-H et al. submitted)

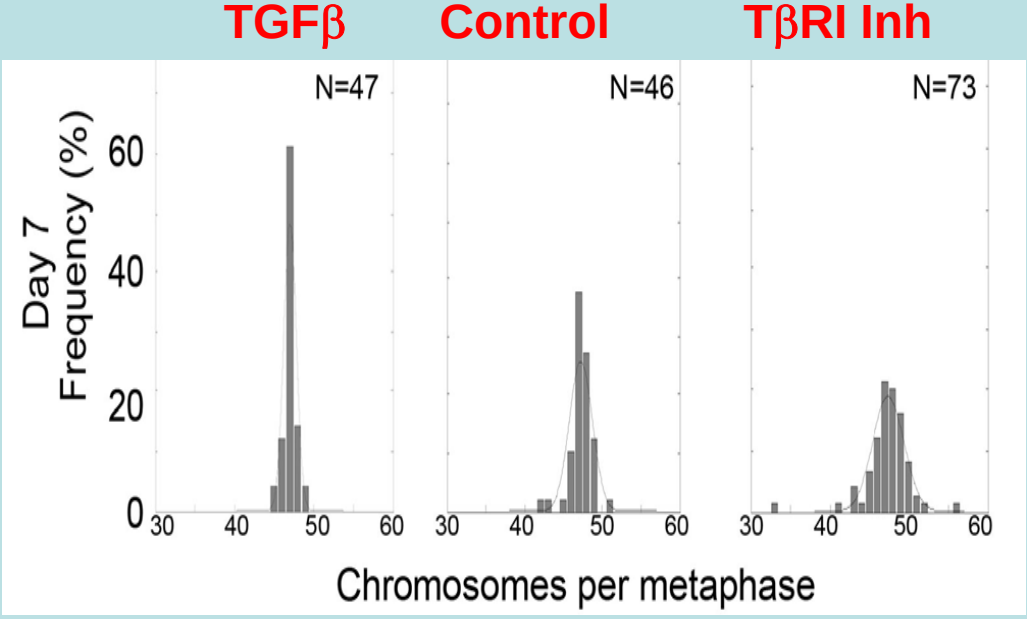
Dose Dependent Increase in Centrosome Abnormalities in Daughters of Irradiated Cells





TGFβ Deletes Genomically Unstable Cells via p53 dependent apoptosis





MCF10A Human Mammary Epithelial Cells

Promotion by Indirect Induction

Activated phagocytic cells produce genetic effects in co-cultured cells

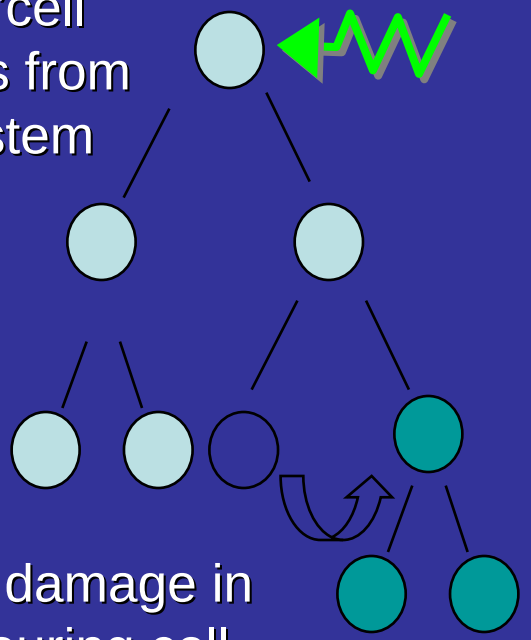
Mutation
Weitzman & Stossel,
Science, **212**, 546, 1981

Cytogenetic changes
Weitberg *et.al.*,
New. Eng.J.Med., **308**, 26-30, 1983

Modification of DNA bases
Dizdaroglu *et.al.*,
Cancer.Res, **53**,1269,1993

Transformation
Weitzman *et.al.*,
Science, **237**, 1231, 1985

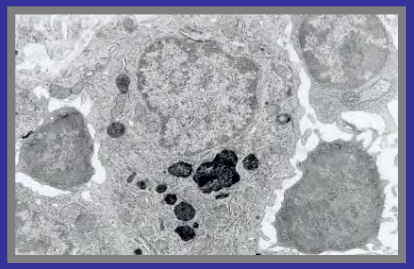
"Activated"cell differentiates from irradiated stem cell



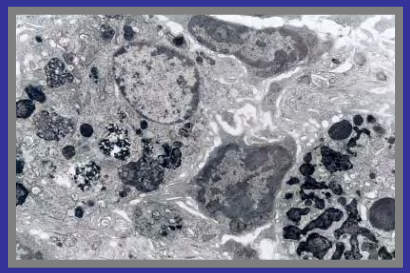
Induces damage in neighbouring cell.
&
process may be autotoxic

Non-Targeted Genomic Instability: Genotype Dependent Macrophage Activation

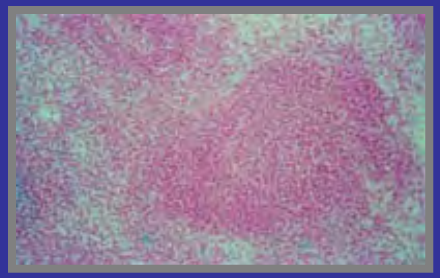
Control

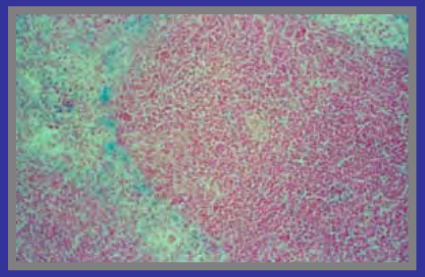


IR



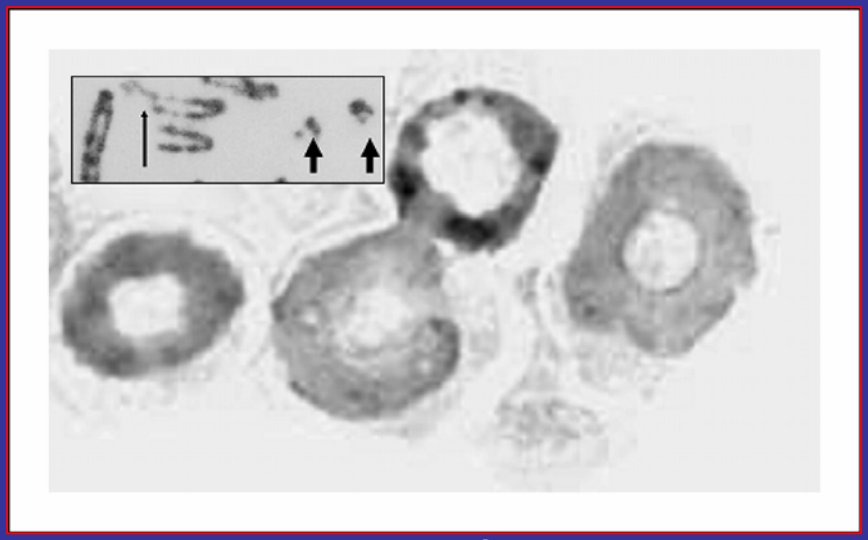
Increased lysosome number and size





↑ lysosomal enzyme activity

Lorimore et.al., *Oncogene,* **20**, 7085, 2001



Phosphorylated H2AX foci in a bone marrow granulocytic cell alongside cells with no evidence of foci and non-clonal chromosomal damage 100 days postirradiation

Lorimore et al. Cancer Res 65(13):5668-73, 2005.

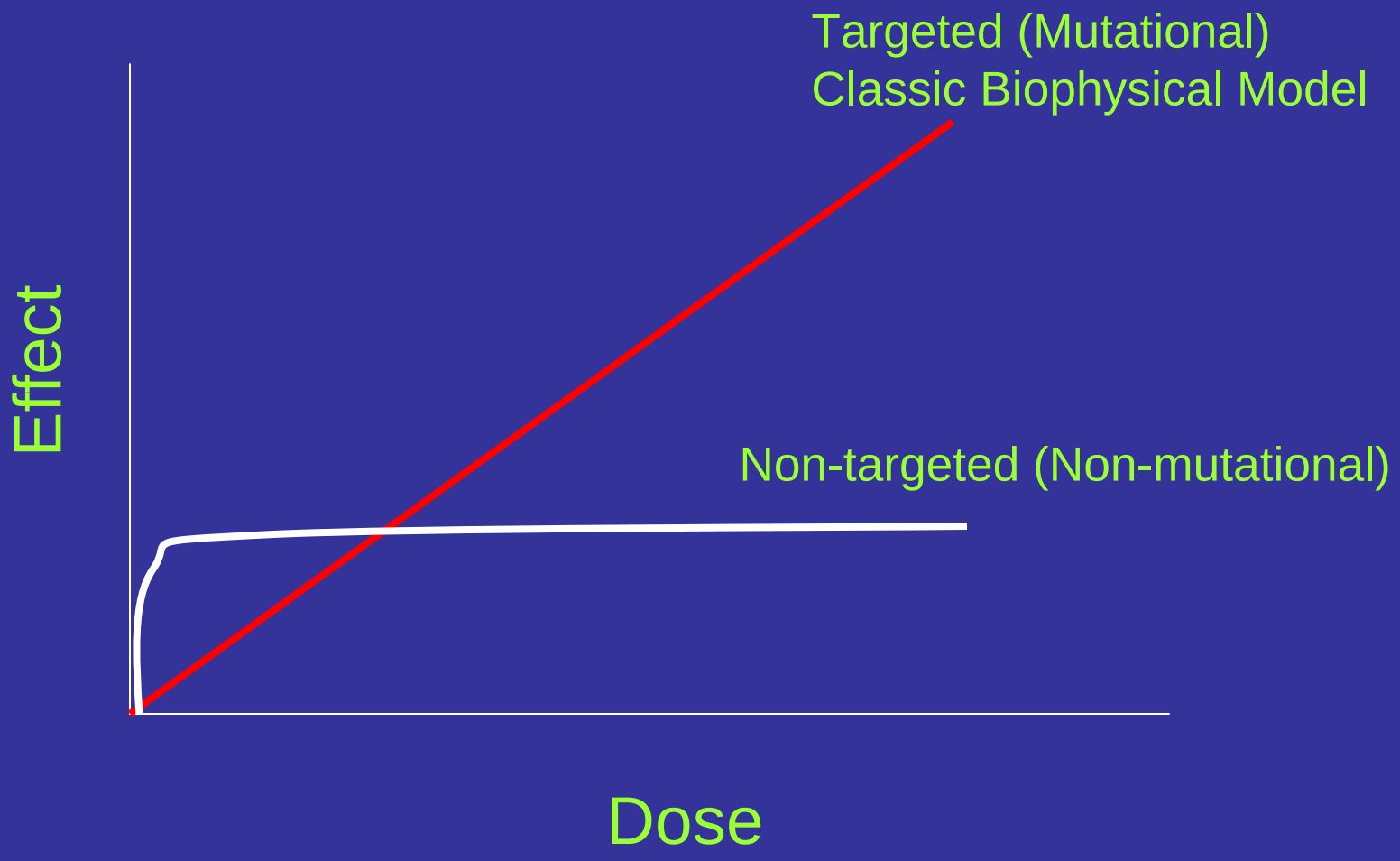
Persistent Subclinical Inflammation Among A-bomb Survivors

Neriishi et.al., *Int.J.Radiat.Biol*., **77**, 475, 2001

"Might contribute, as an epigenetic and/or bystander effect, to development of several radiation-induced disorders."

Radiation Phenomena, Effects and Risk

- Targeted effects of radiation induce random mutations that drives neoplastic transformation
- Non-targeted effects of radiation can persistently alter:
  - Genomic instability
  - Signaling (surveillance, phenotype, behaviors)
  - Epigenetics
- How do these fundamentally different radiation effects affect risk?


Targeted (Mutational)
Classic Biophysical Model
Non-targeted (Non-mutational)
Effect
Dose

Hypothesis: NTE is required for carcinogenesis.

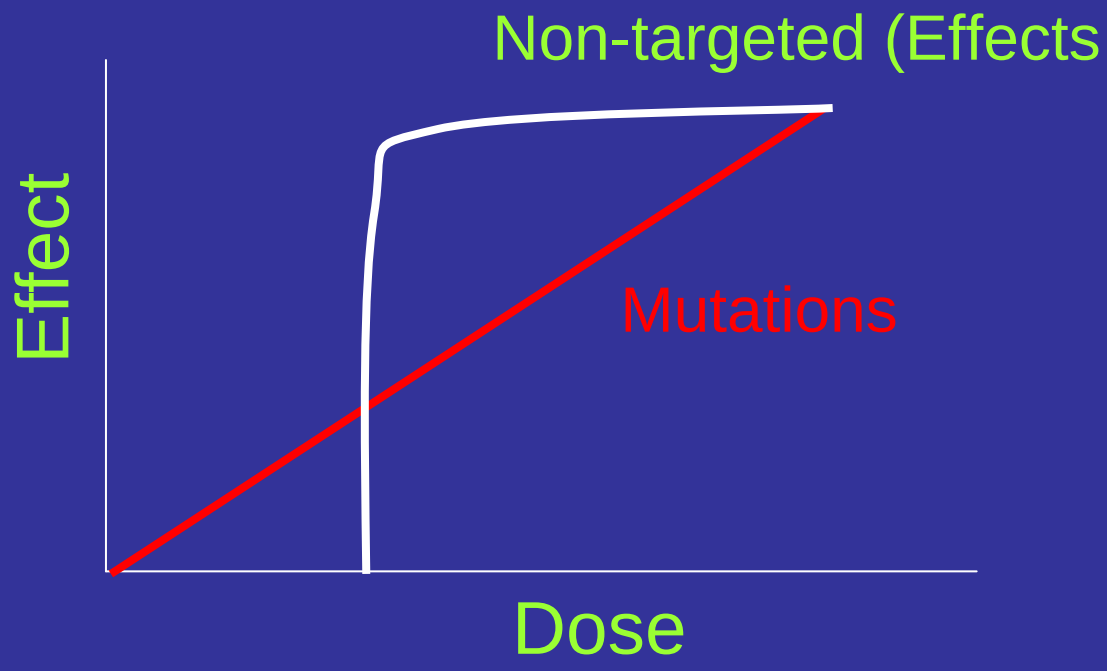
Cancer is two-compartment problem in which mutant cells must modify a restrictive normal tissue.

Radiation can do both.

But mutations are dose dependent while non-targeted effects are switches.

How do these dose responses interact?

Hypothesis: NTE has a threshold



If NTE is required, and if there is a threshold, then the extrapolation for cancer risk is a function of that threshold.

- Non-targeted effects are an additional mode of radiation action that are poorly understood
- Understanding non-targeted responses in cancer may provide avenues for protection after exposure
- Biology of non-targeted effects may underlie non-cancer health effects

How do irradiated tissues become tumors?

A biological model of low (<10 mGy) dose cancer risk would incorporate systems biology principles of complexity and emergence.

Influence of Low-LET Radiation Dose and Dose Rate on Radiation Risk: Life-Span Dog Studies

Antone L. Brooks and P. Elis Eberlein
Washington State University Tri-Cities
Richland WA, 99354

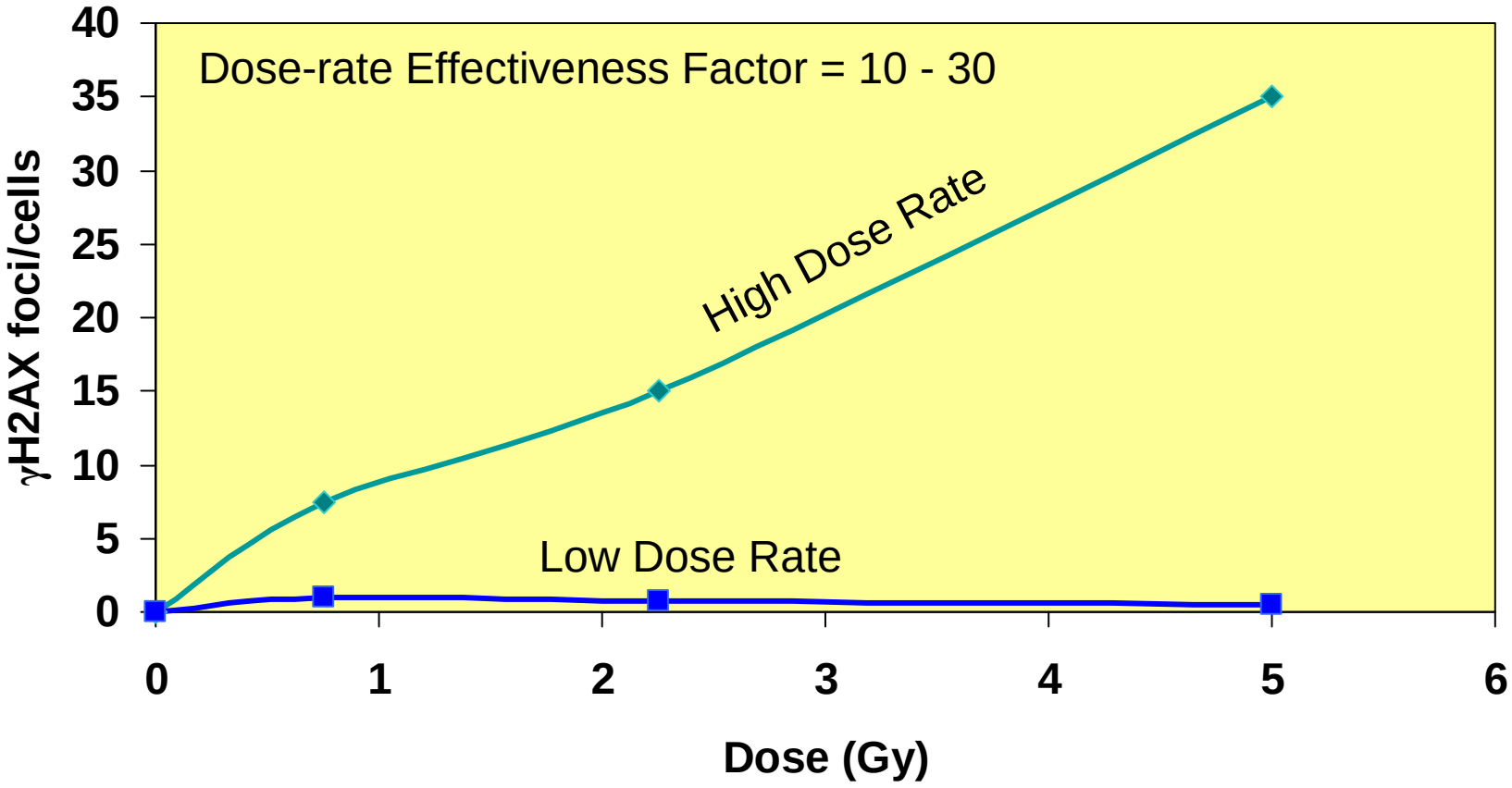
Why am I Presenting These Data?

- I could not convince Dr. Bruce Boecker or Dr. Gayle Woloschak to do it.
- I have had a life time interest in these data even though I was not involved in generating the data.
- It is very important that the scientific community be aware of this rich and well characterized data set and the potential to use for modern studies.
- These life-time studies that make it possible to evaluate the influence of dose-rate effectiveness factor (DREF) and dose-distribution (tissue weighting factors) on life shortening, non-cancer diseases and cancer in long lived animals.
- Critical information to understand the impact of radiation delivered at low dose rates to provide the baseline for decisions on relocation and other actions after terrorist activities or nuclear accidents.

Radiation Dose-Rate Effectiveness Factors (DREF)

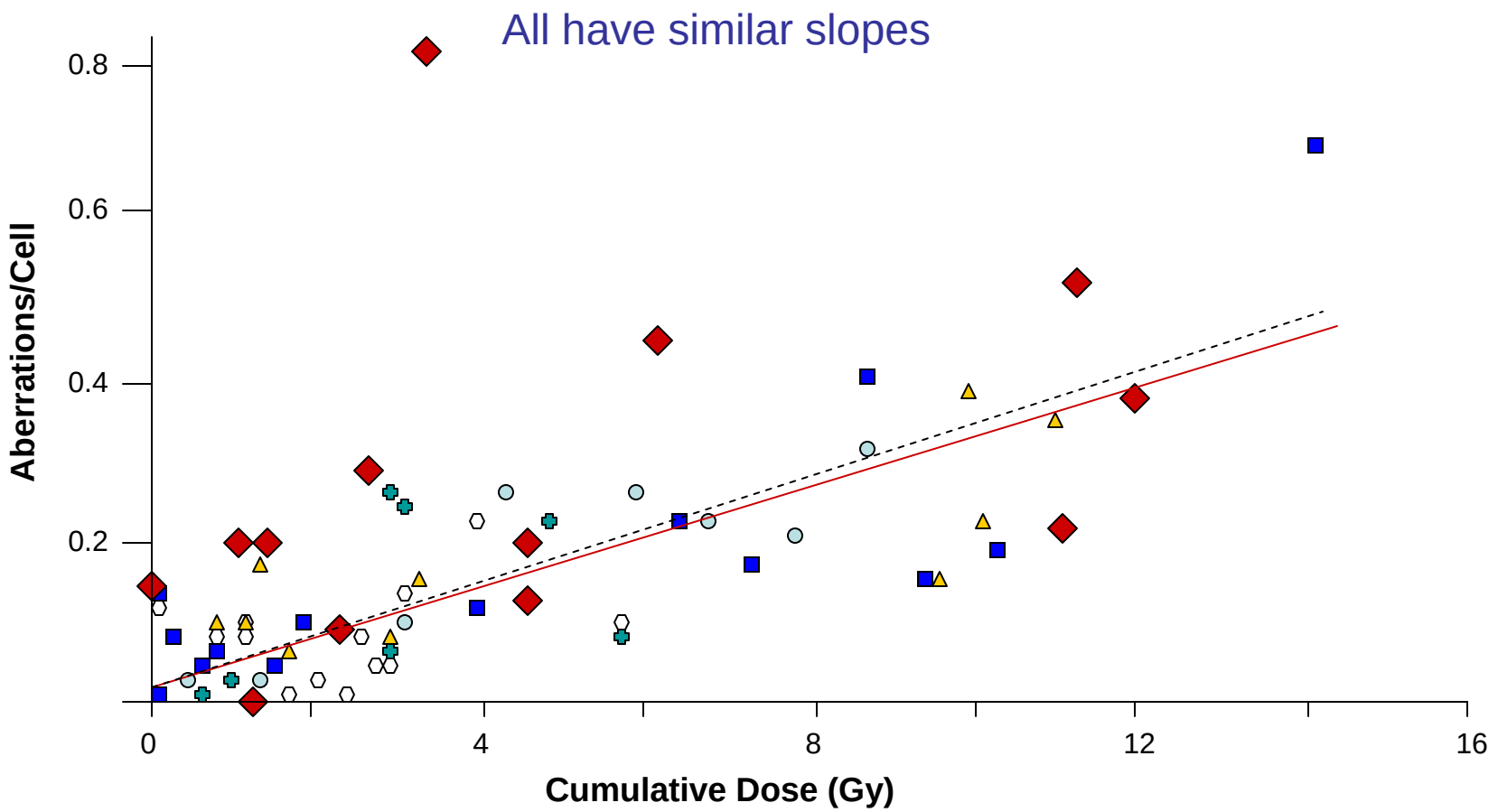
- Molecular
  - Many of these show adaptive changes as a function of dose and dose-rate
- Cellular
  - Chromosome damage
  - Cell transformation
- Tissue
  - Lung
  - Life shortening, non-cancer and cancer risk
- Animal
  - Mice
  - Dogs
    - Dogs that inhaled insoluble particles

Radiation-induced γ H2AX

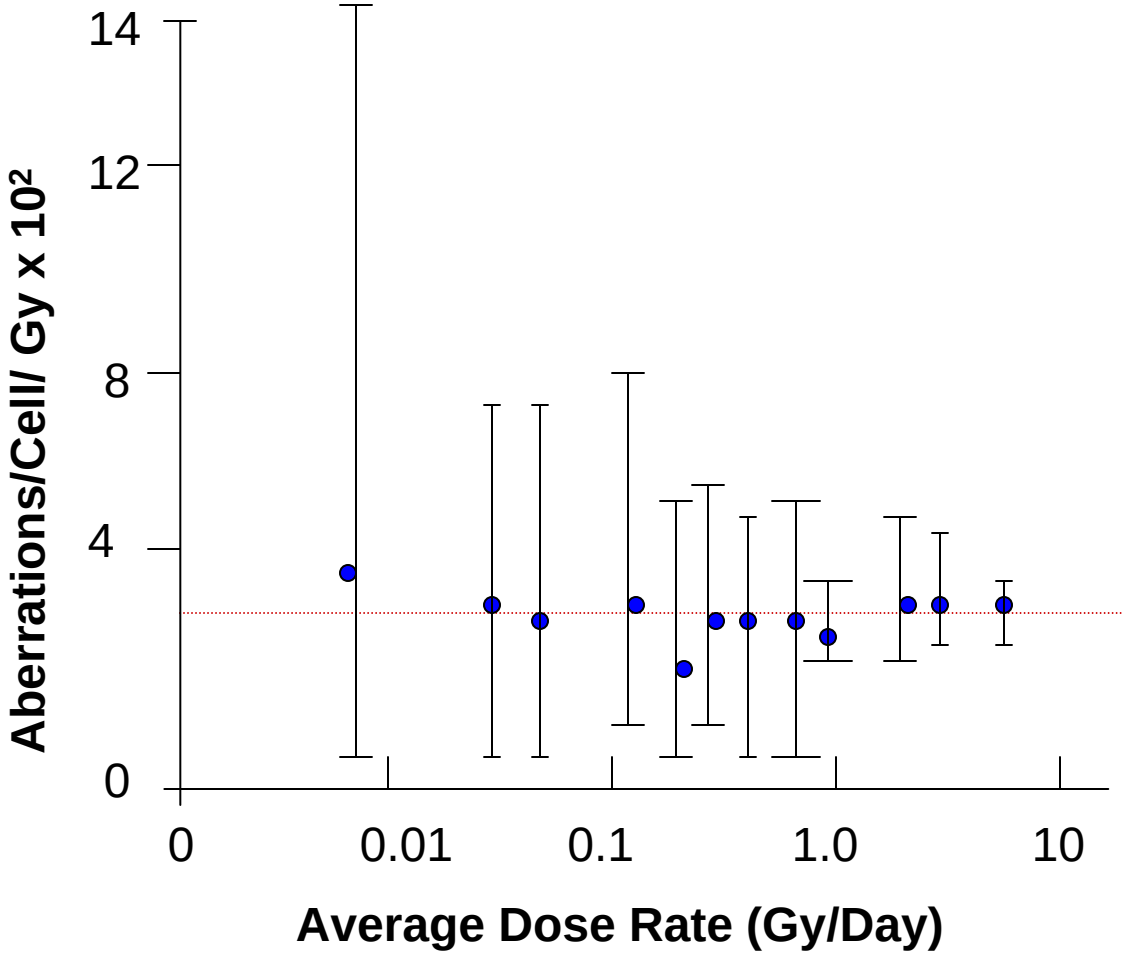


Ishizaki et al. 2004

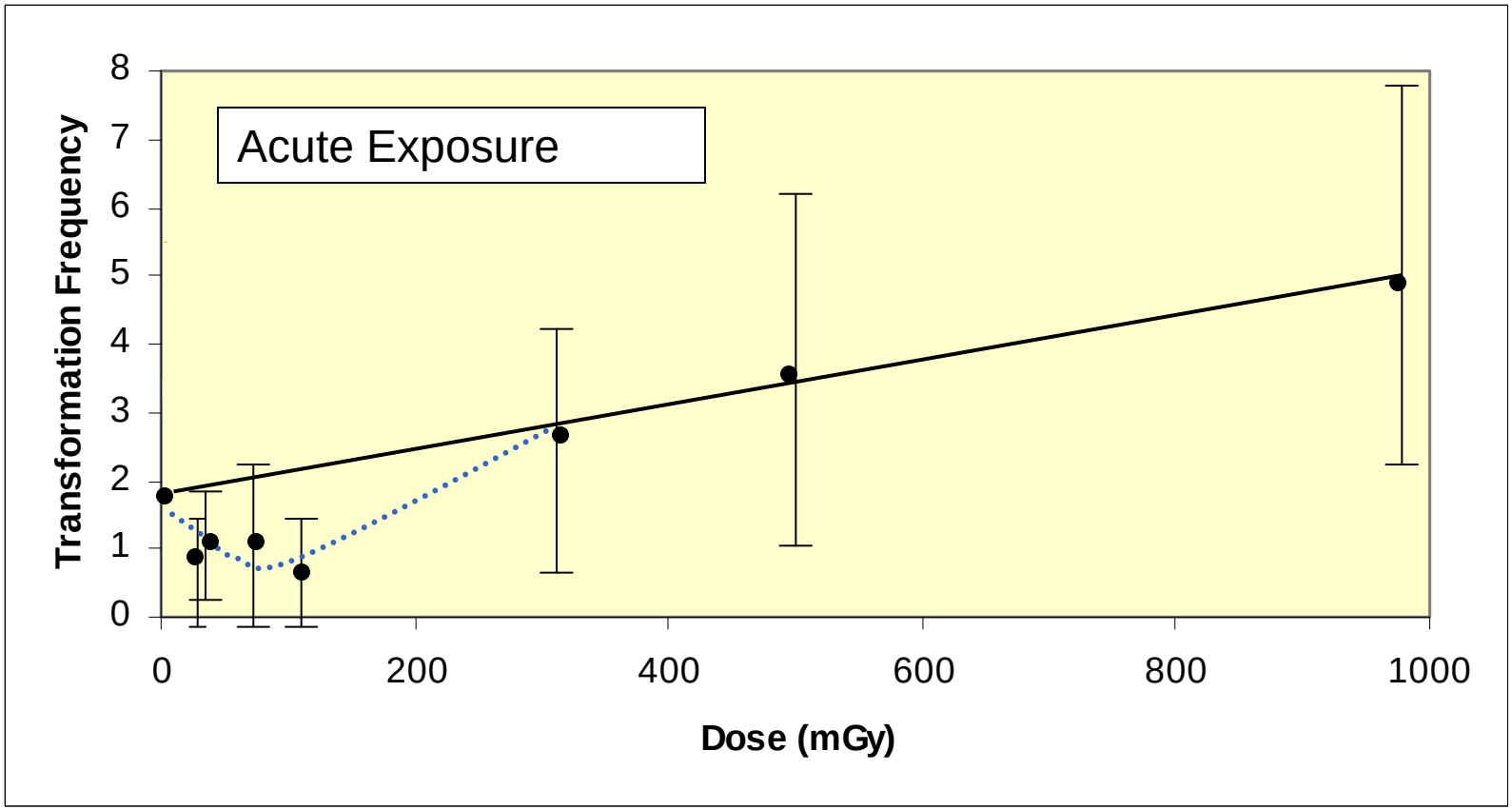
The Influence of Low Dose-rate from ^{144}Ce Citrate on Chromosome Aberrations in Liver of Chinese Hamster



Effect of Radiation Dose-rate on the Dose-response Relationship following Protracted Exposure to ^{144}Ce-^{144}Pr

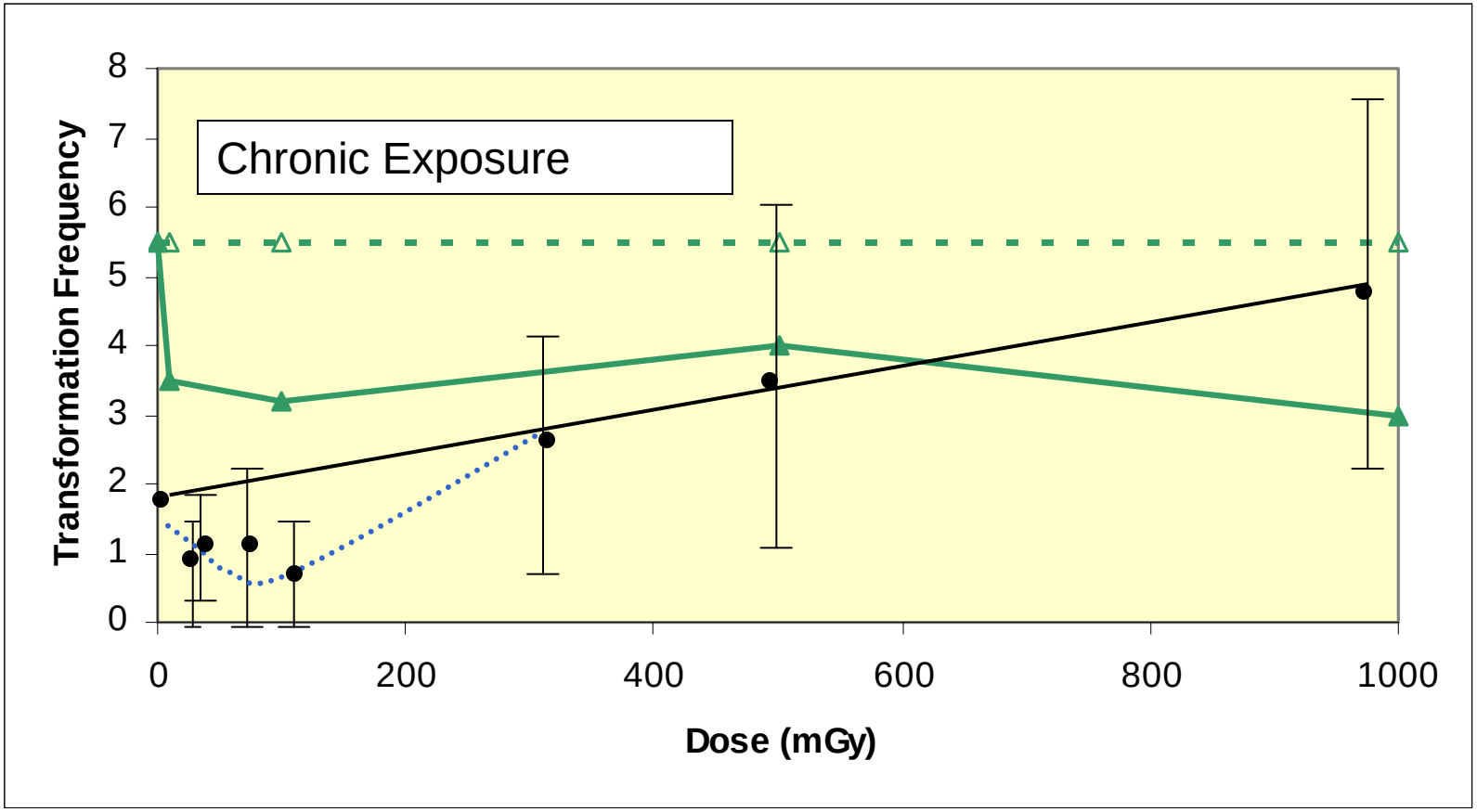


Adaptive Response
Sub-linear Dose-response



Elmore et al. 2006

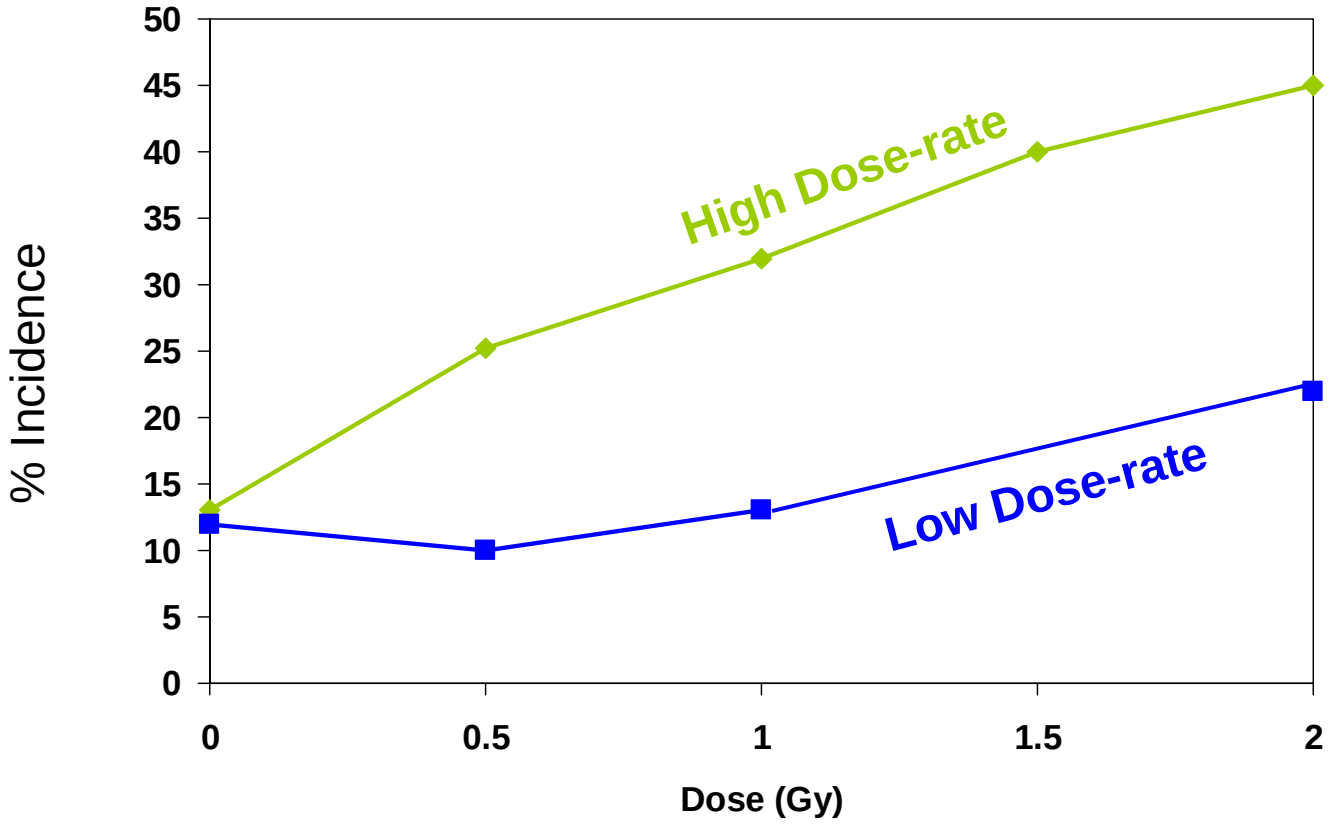
Adaptive Response
Sub-linear Dose-response



Elmore et al. 2006

Dose-rate Effects

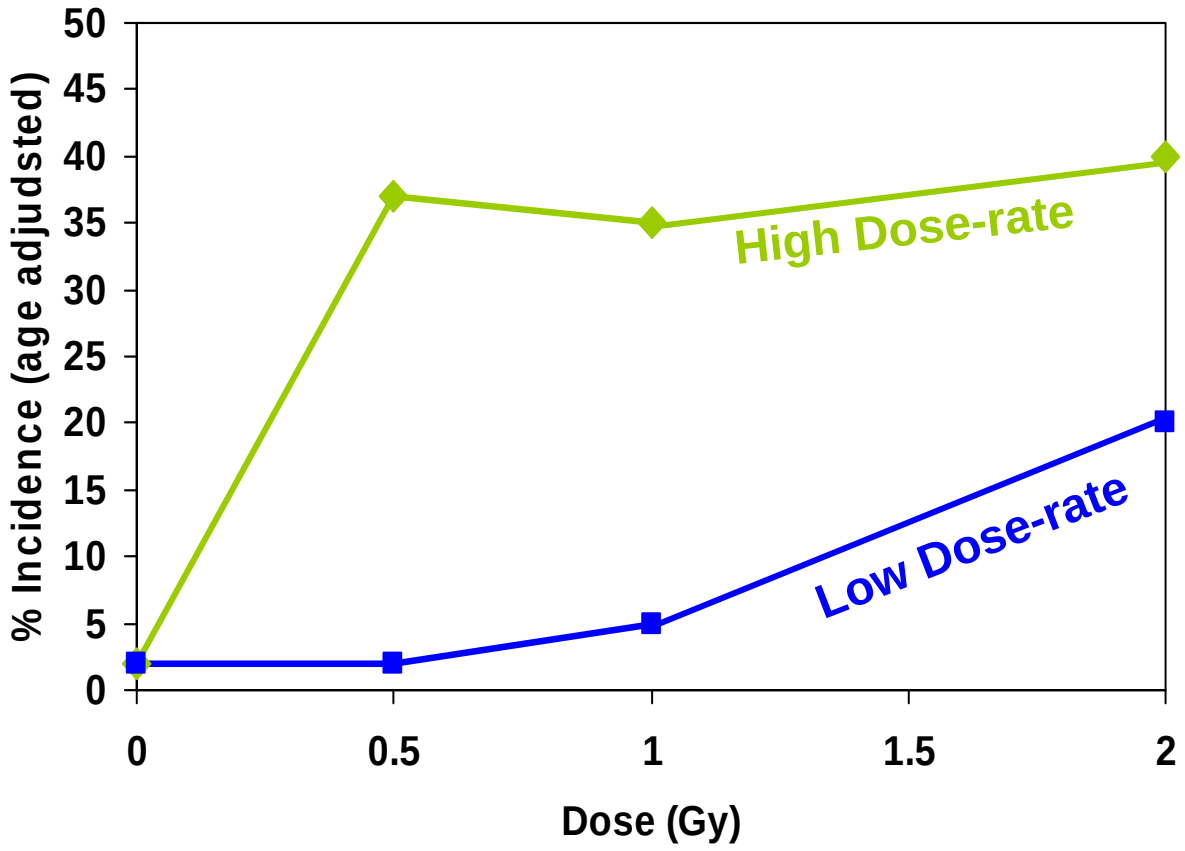
Incidence of thymic lymphoma in RFM mice



Ullrich and Storer 1979

Dose-rate Effects

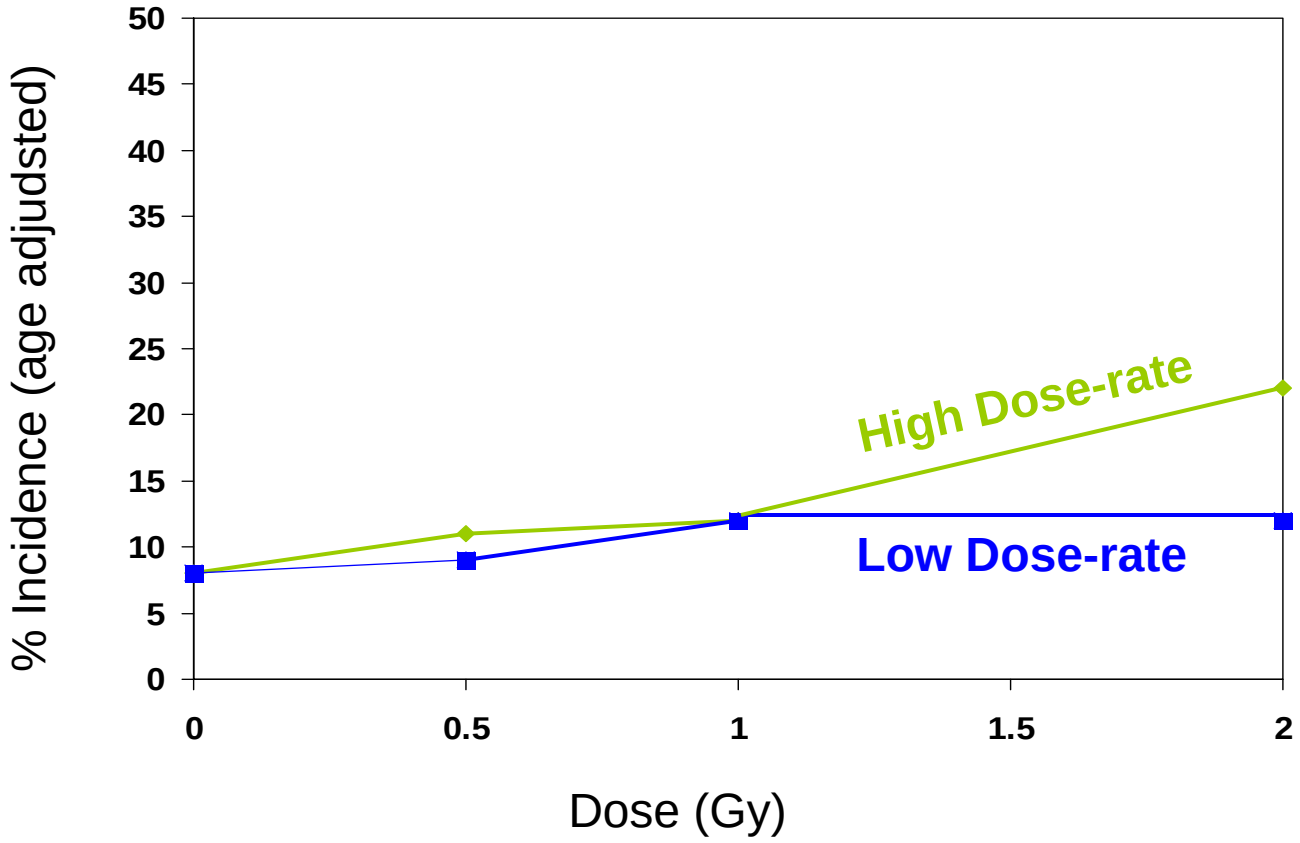
Incidence of ovarian tumors in RFM mice



Ullrich and Storer 1979

Dose-rate Effects

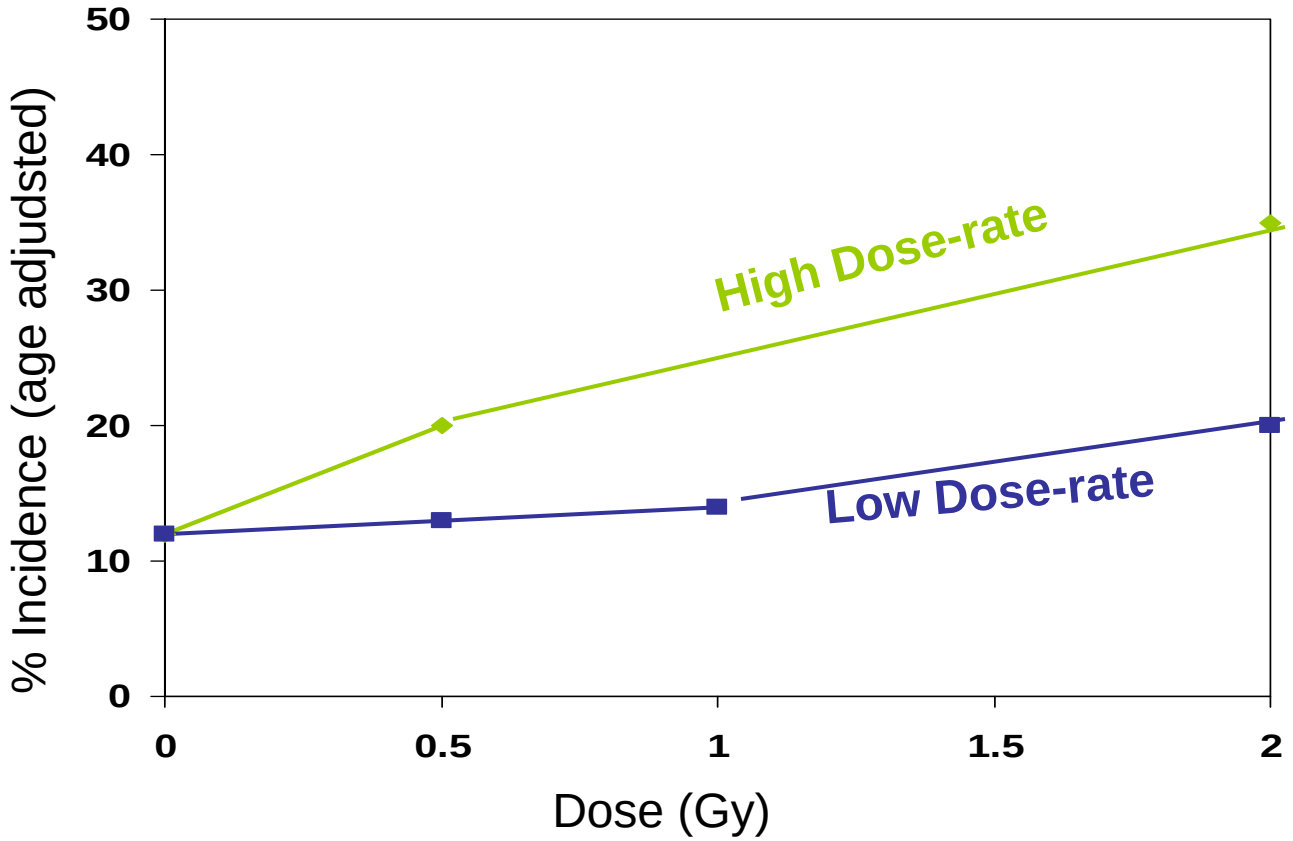
Incidence of mammary tumors in Balb/c mice



Ullrich and Storer 1979

Dose-rate Effects

Incidence of lung adenocarcinomas in BALB/c mice



Ullrich and Storer 1979

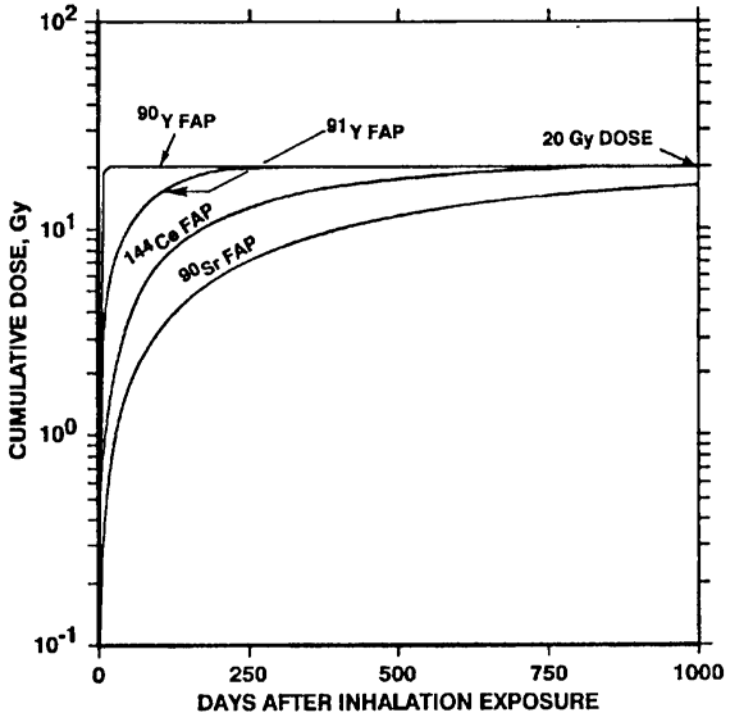
Tissue Archive from Long-Term Animal Irradiation Experiments

- **Program studying acute and chronic radiation injury in mice and dogs was conducted from 1969 to 1992 at Argonne National Laboratory**
- **Irradiated 49,000 mice: Death records 42,000 mice; gross pathology 39,000 mice; paraffin tissues**
- **Irradiated 7,000 dogs—Death records, gross pathology examination results, and paraffin embedded tissues**
- **Pathology databases describe and cross-reference: type and source of radiation [gamma, neutrons]; dose and dose rate [including life span irradiation]; type and presence/absence of radioprotector treatment; tissue/animal morphology and pathology; etc.**
- **Website for database: http://janus.northwestern.edu**

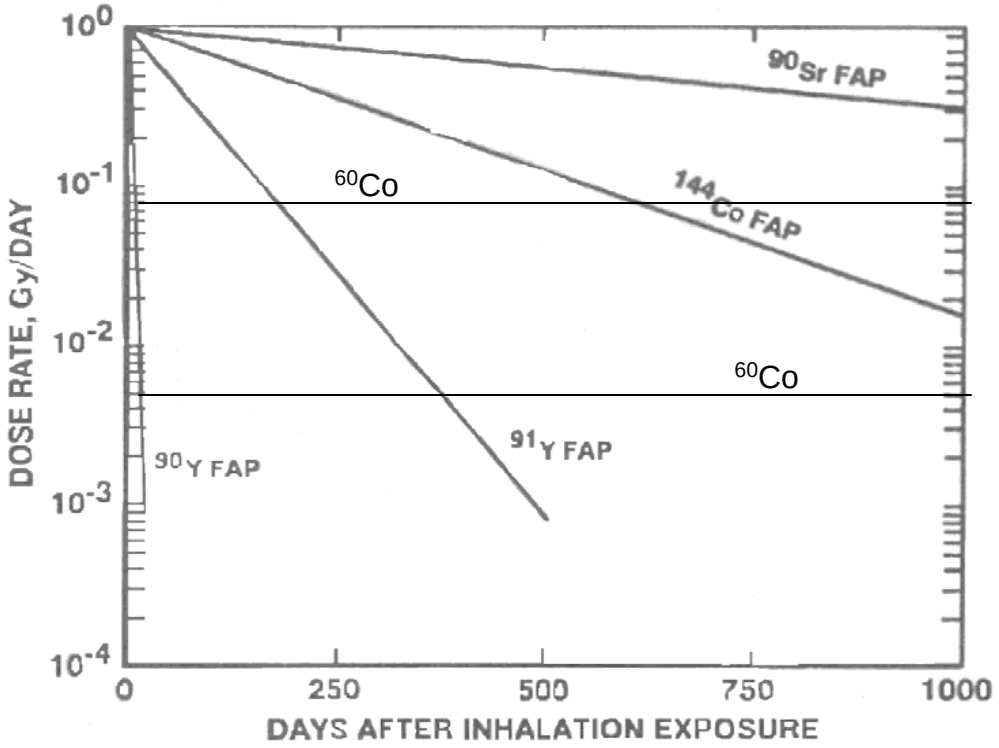
Low-LET Studies

	Utah	Davis	Argonne	ITRI
Injection	1954 ^{90}Sr	1963 ^{90}Sr	1956 ^{90}Sr (Transplacental) 1957 ^{90}Sr (Subcutaneous) 1960 ^{144}Ce 1961 ^{137}Cs	
Ingestion		1961 ^{90}Sr		
Inhalation				1970 ^{90}Sr(insol) 1967 ^{144}Ce (insol) 1970 ^{91}Y (insol) 1969 ^{90}Y (insol) 1965 ^{90} Sr (soluble) 1966 ^{144}Ce (soluble) 1972 ^{144}Ce (juvenile) 1972 ^{144}Ce (aged) 1972 ^{144}Ce (multiple exposures) 1968 ^{137}Cs (soluble) 1966 ^{91}Y (soluble)

Tissue Dose following Inhalation of Fused Clay Particles



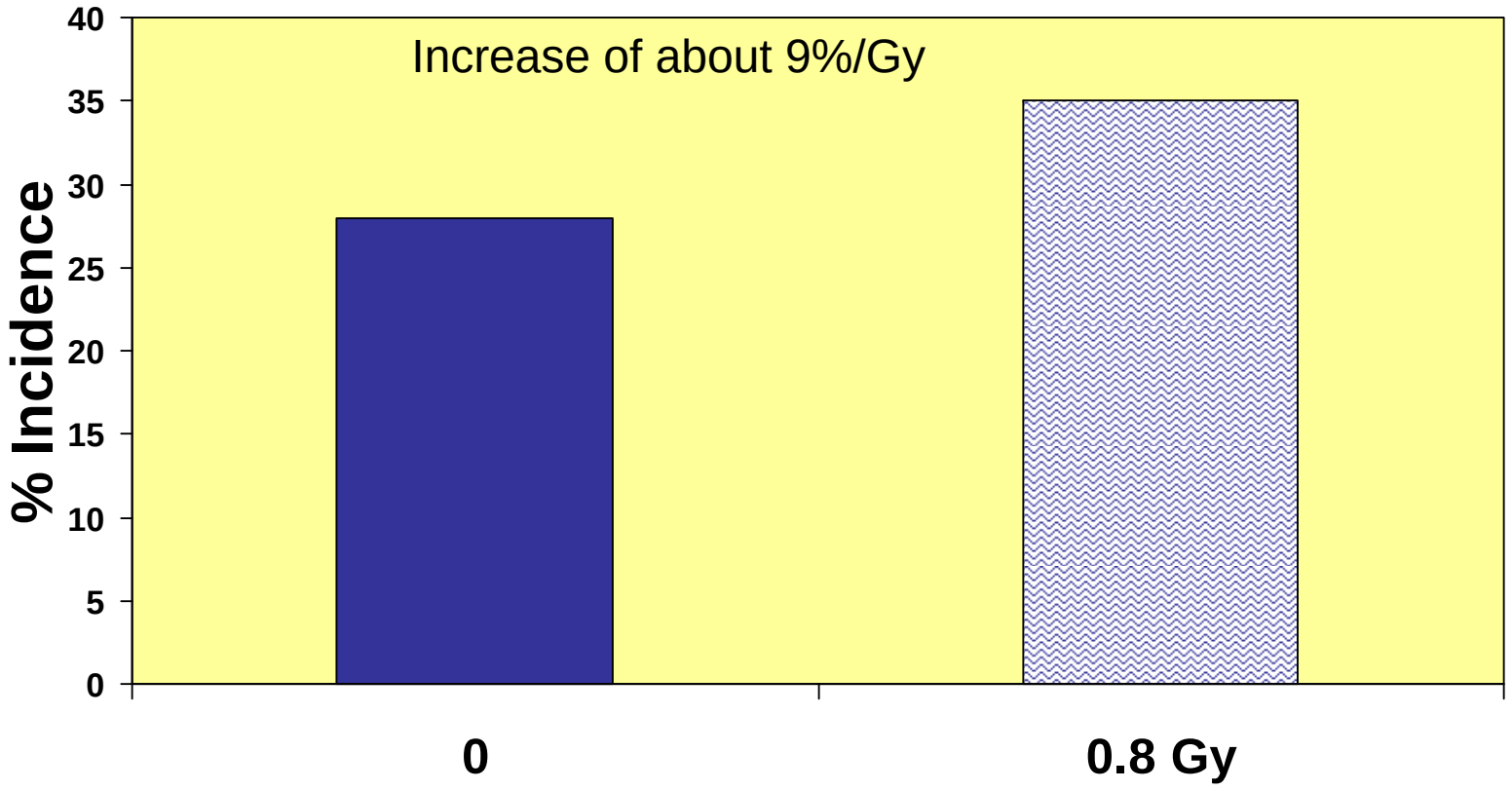
DOSE RATES TO DOGS EXPOSED TO CHRONIC RADIATION



CUMULATIVE DOSE

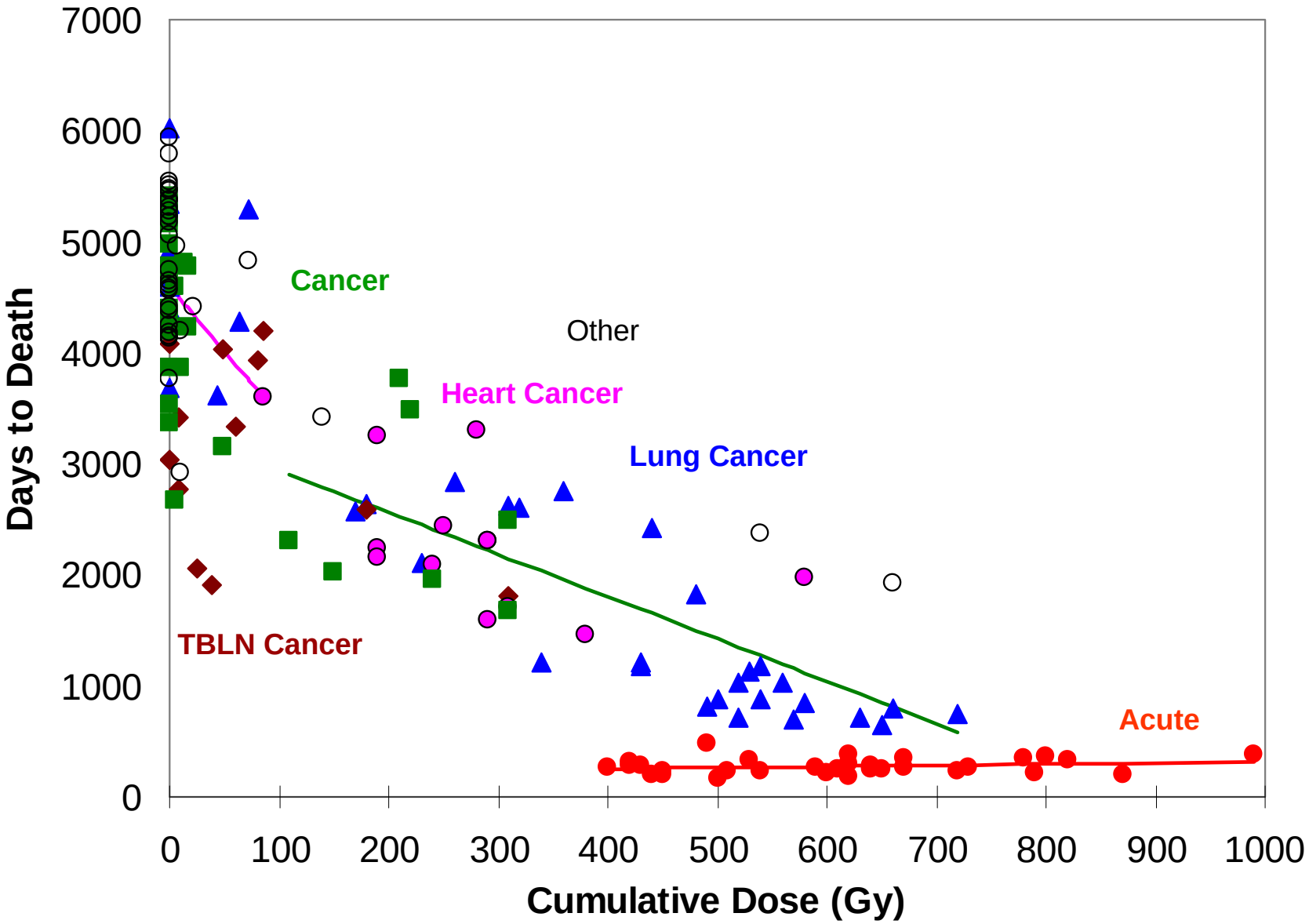
Nuclide	Effective Halflife	Time to 90% of Dose
^{90}Y	2.5 d	8 d
^{91}Y	50 d	0.5 y
^{144}Ce	180 d	1.6 y
^{90}Sr	600 d	5.5 y

Cancer in Beagle Dogs following Acute Whole-body Radiation Exposure

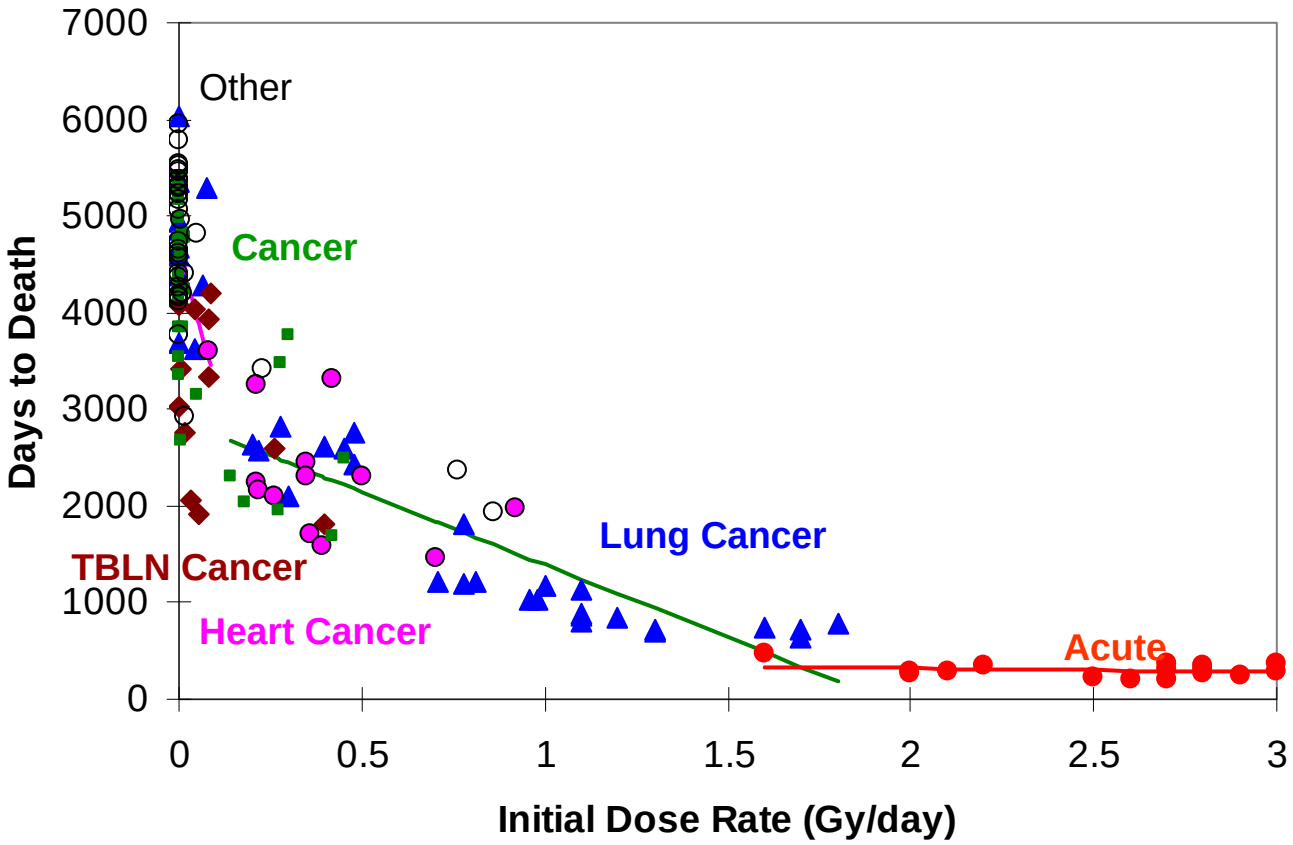


Benjamin et al 1998

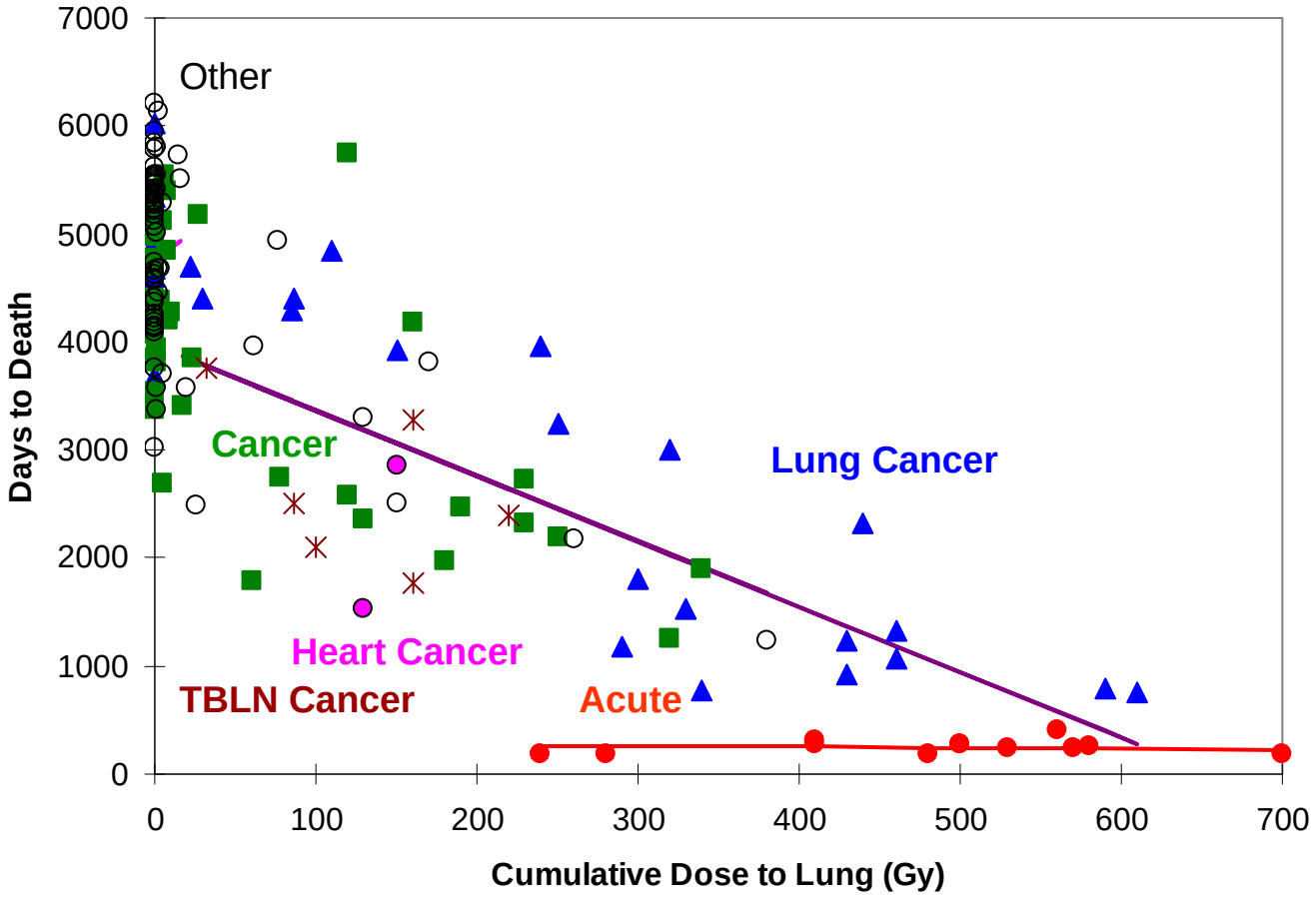
Dose Response for Life Shortening Following Inhalation of 90-Strontium Fused Clay Particles



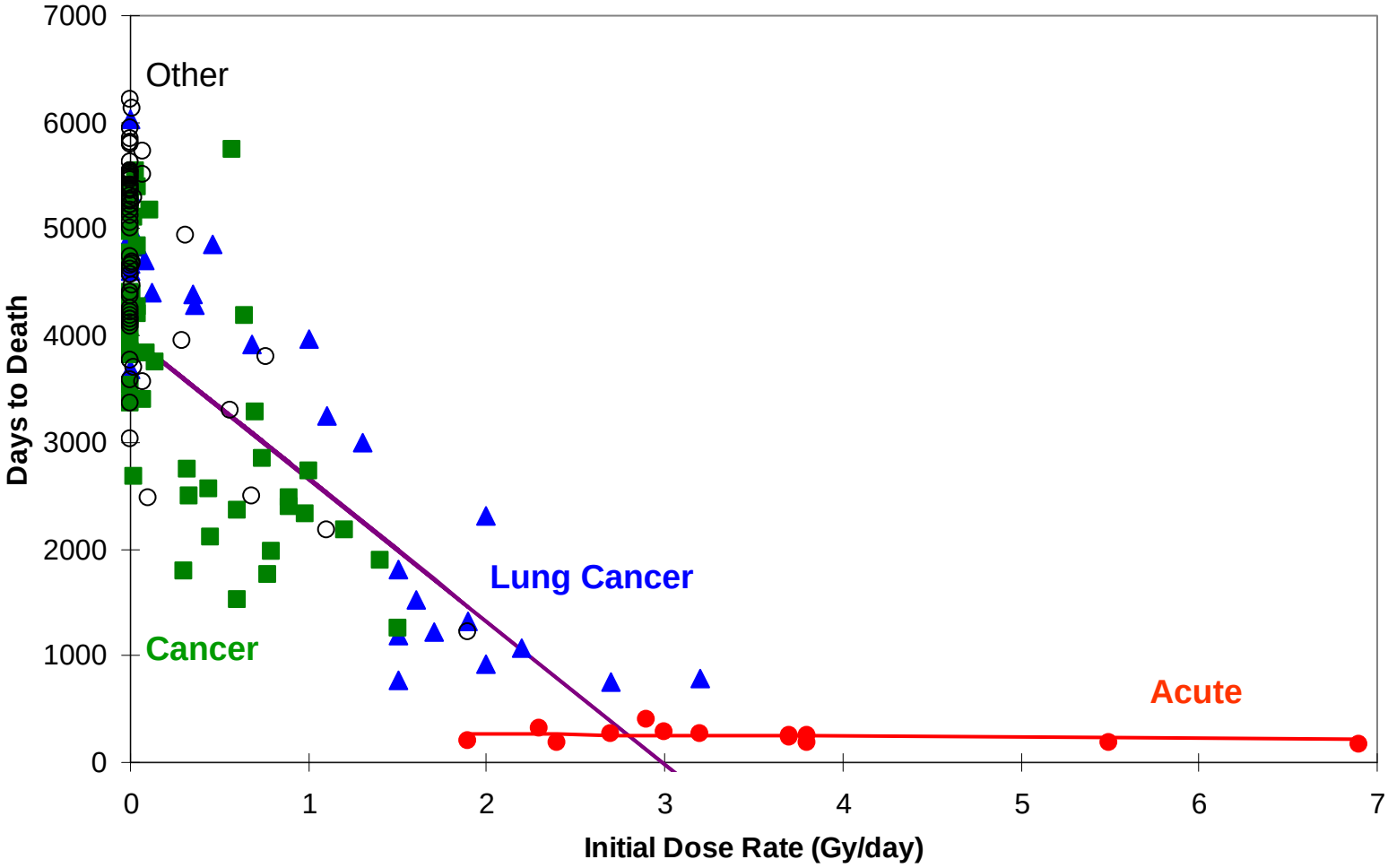
Dose Rate Response for Life Shortening Following Inhalation of 90-Strontium Fused Clay Particles



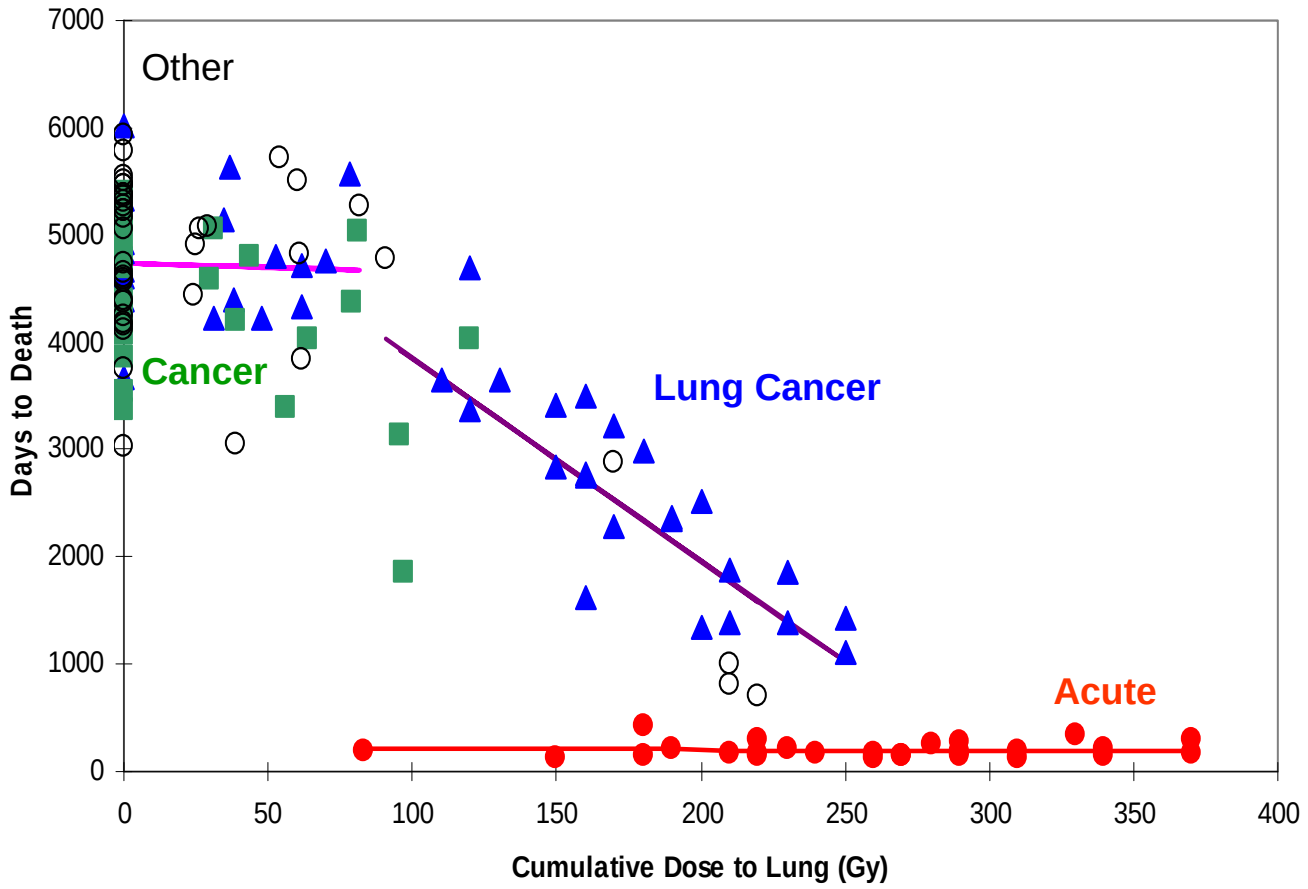
Life Shortening Response to Cumulative Dose to Lung Following Inhalation of 144-Cerium FAP



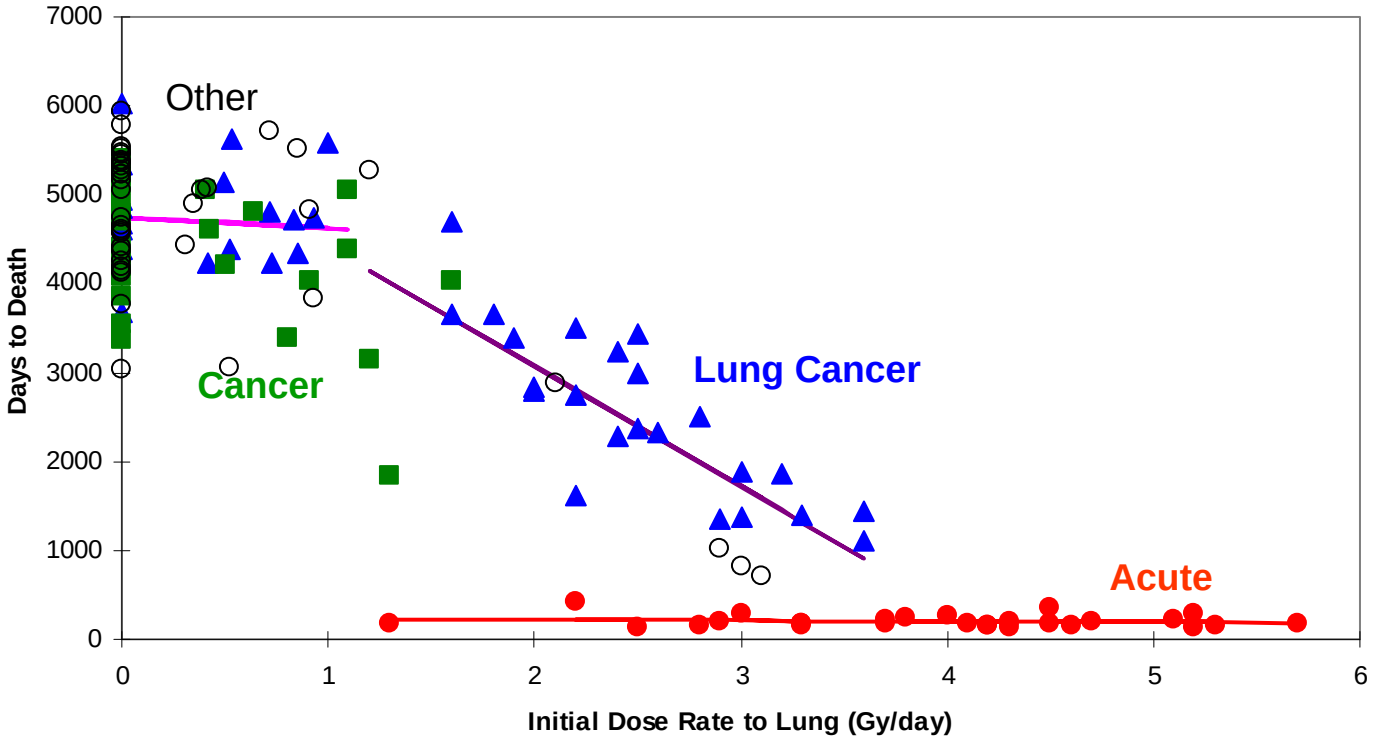
Life Shortening Response to Initial Dose Rate to Lung Following Inhalation of 144-Cerium FAP



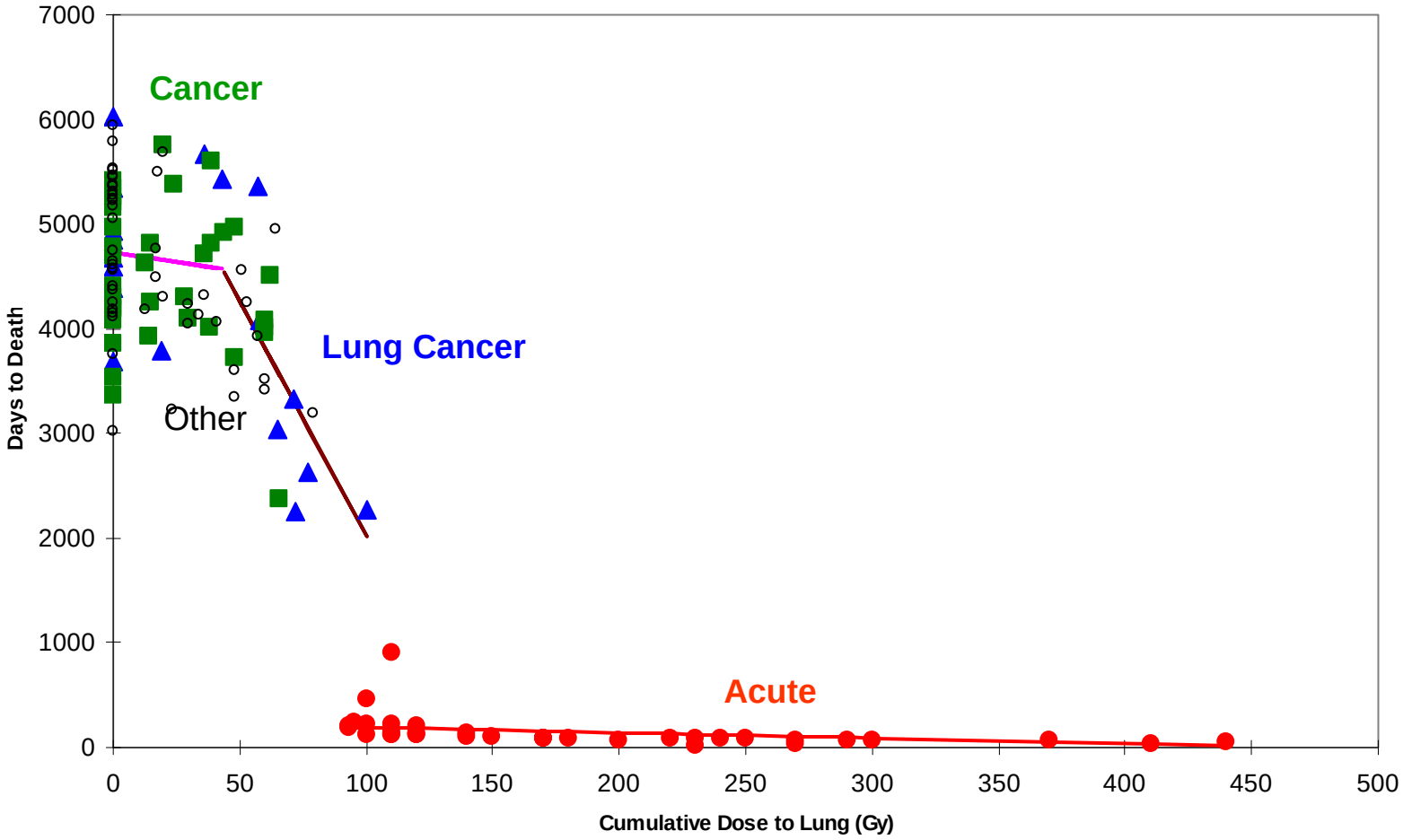
Life Shortening Response to Cumulative Dose to Lung Following Inhalation of 91-Yttrium FAP



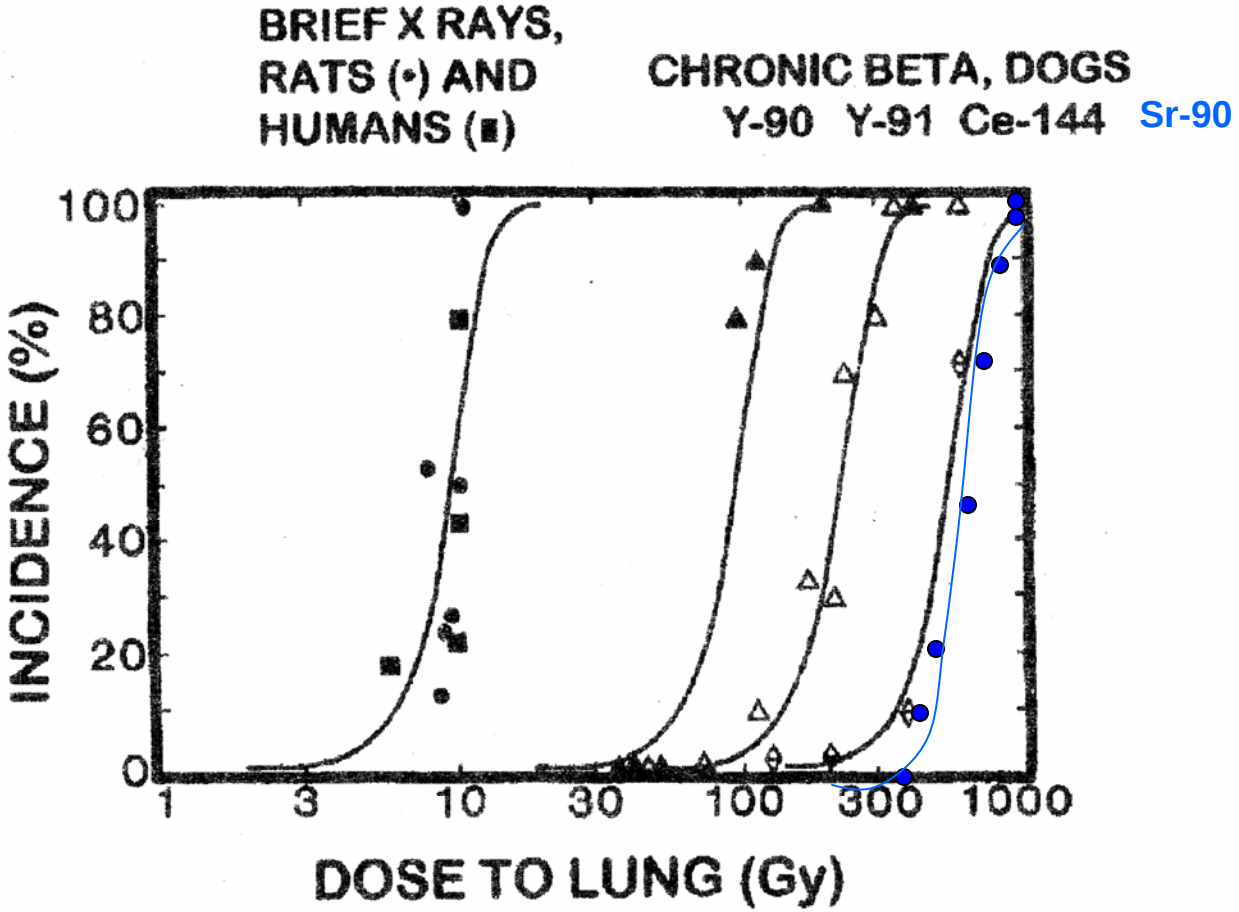
Life Shortening Response to Dose Rate to Lung Following Inhalation of 91-Yttrium FAP



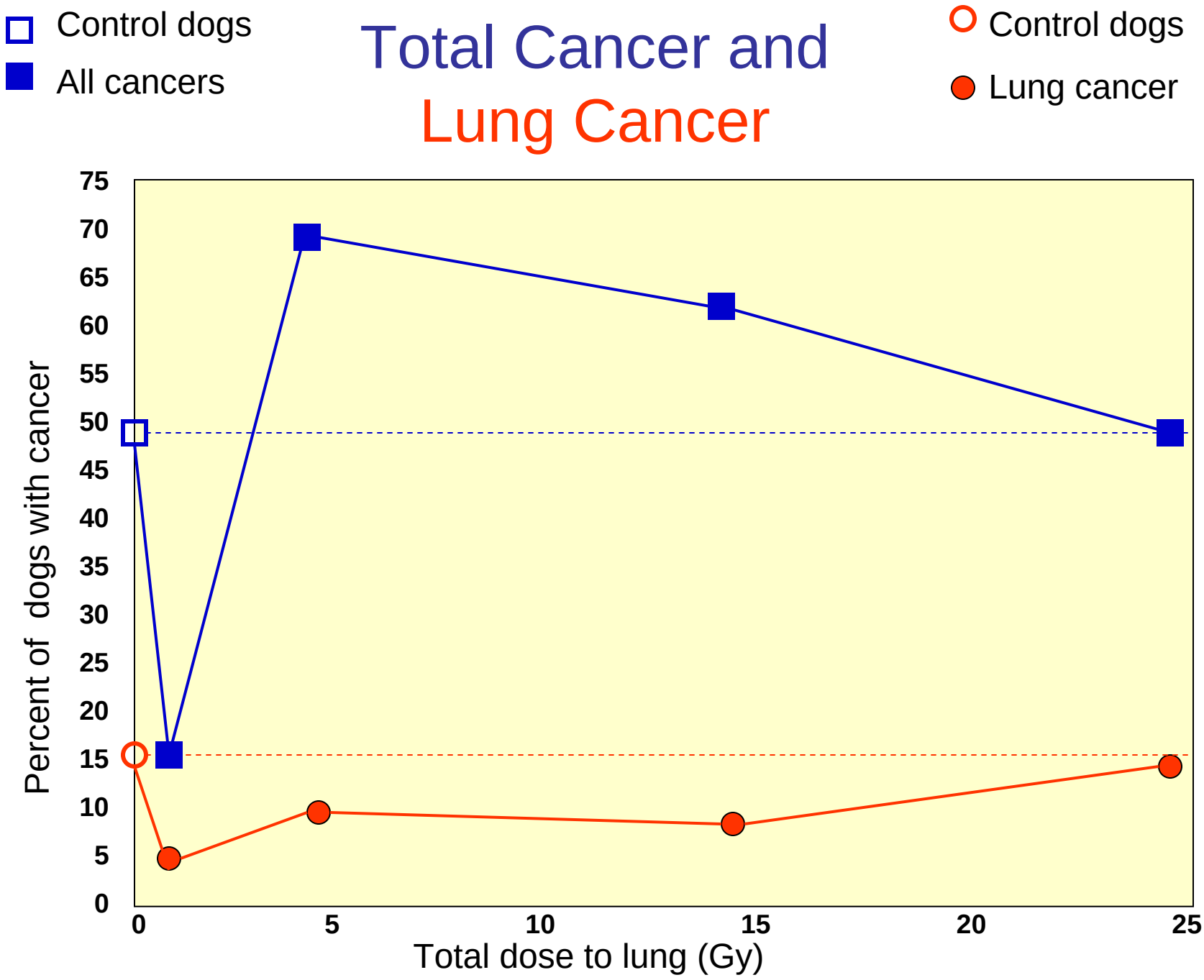
Life Shortening Response to Cumulative Dose to Lung Following Inhalation of 90-Yttrium FAP



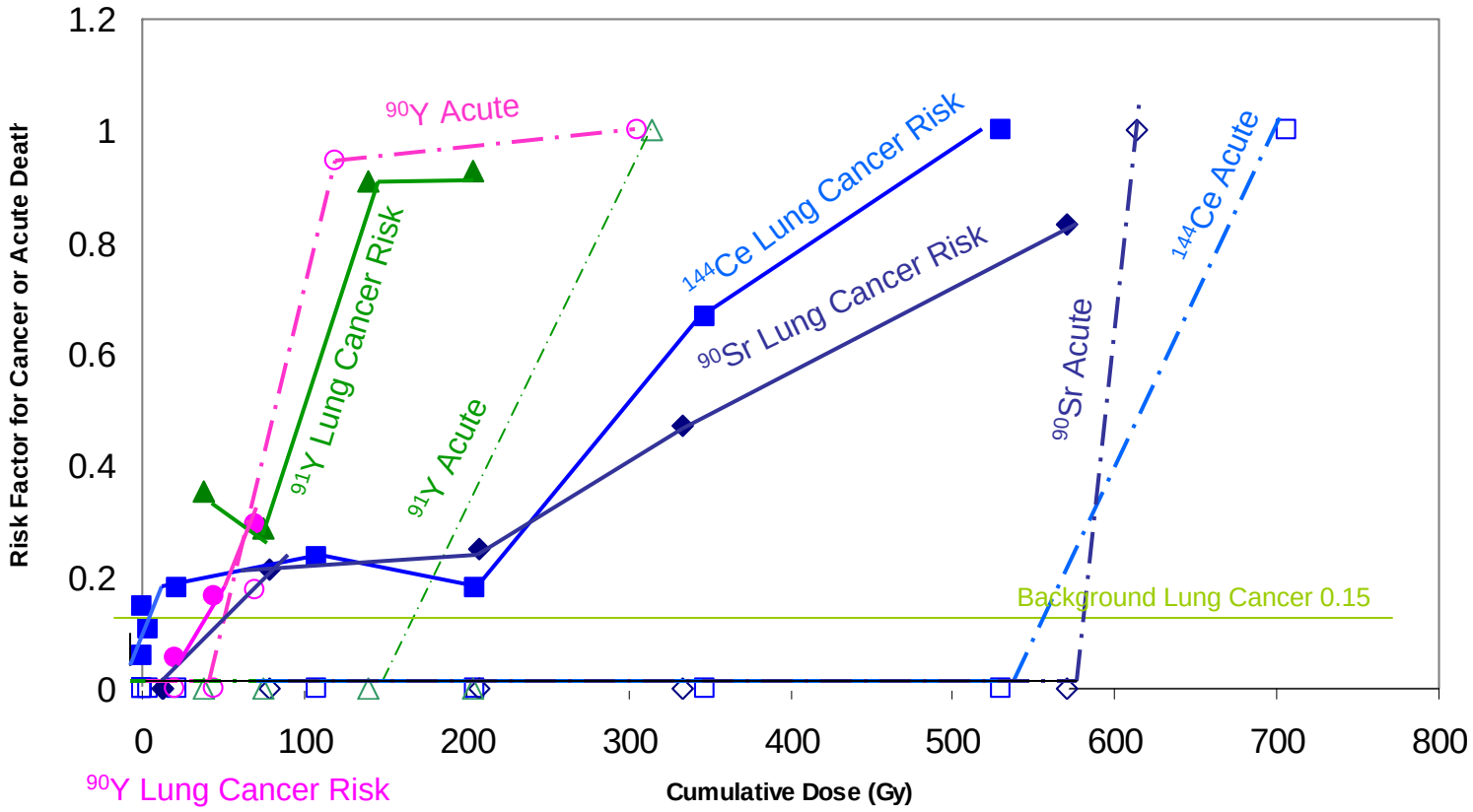
DOSE-RATE EFFECTS FOR EARLY-OCCURRING LUNG DISEASE



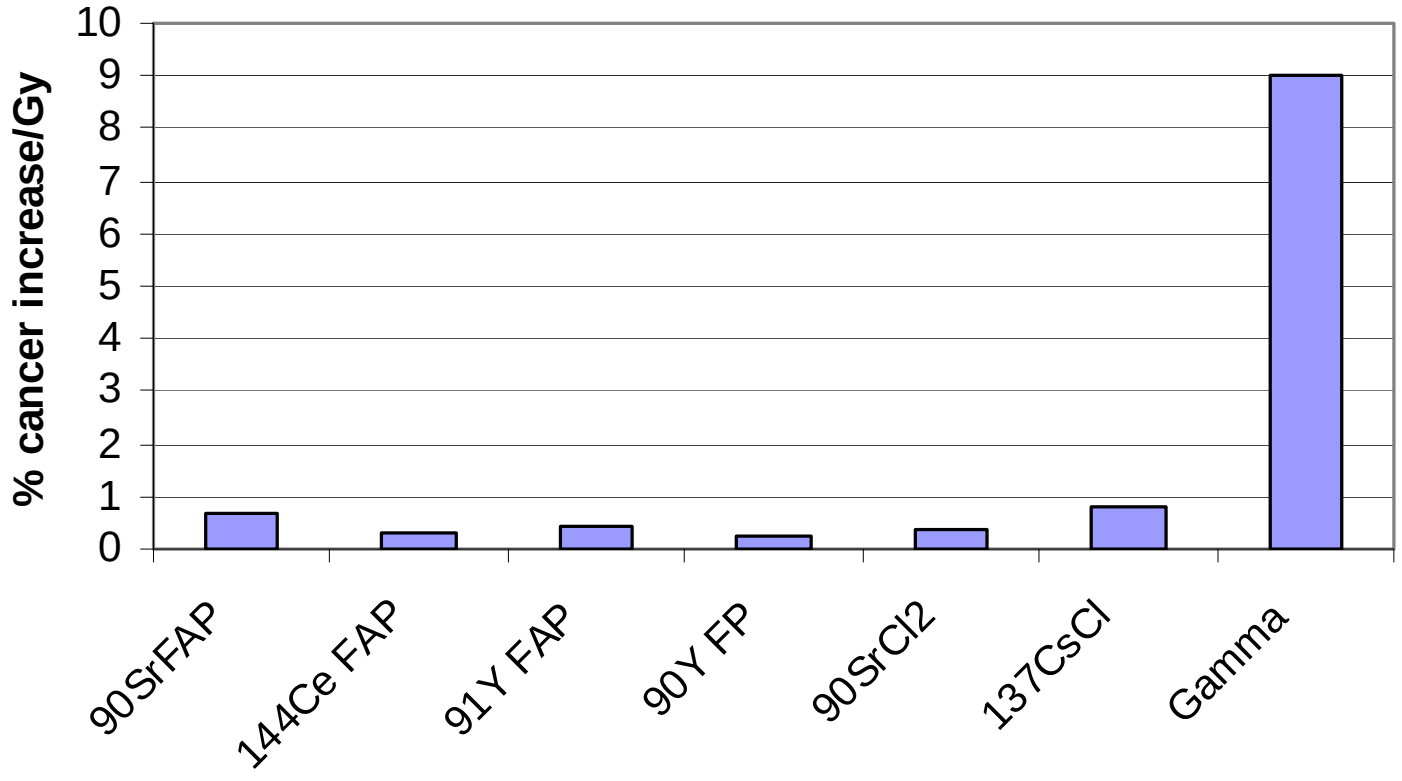
Modified from Scott et. al 1989


Control dogs
All cancers
Total Cancer and
Lung Cancer
Control dogs
Lung cancer
Percent of dogs with cancer
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
0
5
10
15
20
25
Total dose to lung (Gy)

Dose Response for Acute Death and Lung Cancer following Inhalation of FAP



Estimate of Cancer Risks in the High Dose Range (50-500 Gy) following Low Dose-Rate Exposure from Internally Deposited Radioactive Materials



Dose and Dose-Rate Effects

DDREF derived with curve fitting of the human data.

- DDREF 1.5 BEIR VII
- DDREF 2.0 ICRP (2007)

DREF derived from animal and experimental data.

• Experimental Molecular/Cellular	4-???
• Chromosome Aberrations	4-6
• Mouse data	
– Lung Adenocarcinoma	3-7
– Ovarian Tumors	7-35
– Thymic lymphoma	10-30
– Mammary tumors	1-4
– Myeloid Leukemia	2-6
• Dog Data	
– (Acute Bone Marrow)	3-4
– (Acute Lung)	10-30
• Dog Data (Cancer)	15-40

Summary

- A large dose-rate effectiveness factor is required due to the marked decrease in biological effects observed following low dose-rate radiation exposure.
- At radiation doses less than 20 Gy (20,000 mGy) to the lung following inhalation of radioactive materials, there is little life shortening and a decrease in the frequency of lung cancer.
- When the dose delivered at a low dose-rate gets very, very large (80-220 Gy in Bone and 100-700 Gy in lung), the cancer frequency approaches 100%.
- At low dose-rates the total dose required to produce acute radiation lethality is similar to the dose required to produce a high cancer frequency.
- Genetic background plays an important role in the response to large total radiation doses delivered at a low dose-rate.
- Such data should be considered in decisions about evacuation (10-50 mSv projected dose) and relocation (20 mSv projected dose first year) of the public following radiation accidents or terrorist events.

Variations in Radiosensitivity Among Individuals: A Potential Impact on Risk Assessment?

J.S. Bedford
Colorado State University

Mouse strains differ greatly in carcinogenic radiosensitivity.

Examples:

- **CBA vs C57BL/6 -- AML**
- **BALB/c vs C57BL/6 -- Mammary Cancer**
- **Balb/c vs MSM vs (B x M) F1 hybrids – Lymphomas**
- **STS(resistant) x BALB/c(sensitive) Recombinant congenics**
  20 strains – B-cell; T-cell; and Myeloid tumors

CBA vs C57BL/6

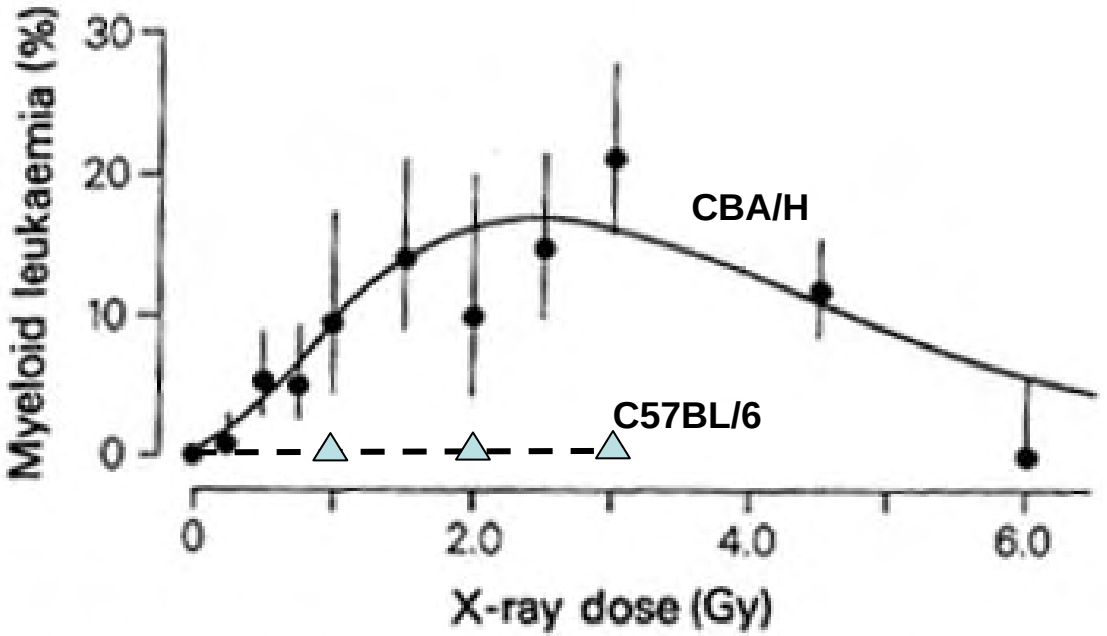


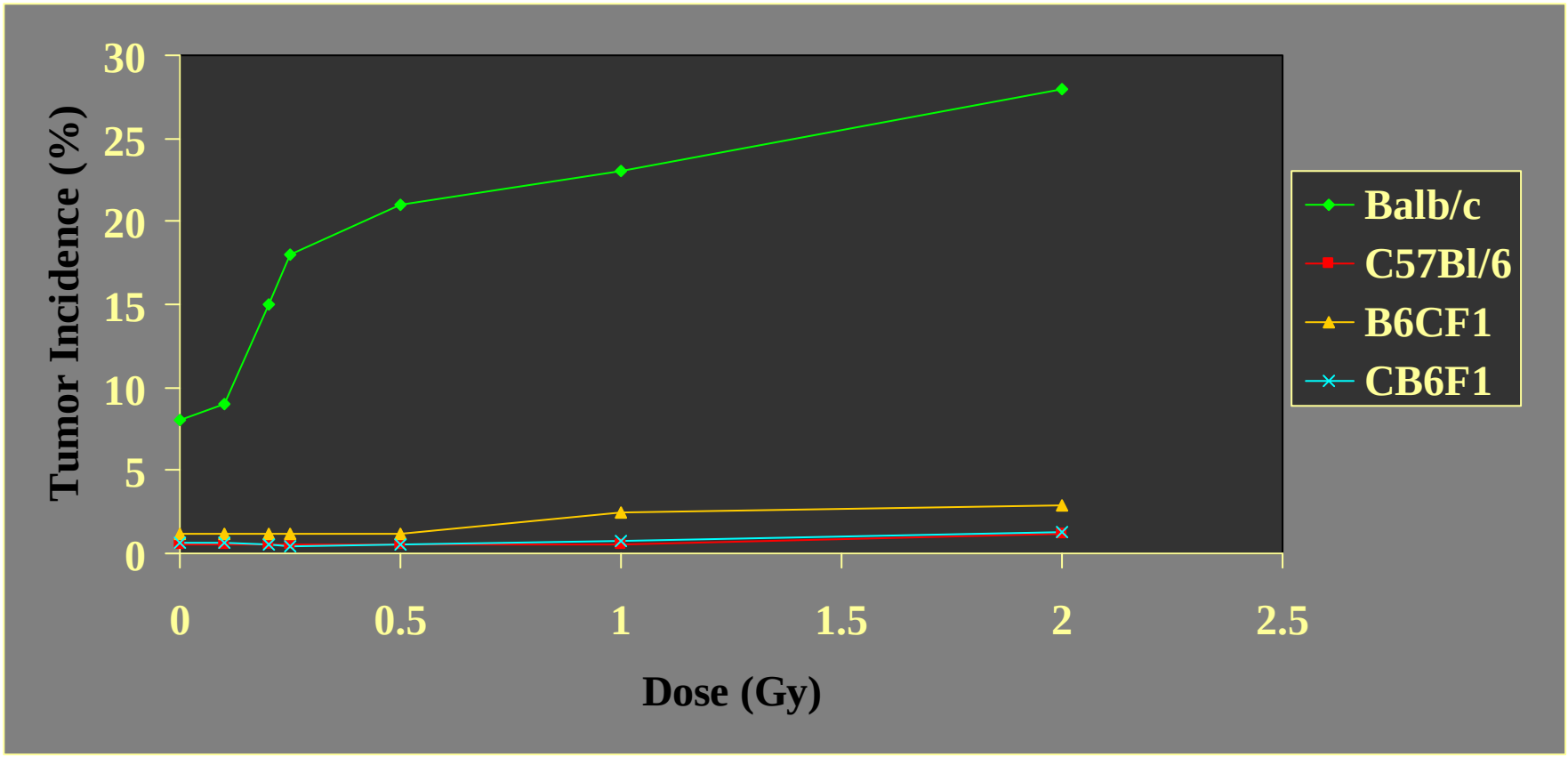
Figure 2 Myeloid leukaemia frequency % with ±80% binomial confidence limits after whole body exposure of male CBA/H mice to 250 kVp X-rays giving tissue doses in the range 0.25–6.0 Gy. No case has been seen in over 800 unirradiated controls so far fully examined. The fitted curve is $aD^2 e^{-\lambda D}$ (Table II).

CBA from: R.H.Mole, D.G.Papworth, and M.J.Corp, Br. J. Cancer 47, 285-291 (1983)

Radiation-Induced Mammary Cancer as a Function of Genetic Background

Ullrich, et al.

BALB/c vs C57BL/6



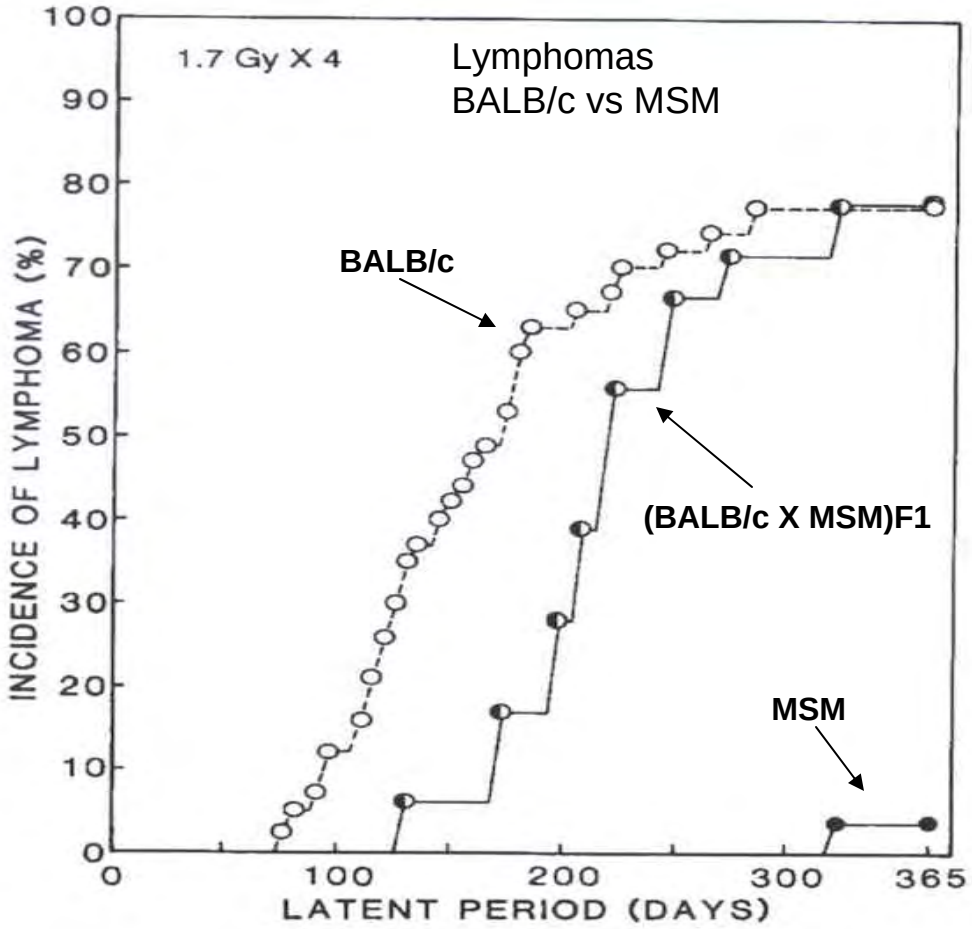


Fig. 1. Cumulative incidences of lymphomas in females MSM, BALB/cHeA and (BALB/cHeA × MSM) F_1 mice exposed to four doses of 1.7 Gy of X-rays. –●–: MSM, –○–: BALB/cHeA, –◐–: (BALB/cHeA × MSM)F_1.

M.Okumoto, et al, Exp.Anim 44, 43-48 (1995)

P.Demant---- STS (resistant) x BALB/c Recombinant Congenics

(**Each strain carries 12.5% of genes of resistant strain on genetic background of sensitive strain**)

4 x 1.5 Gy @ 1 Wk intervals

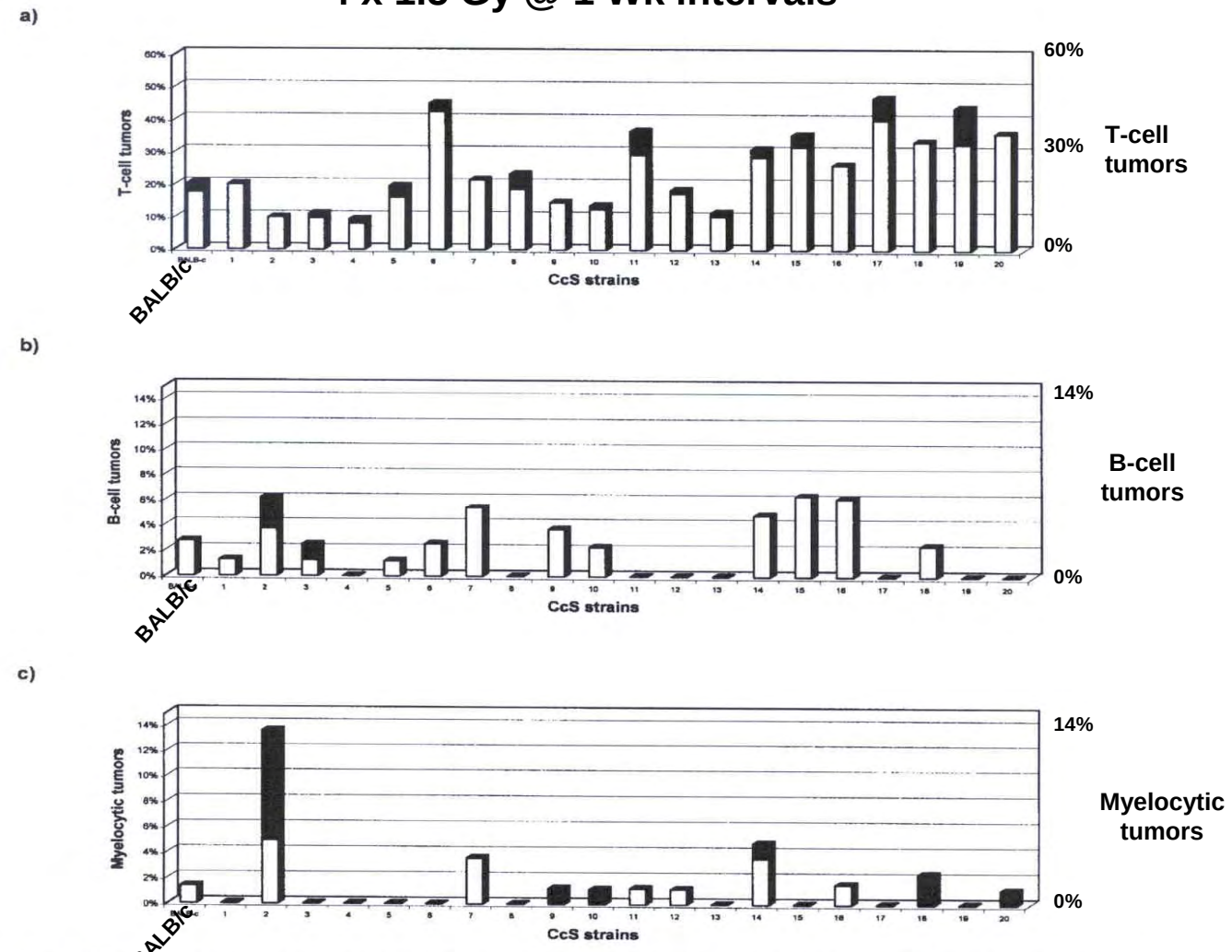


FIGURE 1 – Incidence of tumors in irradiated mice of strains BALB/c and Ccs-1–CcS-20. The closed parts of the bars indicate disseminated (leukemic) tumors. Note that the y-axis scales of *a*, *b*, and *c* are different.

Szymanska, et al, Int.J.Cancer 83, 674-678 (1999)

Humans

Variation in Cancer Susceptibility among Individuals

1) Spontaneous

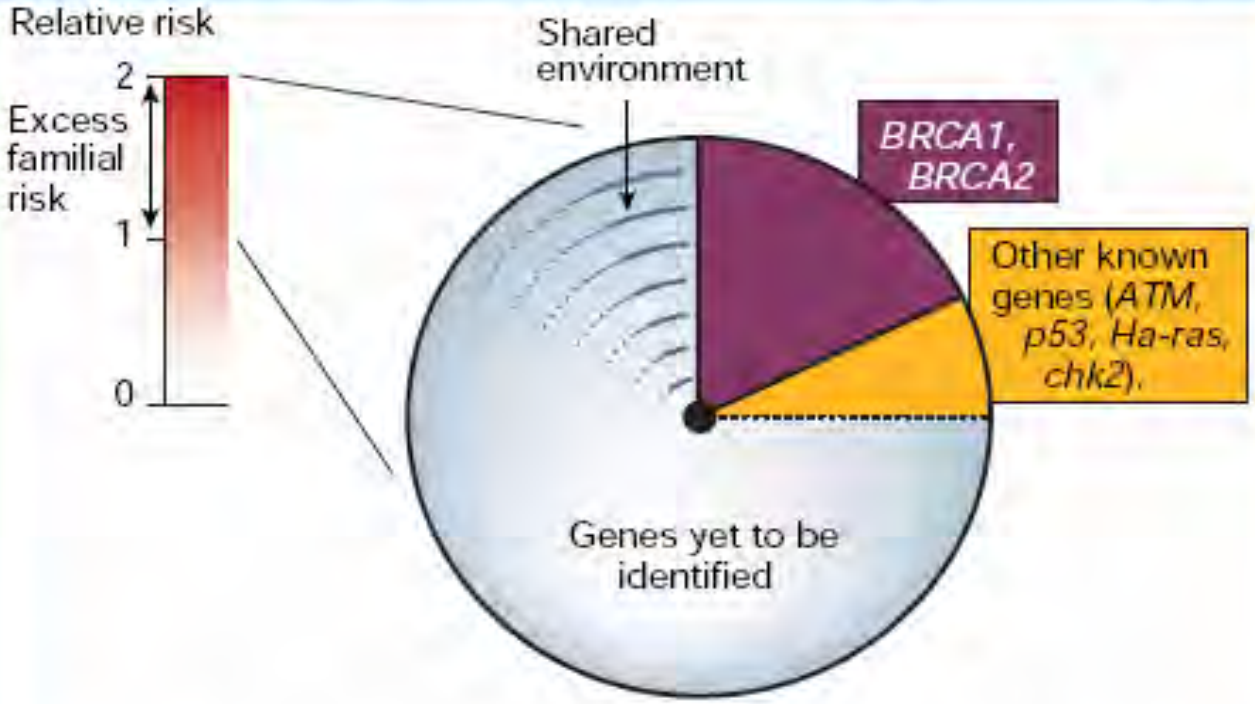
2) Radiation Induced

We already know some phenotypes with wide variation…
without any cell or molecular studies.
eg., age, sex

From: ***B.A.J. Ponder, Cancer Genetics, Nature 411 336-341 (2001)***

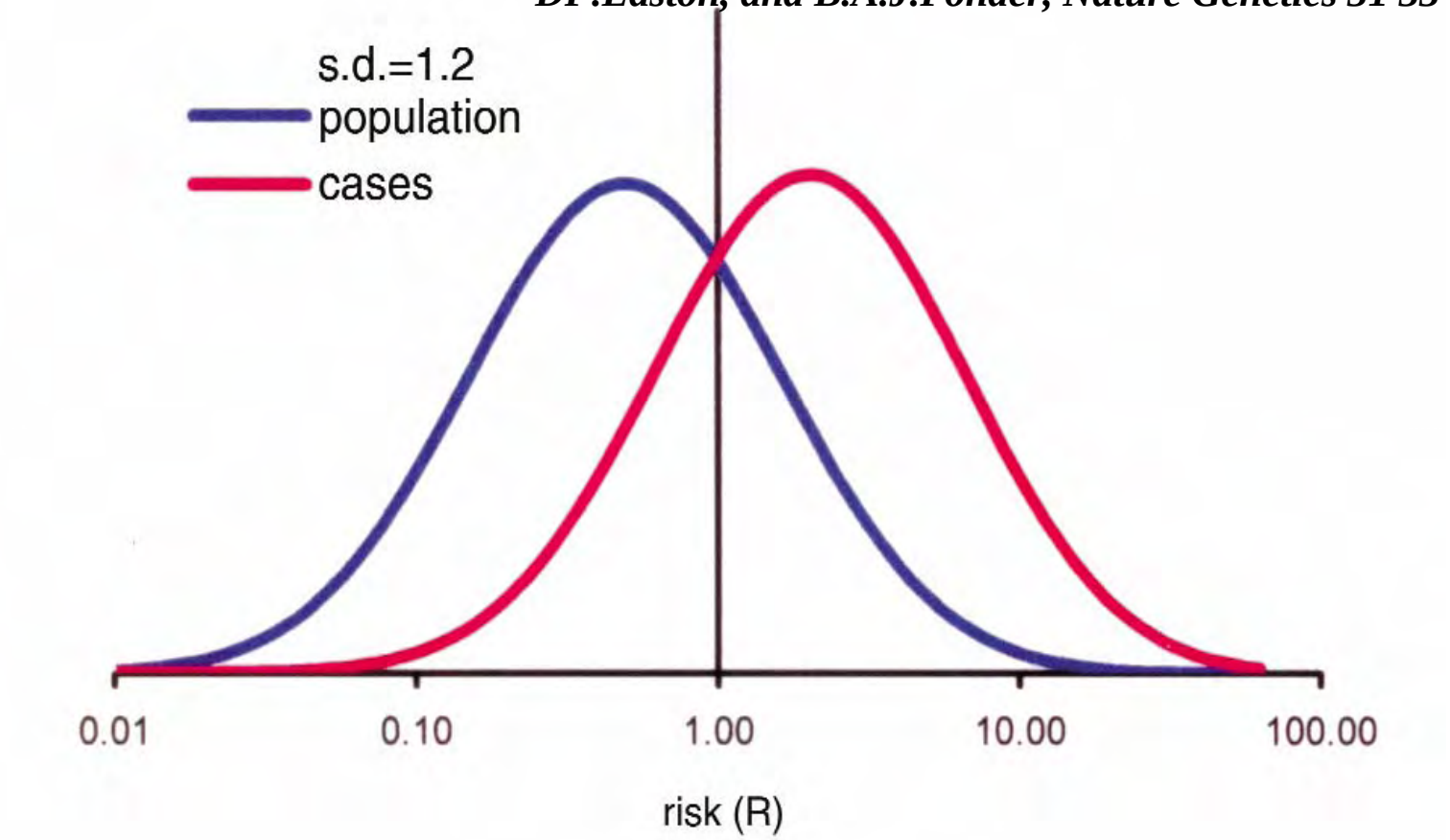
Box 1

What genes might account for familial breast cancer?



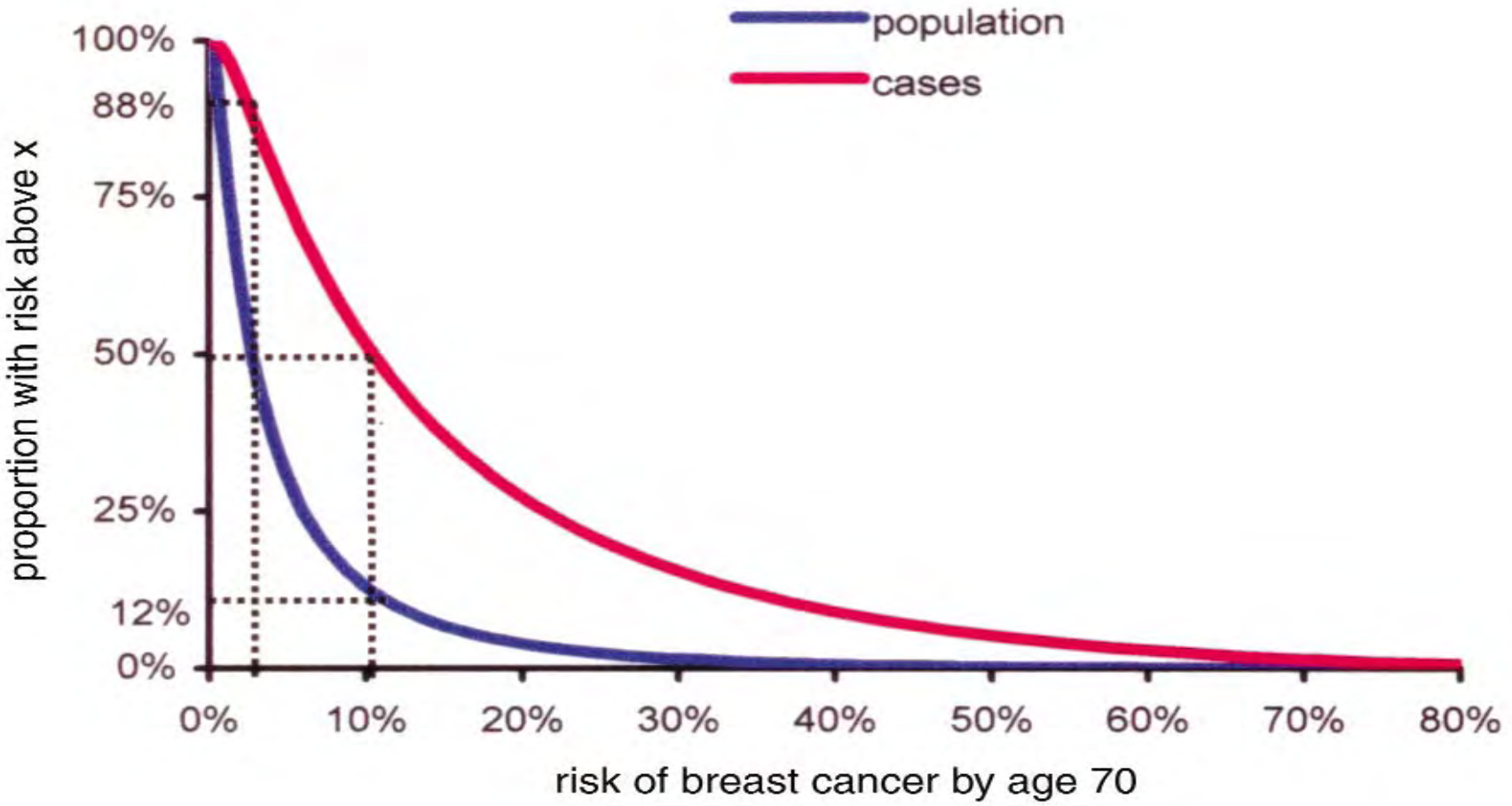
Averaged across all ages, the risk of breast cancer to the sister, mother or daughter of a case is increased about twofold, as illustrated in the figure above. This excess familial risk provides an upper estimate (assuming all the risk is genetic) of the genetic effect that must be explained.

From: P.D.P. Pharoah, A.Antoniou, M.Bobrow, R.L.Zimmerman, DF.Easton, and B.A.J.Ponder, Nature Genetics 31 33-36 (2002)



Distribution of breast cancer risk in the population and in individual cases. Risks are shown on a log scale; the arithmetical average risk for the entire population has been set at 1.0 (see Methods). The risk distribution in individuals who will develop breast cancer (cases) is shifted to the right. The standard deviation describes the spread of risk between high and low values within the population, and thus the potential to discriminate different levels in different individuals.

From: P.D.P. Pharoah, A.Antoniou, M.Bobrow, R.L.Zimmerman, DF.Easton, and B.A.J.Ponder, Nature Genetics 31 33-36 (2002)



Proportion of population above a specified absolute risk of breast cancer and proportion of cases occurring in that fraction of the population. Fifty percent of the population have a risk of breast cancer greater than 3% by age 70, and 88% of all breast cancers occur in this half of the population. Half of all cases occur in the 12% of the population with an 11% or greater risk of breast cancer by age 70.

The *Tinea Capitis* Study

Genetic predisposition for the development of radiation associated meningioma: an epidemiological study

Pazit Flint-Richter, Siegal Sadetzki, Lancet Oncology 8: 403-410 (2007)

1) Radiation is the only environmental causative factor known for meningiomas,
2) it occurs in less than 1% of irradiated individuals, and
3) spontaneously, it rarely aggregates in families.

Flint-Richter and Sadetzki analyzed data from a large study of cancer incidence in a population of patients irradiated for control of *tinea capitis* in the 1950s. These were mainly children in families from north Africa and the middle east who were prospective immigrants to Israel.

Found: A highly significant clustering of meningiomas in first-degree relatives who were irradiated.

From: P. Flint-Richter and S. Sadetzki; Lancet Oncol. 8, 403-410 (2007)
(Tinea capitis study)

	Meningioma	***No Meningioma***
Radiation	160 families with an index case who was irradiated and also developed meningioma (RAM group)* **17/160 = 11%** **1082 siblings included in study (including index participants)**	145 families with an index control who was irradiated, but did not develop meningioma **1/145 (~1%)** **1058 siblings included in study (including index participants)**
No Radiation	85 families with an index case who was not irradiated but did develop meningioma (non-RAM group) **1/85 (~1%)** **518 siblings included in study (including index participants)**	135 families with an index control who was not irradiated and did not develop meningioma† **2/135 (~1%)** **863 siblings included in study (including index participants)**

Pazit Flint-Richter, Siegal Sadetzki, Lancet Oncology 8: 403-410 (2007)

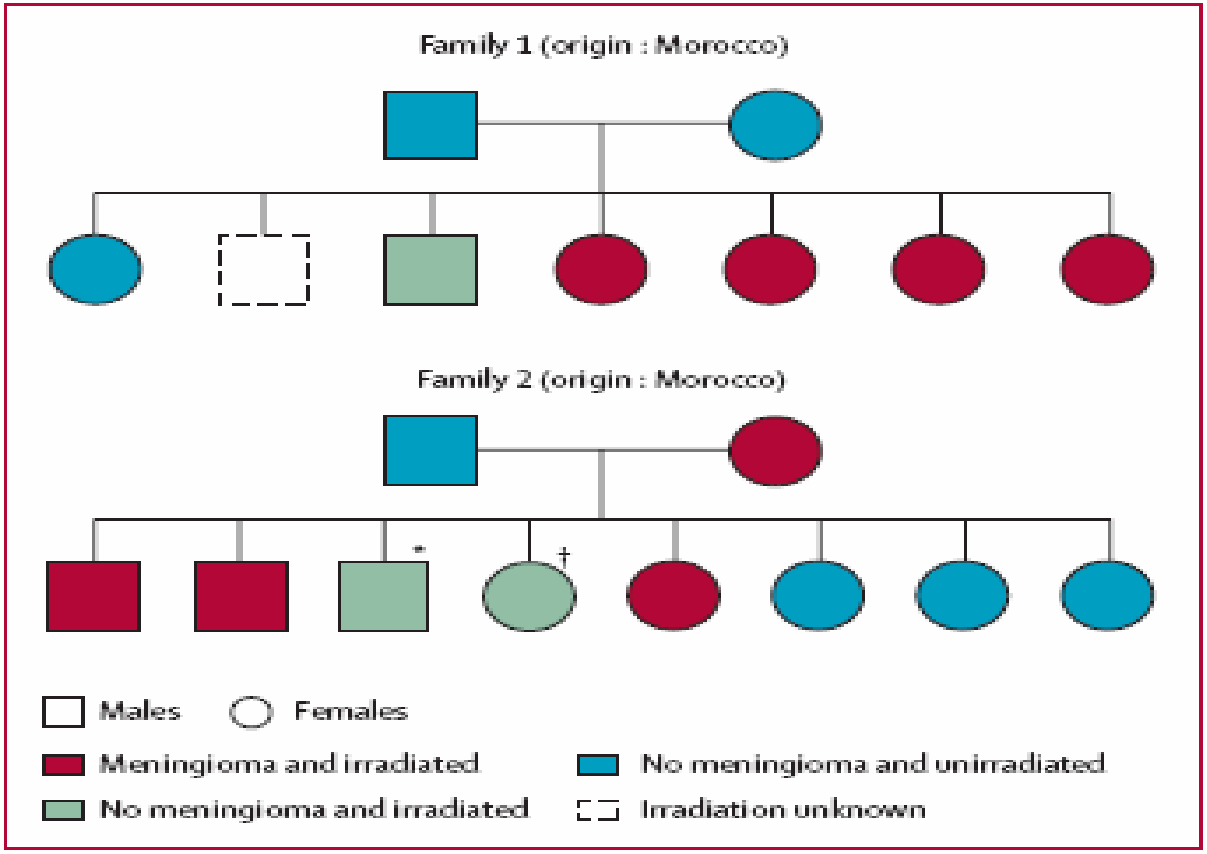


Figure 2: Family tree of two families with four RAM in first-degree relatives
Family 1 includes seven siblings of whom four sisters and one brother were irradiated for tinea capitis and all four sisters developed meningiomas. Family 2 includes an irradiated mother and eight siblings of whom five were irradiated. The mother and three of the irradiated siblings (two brothers, one sister) developed meningiomas. Also, two irradiated siblings were diagnosed with leukaemia (*) or breast cancer (†).

How broad is the spectrum of radiosensitivities among individuals and, and how might it affect the assessment of radiation risk?

Is it a question of only a few people being extremely hypersensitive …

…or are there lots of people who are mildly hypersensitive, and who drive the risk estimates, with the remainder being more resistant and at a much lower risk per unit dose?

HOW DO YOU FIND OUT?

Determining Individual Sensitivities for Radiation Carcinogenesis?

either

1) Sequence genome of each individual,

2) Complete identification and functional characterization of each (or most) gene, that affects radiosensitivity including the ones whose functions are currently unknown,

3) Determine the functional effect of each SNP seen in each of the pertinent genes identified, and

4) Determine the multiple interaction effects of the group of SNPs found

or

1) Develop some surrogate phenotypic assays.

…What characteristics should they have?

Desirable Characteristics for Useful Surrogate Assays for Predicting Radiation Carcinogenesis Sensitivity in Individuals

Should show a dose-response characteristics similar to that for carcinogenesis in the relevant dose range.
(But the dose response characteristics for all tumors is not the same. Different assays for different tumors of major concern for effects in humans?)

Should show characteristics changes for RBE vs LET and dose-rate effects similar to those for carcinogenesis.

Should reliably resolve, say, 1.5 to 2.0-fold differences in radiosensitivity

May (is likely to?) require more than one assay.

Should be robust and minimally invasive.

Would be useful for mechanistic studies to connect with a damage known to be related to carcinogenesis….thus, the past emphasis on mutagenesis, cytogenetics, DNA damage processing, cell killing, apoptosis, checkpoint responses, etc. in cellular systems.

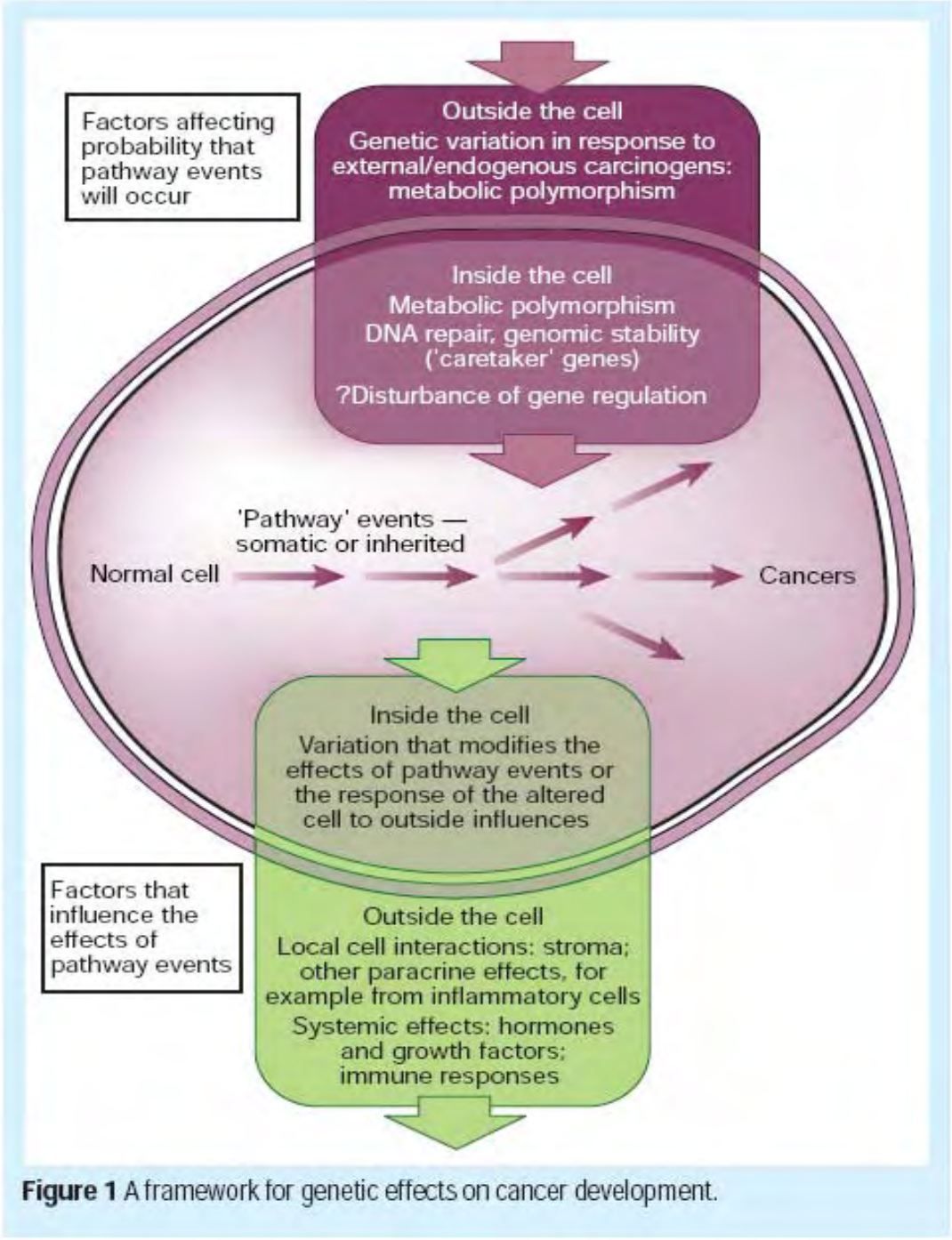


Figure 1 A framework for genetic effects on cancer development.

From:
B.A.J. Ponder,
Cancer Genetics,
Nature 411 336-341 (2001)

For radiation, in particular:

Radiation induces mutations.

Radiation induces cancer.

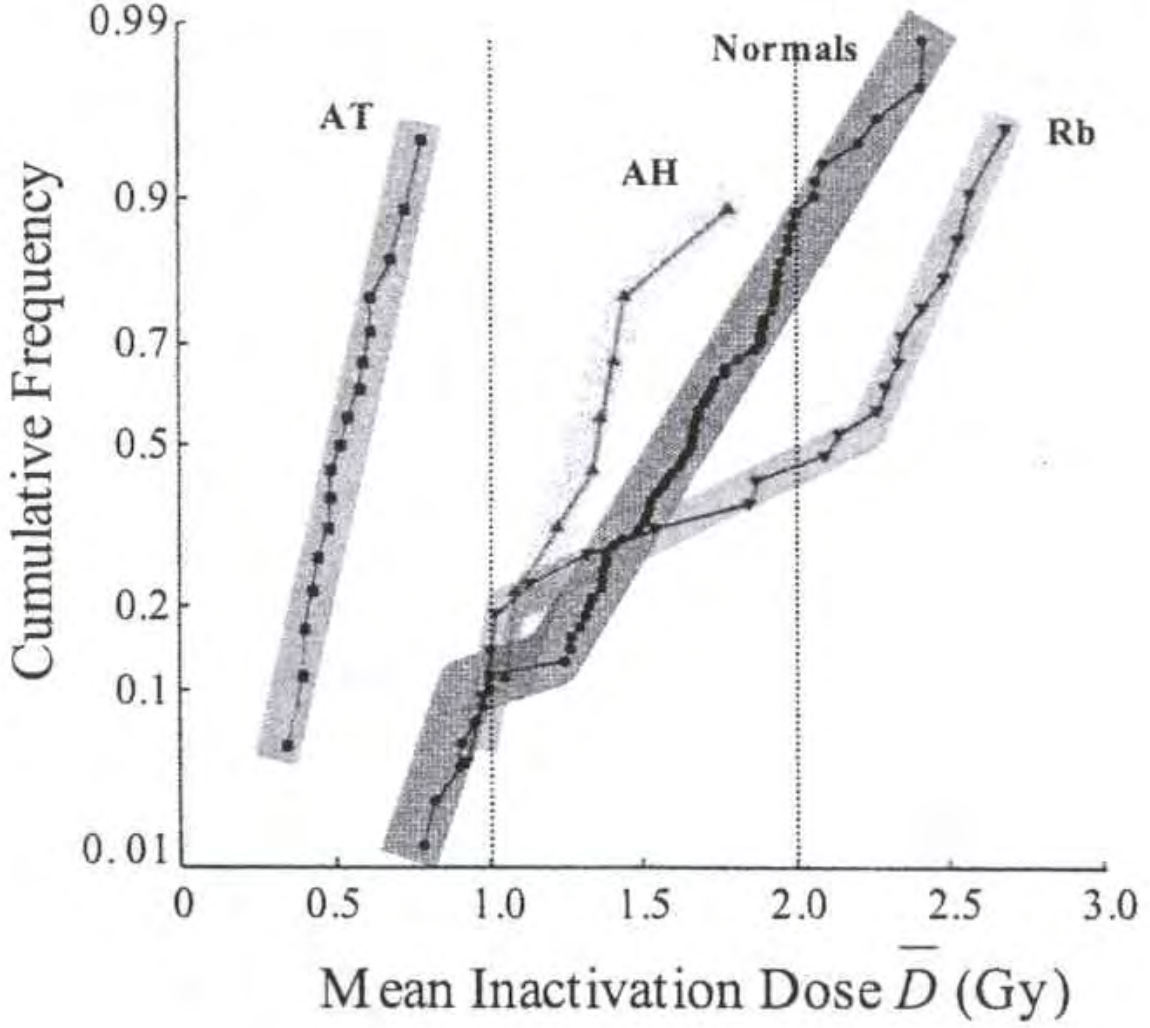
Some mutations (a sub-set) are involved in cancers

In mammalian cells most **radiation**-induced mutations are large… often visible cytogenetically.

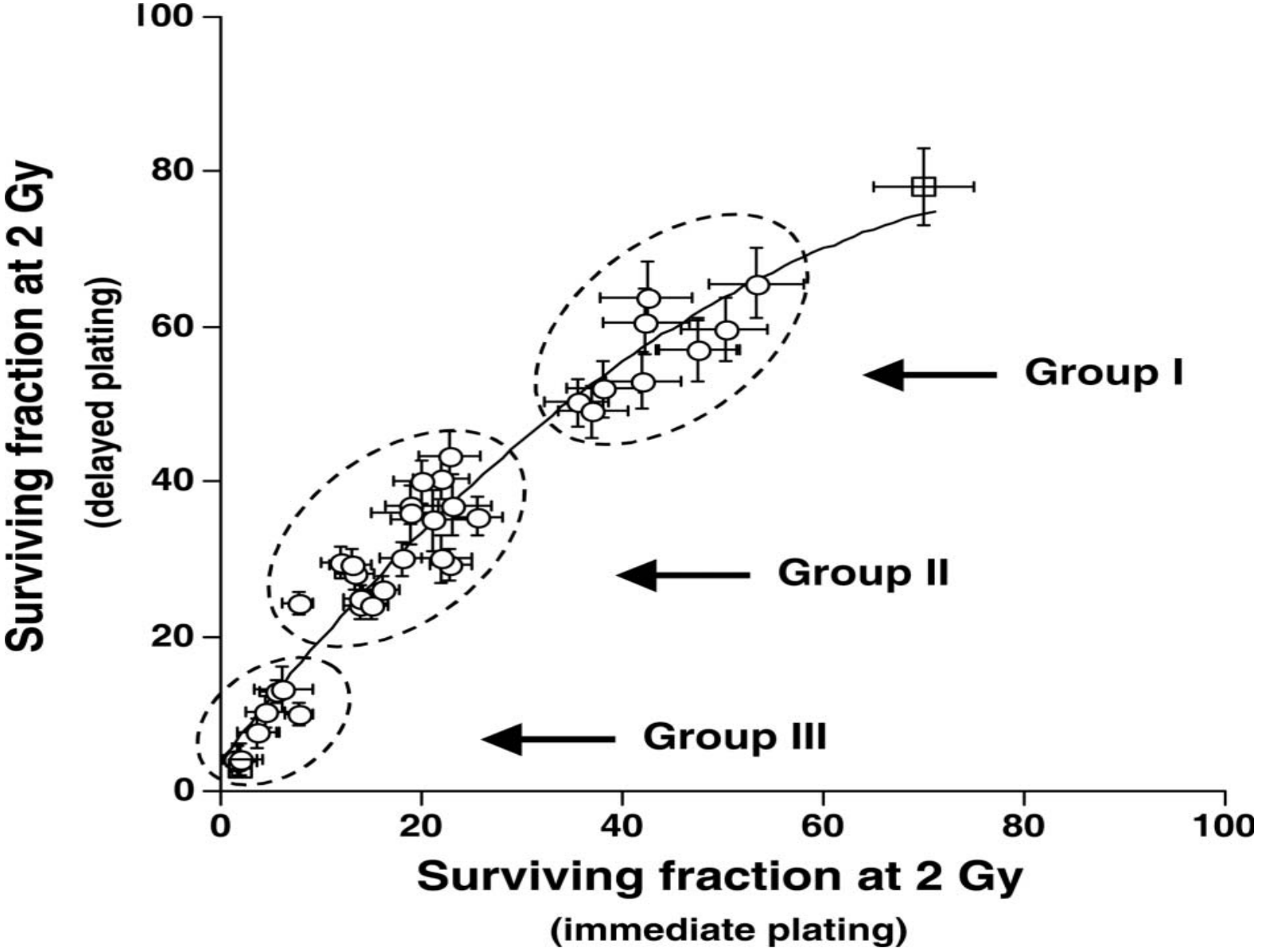
A sub-set of chromosome aberrations kill cells another sub-set can initiate cancer…shown in at least in some systems

Instabilities vs initial genetic changes

Radiosensitivity is under genetic control.



A summary from the literature due to P.J. Deschavanne, D. Debieu, B. Fertil, and E.P. Malaise. Int.J.Radiat. Biol. 50, 279-293, (1986)



Joubert, et al, Int. J. Radiat. Biol., 84, 1-19 (2008)
(Also compared sensitivity for PCC & DSB rejoining)

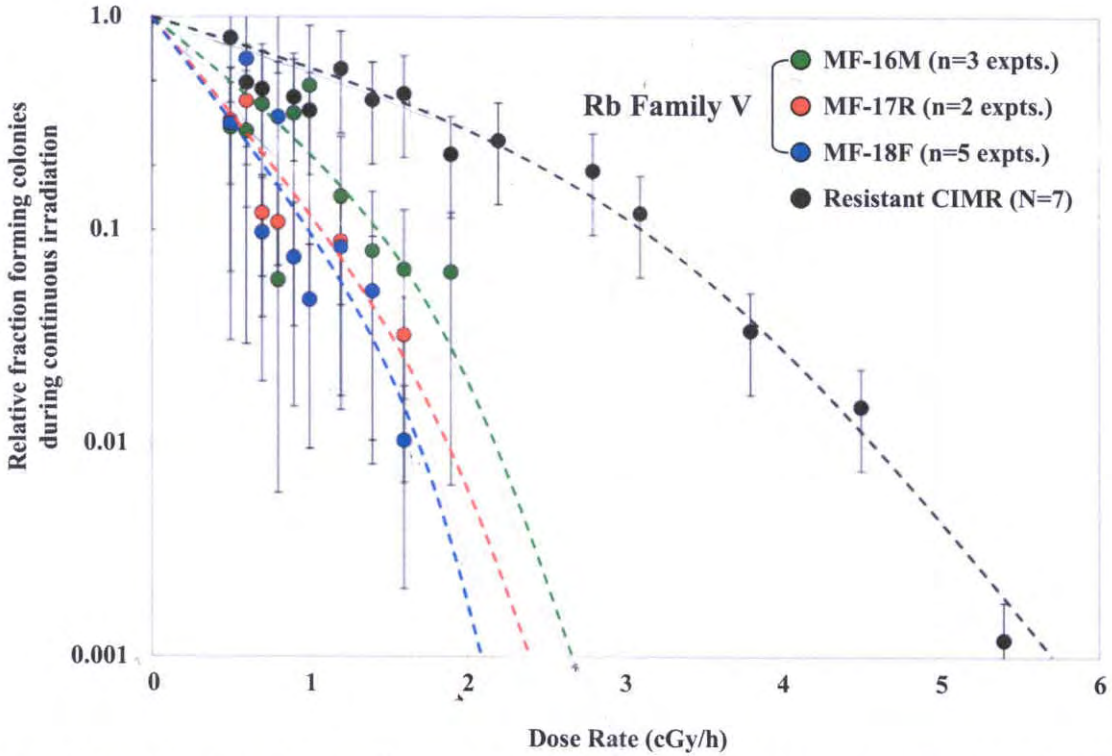
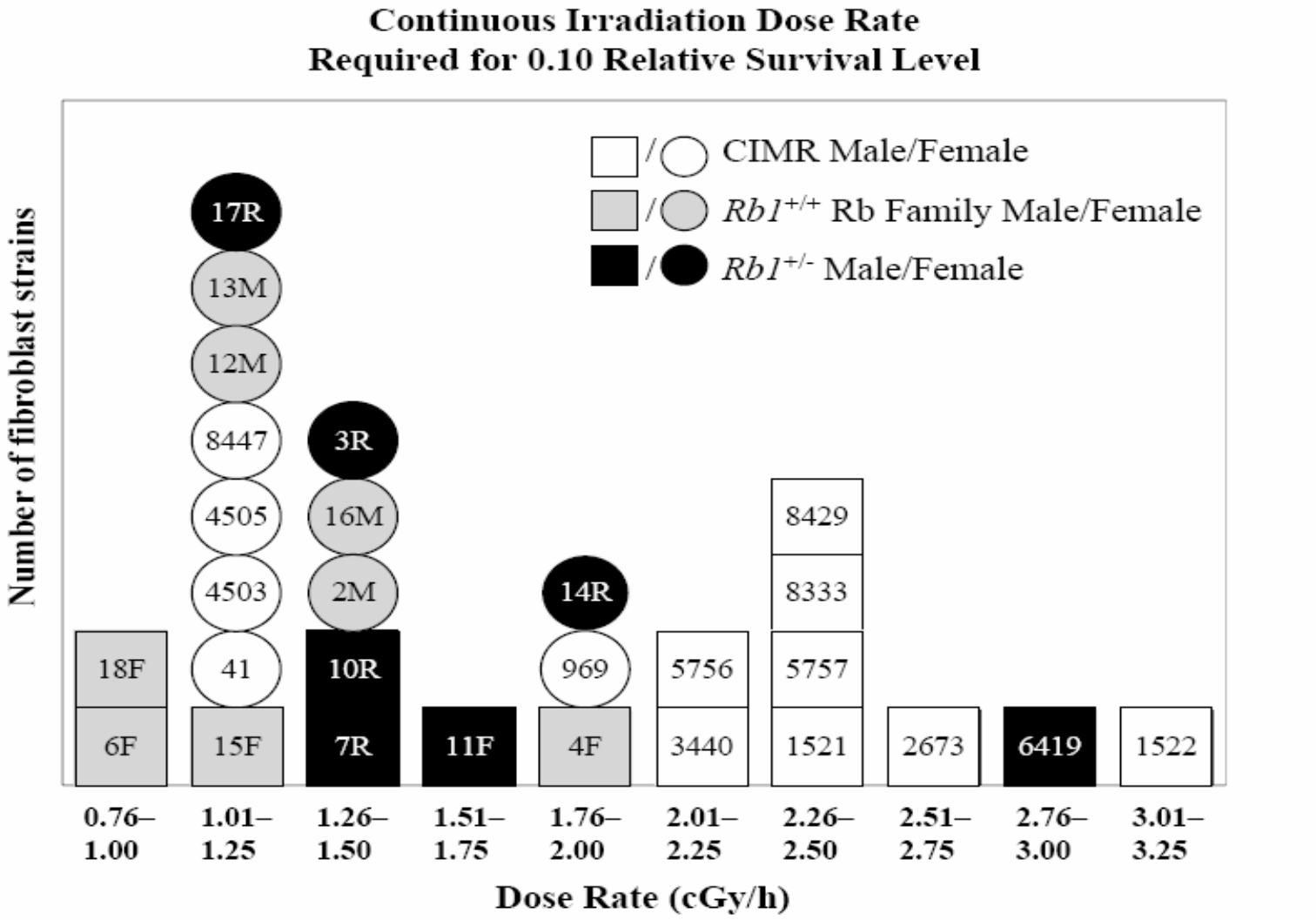


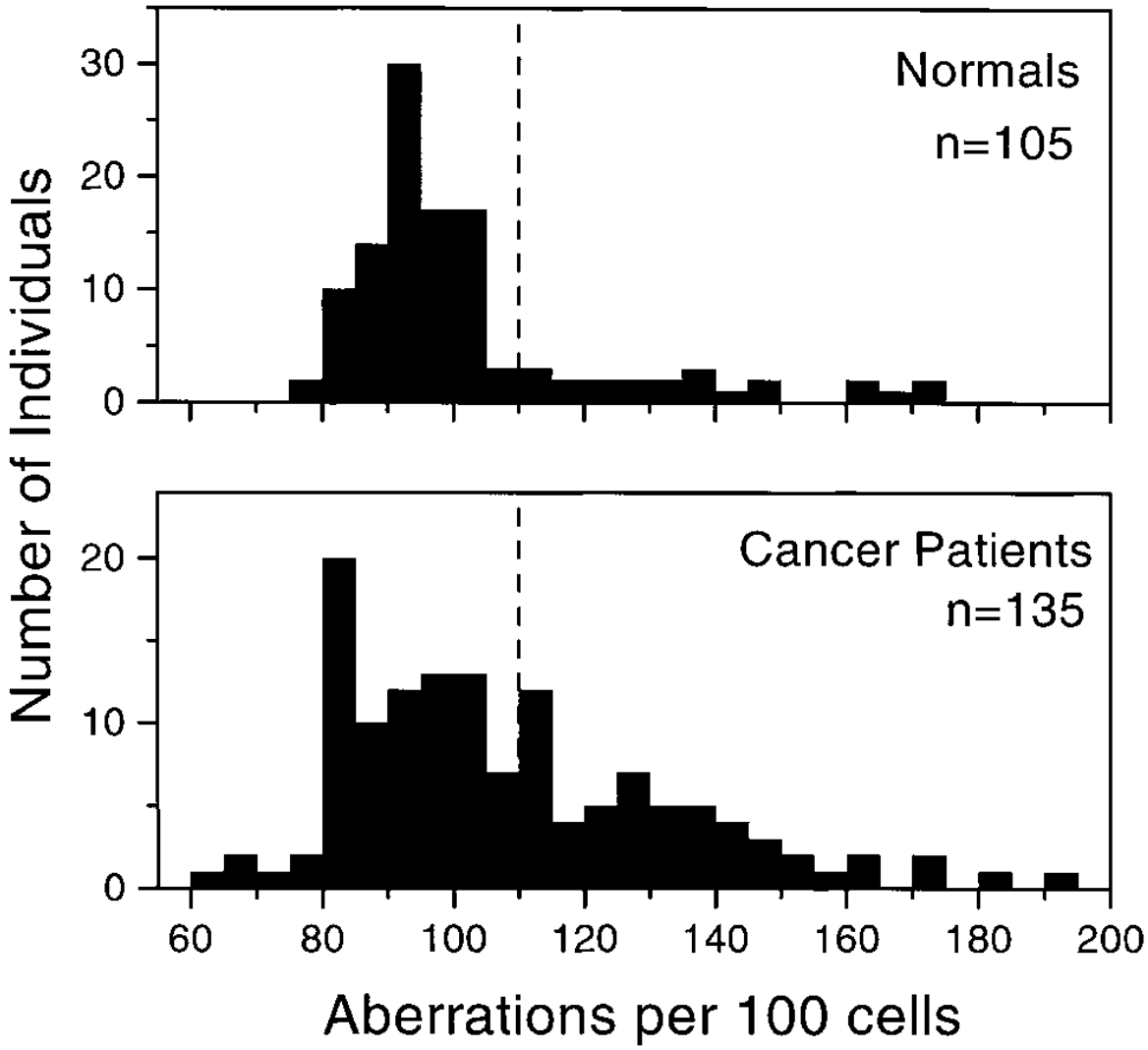
Figure 5.15. Results of the continuous LDR irradiation colony formation assay for fibroblast strains derived from members of Rb Family V: MF-16M (green circles), MF-17R (red circles), and MF-18F (blue circles), compared to the average response of the 7 radioresistant CIMR control fibroblast strains (black circles; see Tables 5.2 and 5.3 and Figure 5.10). Individual strain error bars represent standard errors of the mean, n = number of experiments.

Paul F. Wilson, 2006



Some RB probands; their unaffected parents, and some other apparently normal, low passage human cell strains
Paul Wilson (2006)

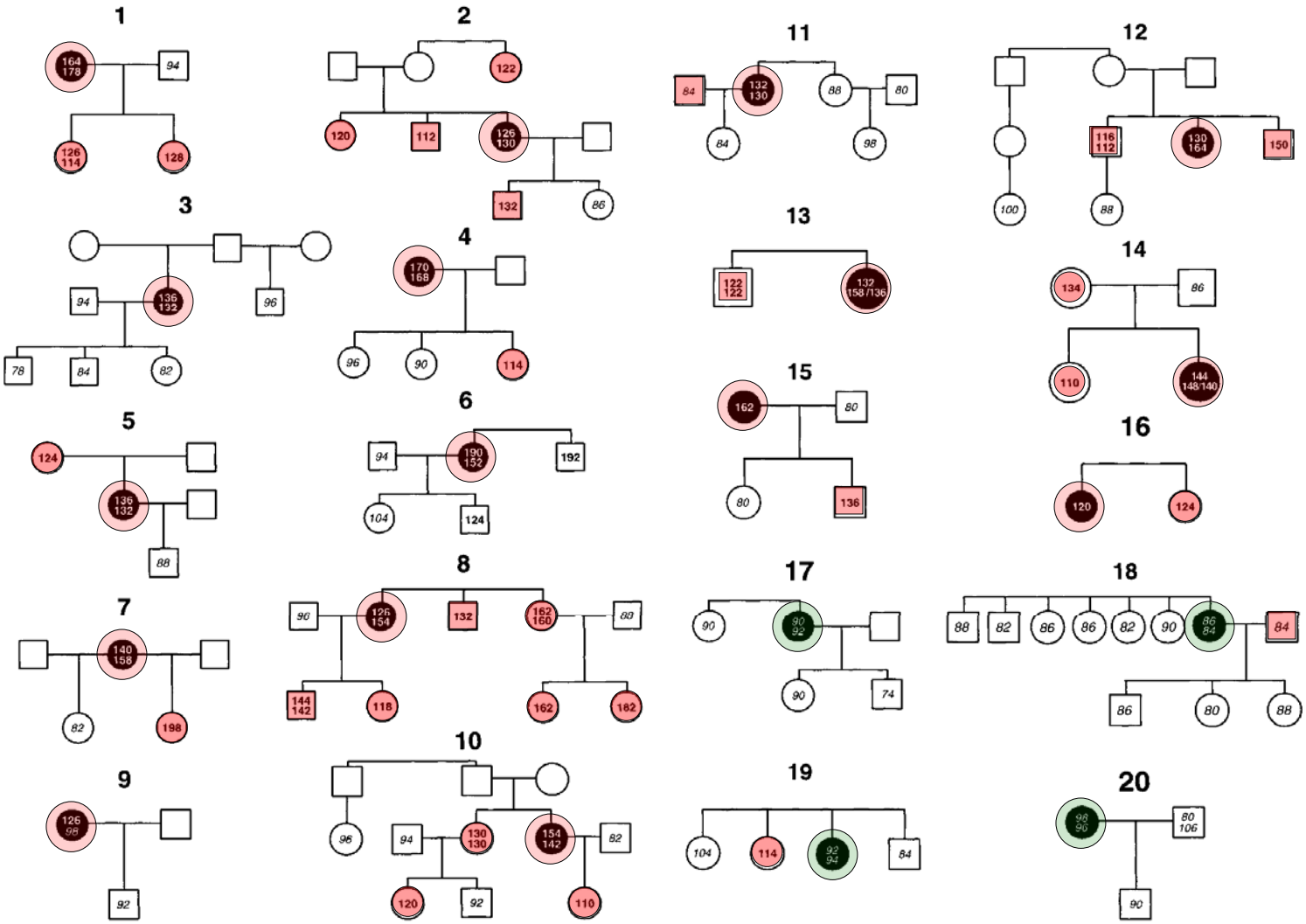
G2 Chromosomal Radiosensitivity -- 0.5Gy Human PBL



S. A. Roberts, A. R. Spreadborough, B. Bulman, J. B. P. Barber, D. G. R. Evans, and D. Scott
Heritability of Cellular Radiosensitivity: A Marker of Low-Penetrance Predisposition Genes in Breast Cancer? Am. J. Hum. Genet. 65:784–794, 1999

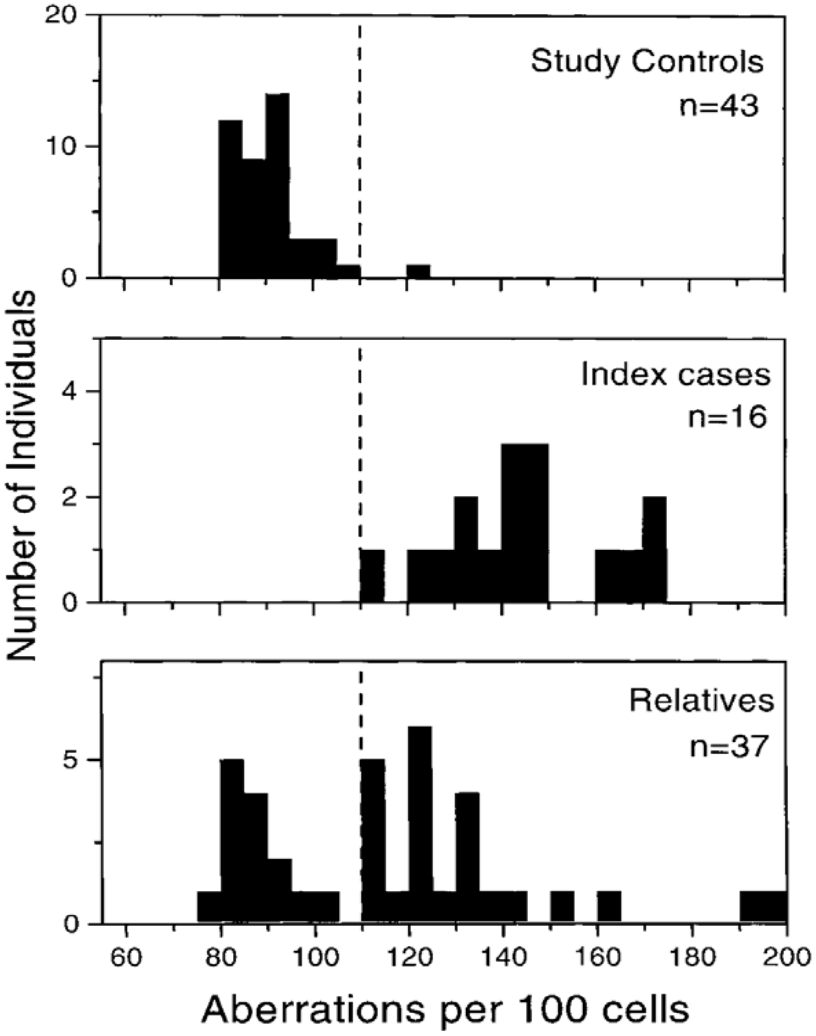
G2 Chromosomal Radiosensitivity

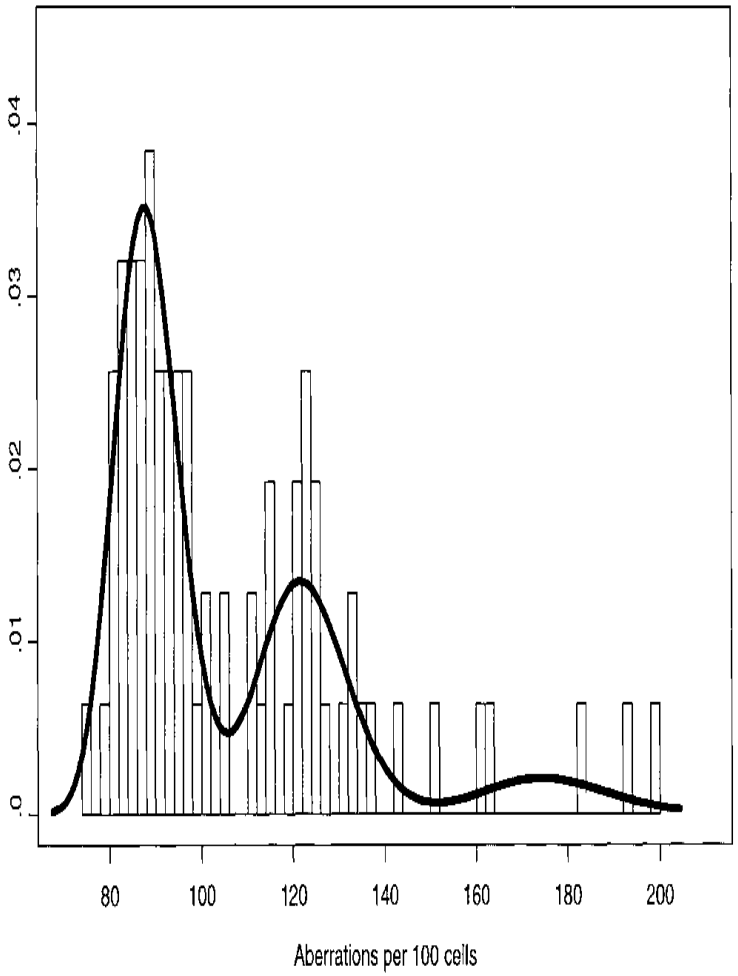
(0.5Gy) PBL from Breast Cancer Patients and 1st Degree Relatives



S. A. Roberts, A. R. Spreadborough, B. Bulman, J. B. P. Barber, D. G. R. Evans, and D. Scott
Heritability of Cellular Radiosensitivity: A Marker of Low-Penetrance Predisposition Genes in Breast Cancer? Am. J. Hum. Genet. 65:784–794, 1999

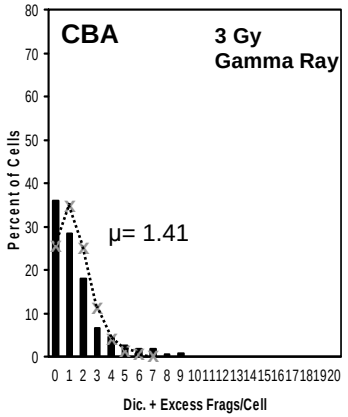
G2 Chromosomal Radiosensitivity (0.5Gy) PBL from Breast Cancer Patients and 1st Degree Relatives

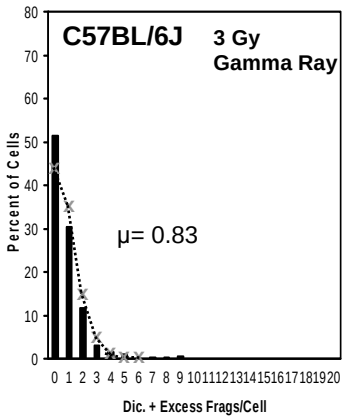


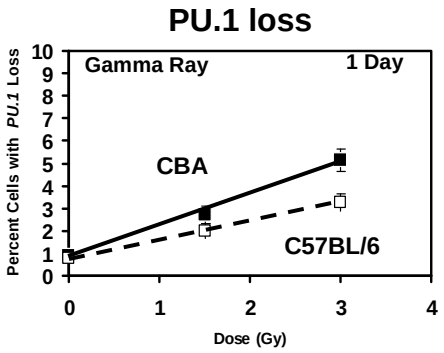


S. A. Roberts, A. R. Spreadborough, B. Bulman, J. B. P. Barber, D. G. R. Evans, and D. Scott *Heritability of Cellular Radiosensitivity: A Marker of Low-Penetrance Predisposition Genes in Breast Cancer?* Am. J. Hum. Genet. 65:784–794, 1999

Radiosensitivity for gross chromosome aberrations, and deletions in chromosome 2 containing *PU.1*
vs.
Radiosensitivity for leukemia induction *CBA vs C57BL/6*







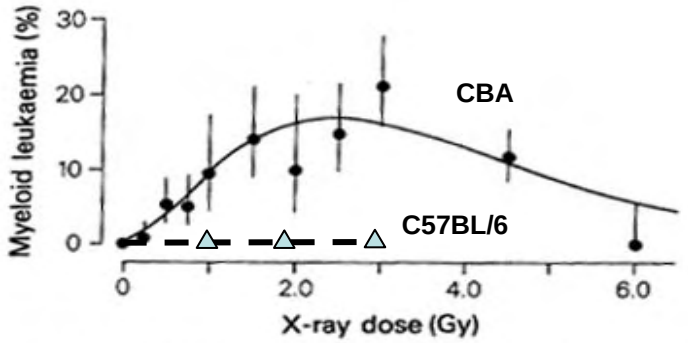


Figure 2 Myeloid leukaemia frequency % with ±80% binomial confidence limits after whole body exposure of male CBA/H mice to 250 kVp X-rays giving tissue doses in the range 0.25–6.0 Gy. No case has been seen in over 800 unirradiated controls so far fully examined. The fitted curve is $aD^2 e^{-\lambda D}$ (Table II).

CBA from: R.H.Mole, D.G.Papworth, and M.J.Corp, Br. J. Cancer 47, 285-291 (1983)

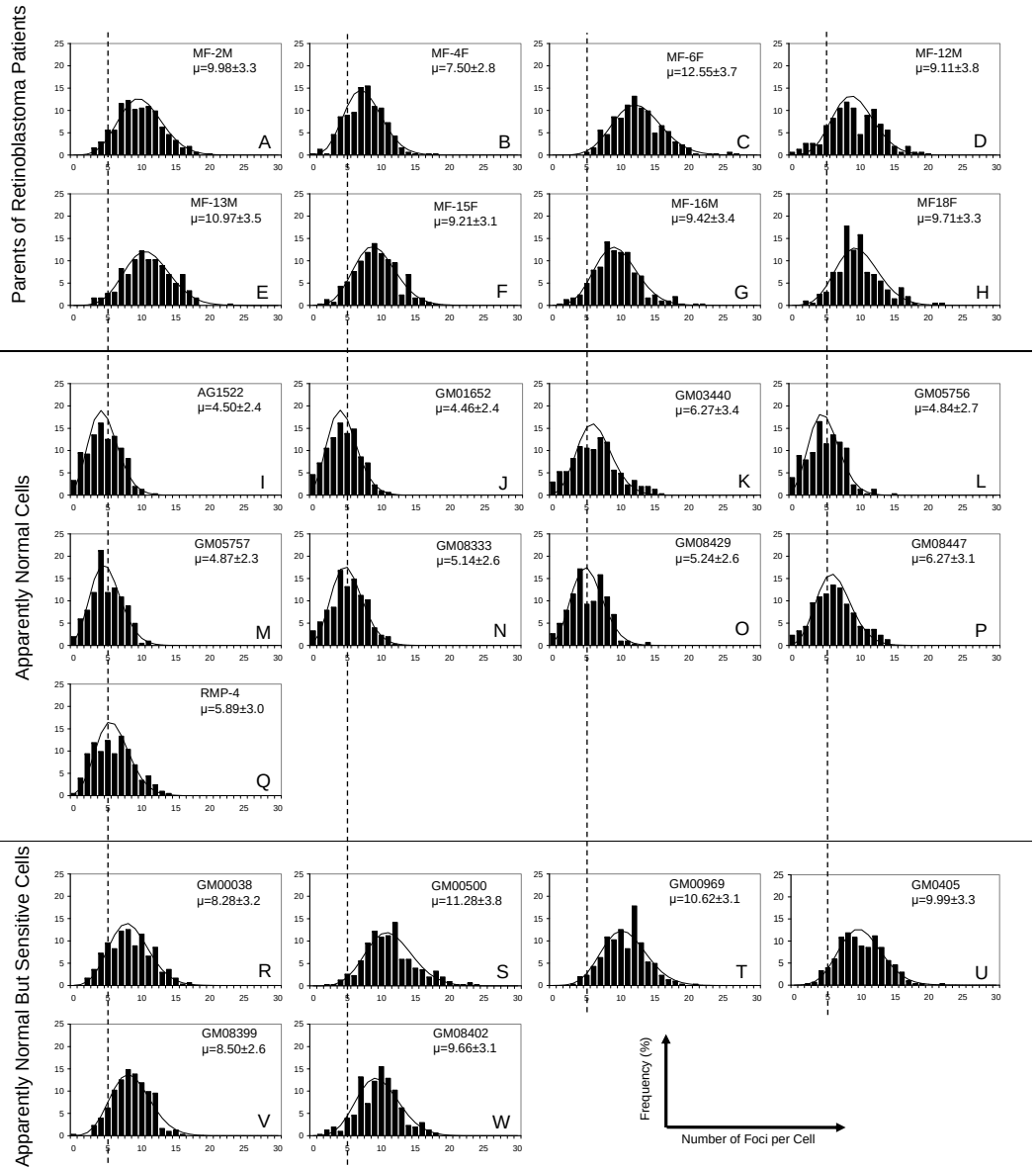
Darakhsham, et al, Evidence for complex multigenic inheritance of radiation AML susceptibility In mice revealed using a **surrogate phenotypic** assay Carcinogenesis 27 311-318 (2006)

Table II. Variation in 3 Gy X-ray induced chromosome aberration scores for inbred strains and F1 hybrids between C57BL and CBA/H

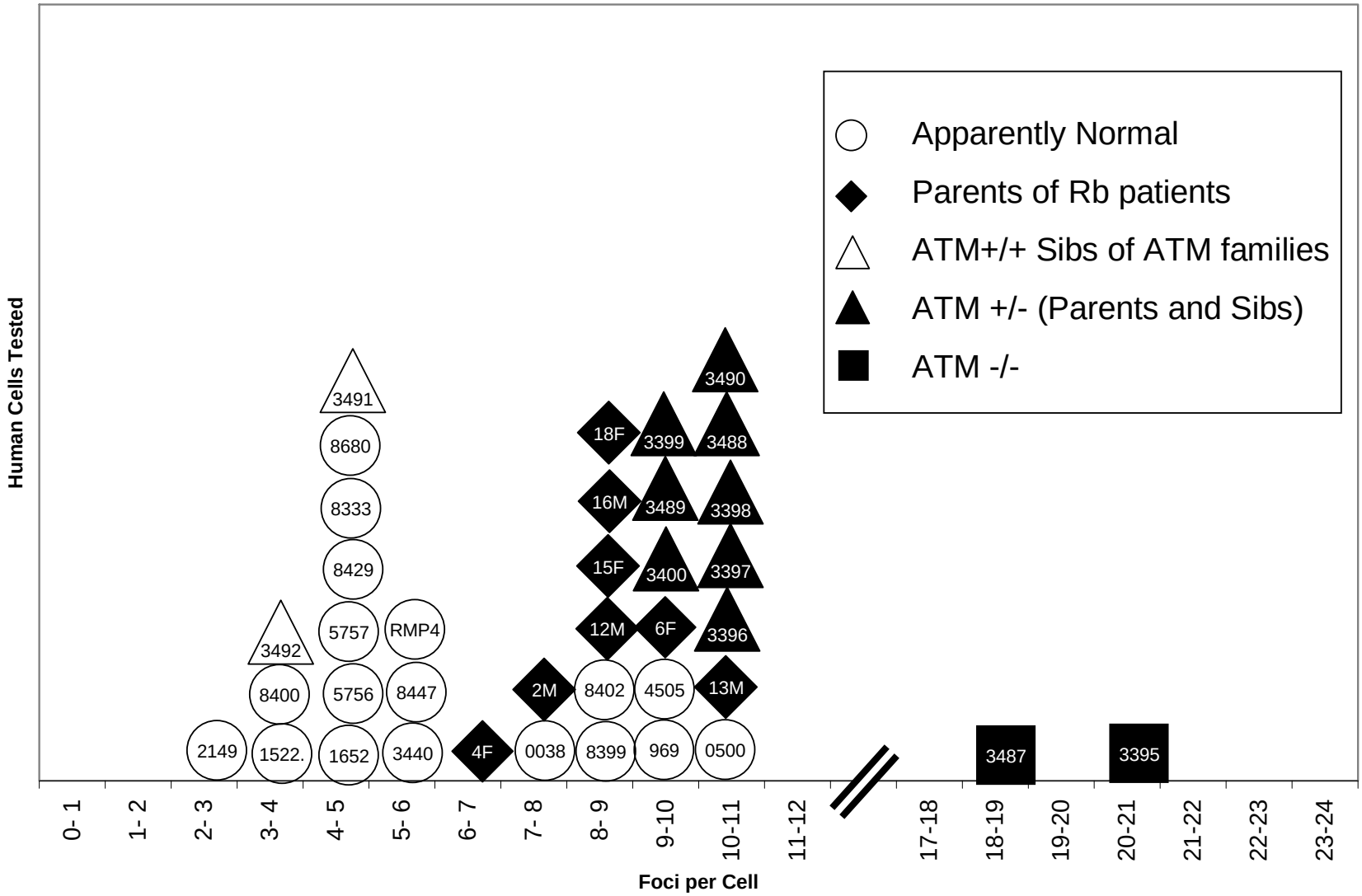
Strain	Painting protocol[a]	Aberration score per 100 cells			VMR ± SE[b]	χ^2 *P*-value[c]	Sensitivity ratio for chr2[d] $\frac{(2 \times \text{chr2})}{(\text{chr1} + \text{chr3})}$	
		chr1	chr2	chr3				
C57BL/6	S	8.16 ± 1.3	7.44 ± 1.1	11.94 ± 2.0	1.46 ± 0.06	NS	0.74	→ **0.74**
NON	T	13.62 ± 2.2	12.81 ± 2.2	12.53 ± 7.2	1.84 ± 0.07	NS	0.98	
NOD	T	18.75 ± 2.4	17.75 ± 2.4	16.75 ± 2.4	1.56 ± 0.07	NS	1.00	
A	S	7.80 ± 1.9	8.26 ± 2.0	8.81 ± 1.7	1.12 ± 0.05	NS	1.00	
AKR	S	6.67 ± 1.5	9.88 ± 1.7	7.51 ± 1.7	1.12 ± 0.09	NS	1.39	
DBA/2	S	13.06 ± 2.3	21.25 ± 2.5	17.29 ± 2.4	1.14 ± 0.08	NS	1.40	
BALB/c	S	8.33 ± 1.7	18.27 ± 2.3	15.85 ± 3.0	1.40 ± 0.08	< 0.001	1.51	
CBA/H	S	13.65 ± 2.5	19.90 ± 2.8	11.11 ± 3.0	1.67 ± 0.08	~0.05	1.61	→ **1.61**
CBA/Ca	T	17.94 ± 3.0	33.59 ± 4.1	22.14 ± 3.6	1.58 ± 0.09	~0.01	1.68	→ **1.68**
SJL	T	9.33 ± 1.8	23.33 ± 3.1	17.33 ± 2.9	1.85 ± 0.08	< 0.001	1.75	
LP	T	6.75 ± 1.4	16.50 ± 2.2	11.25 ± 1.8	1.99 ± 0.07	< 0.001	1.83	
C3H	S	12.39 ± 3.0	20.56 ± 4.3	9.38 ± 2.6	1.58 ± 0.10	~0.05	1.89	
RFM	S	6.10 ± 2.1	13.16 ± 3.2	4.86 ± 2.0	1.22 ± 0.11	< 0.05	2.40	
CBB6F1	S	17.50 ± 3.3	19.62 ± 4.0	9.40 ± 2.2	1.36 ± 0.07	< 0.05	1.46	
B6CBF1	S	10.10 ± 1.9	19.78 ± 2.4	12.90 ± 2.1	1.43 ± 0.10	~0.01	1.72	

γ-H2AX foci, reflect the presence of DNA DSBs, and provide a sensitive assay to help link a *relevant* molecular radiation damage and its repair to important biological effects in a *relevant* dose range.

γ-H2AX Foci 24 Hours Continuous Irradiation at 10 cGy/h
(Apparently Normal, Sensitive Normal, and Rb Parents)



(T.Kato, 2006)


Apparently Normal
Parents of Rb patients
ATM+/+ Sibs of ATM families
ATM +/- (Parents and Sibs)
ATM -/-
Human Cells Tested
Foci per Cell
0- 1
1- 2
2- 3
3- 4
4- 5
5- 6
6- 7
7- 8
8- 9
9-10
10-11
11-12
17-18
18-19
19-20
20-21
21-22
22-23
23-24
2149
1522.
1652
3440
4F
0038
8399
969
0500
3487
3395
3492
8400
5756
8447
2M
8402
4505
13M
3491
8680
8333
8429
5757
RMP4
12M
6F
3396
15F
3400
3397
16M
3489
3398
18F
3399
3488
3490

(T. Kato, 2006)

Suppose we have some assay(s) that can estimate relative radiosensitivities for individuals for risk of radiation-induced cancer….

Who wants to know? Should anyone know? Not know?

Individuals who may be exposed?

Employers of individuals who may be exposed? (Government agencies or private organizations)

Health Insurance industry?

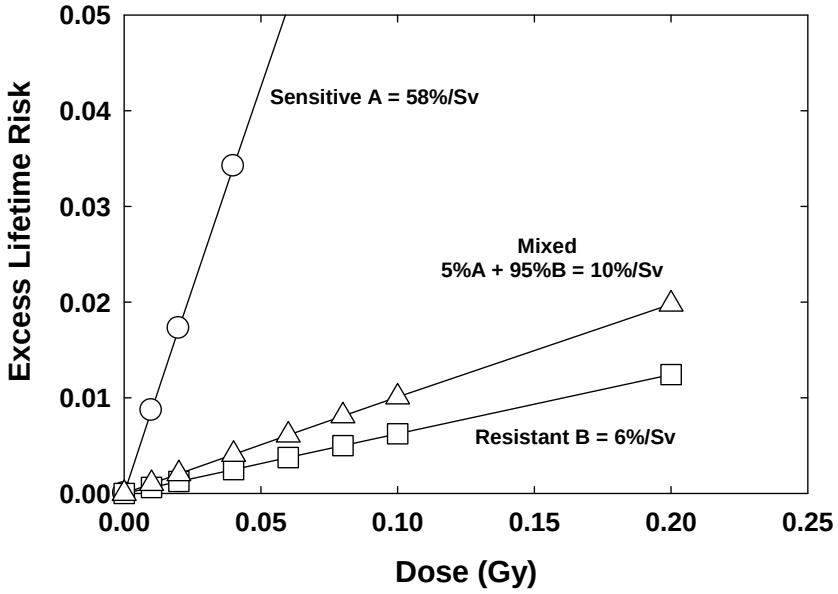
Who decides?

Could there be a significant impact on radiation protection?

It depends largely on the proportion of individuals who are hypersensitive.

If there are 20 to 30%, they should be, some ~2-fold more sensitive than average.

Sensitive Sub-Populations



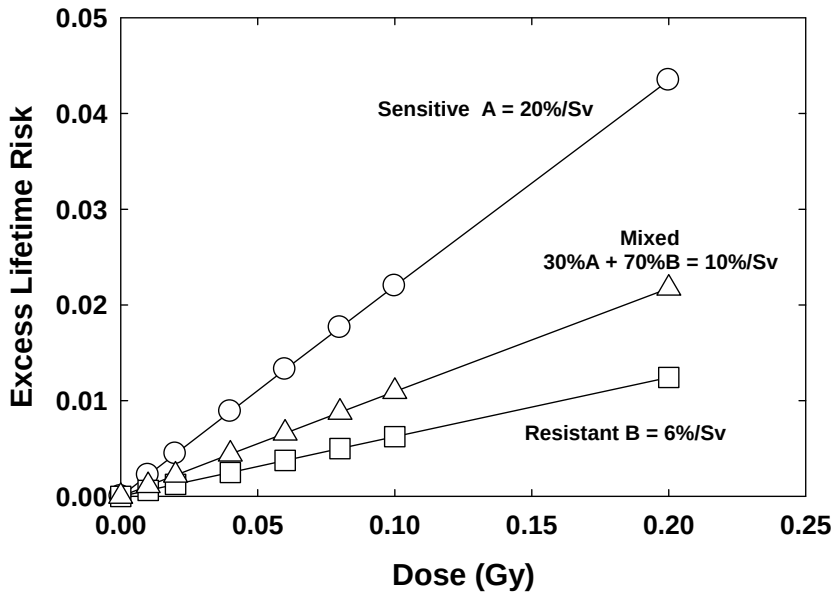


Figure 1

NCRP
National Council on Radiation Protection & Measurements

32nd LAURISTON S. TAYLOR LECTURE

LAURISTON S. TAYLOR LECTURE: YUCCA MOUNTAIN RADIATION STANDARDS, DOSE/RISK ASSESSMENTS, PUBLIC INTERACTIONS, THINKING OUTSIDE THE BOX, AND RECOMMENDATIONS

National Council on Radiation Protection & Measurements,
Bethesda MD 20814-3095
Annual Meeting, April 14, 2008

PRINCIPAL TOPICS

- Introduction to Yucca Mountain
- Genesis of the lecture: Dose Rate Estimates
- Problems develop – Origin
- Understanding Risk vs. Dose
- Difficulties with the Standards
- Comments & Recommendations

NCRP
National Council on Radiation Protection & Measurements

LOCATION OF YUCCA MOUNTAIN, THE REPOSITORY, LATHROP WELLS, THE AMARGOSA VALLEY, AND THE REMEI

GENESIS OF THE LECTURE

DOSE RATE ESTIMATES

- Regulated radionuclides:
  ^{14}C, ^{99}Tc, ^{129}I, ^{228}Ra,
  ^{226}Ra, ^{237}Np, ^{239}Pu, ^{241}Am
- Analyses show that first four of these are "no-never-minds"

PROBLEMS DEVELOP

MULTIPLE ACTORS

- U.S. Congress
- U.S. Environmental Protection Agency
- U.S. Nuclear Regulatory Commission
- U.S. Department of Energy
- National Academy of Sciences – National Research Council

RECOMMENDATION OF THE NRC (1995)

We recommend the use of a standard that sets a limit on the risk to individuals of adverse health effects from releases from the repository

A risk-based standard would not have to be revised in subsequent rulemakings if advances in scientific knowledge reveal that the dose-response relation is different than envisaged today

UNDERSTANDING RISK

Bases: Epidemiological studies of Japanese survivors of atomic bombings at the end of World War II

- DDREF: Dose and dose rate
- Spatial: Transfer of health effects
- Temporal: Transfer of health effects

ESTIMATING FUTURE BASELINE CANCER RATES

REQUIRED INFORMATION

- Percent of population who will be African Americans (skin cancers, i.e., melanomas)
- Percent of young women who will be vaccinated for cervical cancer
- Percent of population receiving colonoscopies (colorectal cancer)
- Age at which women will have their first baby (breast cancer)
- Percent of population who will be smokers (lung cancer)
- Percent of population who will be obese (all cancers)

RESPONSE TO THE NRC RECOMMENDATION

- The EPA staff rejected the NRC recommendation
- They apparently did not comprehend the variable temporal relationship between dose and risk, or the fundamental differences in the repository and other nuclear facilities (i.e., nuclear power plants)
- The USNRC staff also rejected the NRC recommendation

MAJOR CHANGES REQUIRED

- There is an urgent need to develop and promulgate a set of Standards that incorporate a risk limit
- The Standards should be restricted to a single overall risk limit
- If the total risk is acceptable, that from consuming the ground water as a source of drinking water will automatically be acceptable

MAJOR CHANGES REQUIRED

- Apportionment of the risks from individual radiation sources should be avoided; this violates the ALARA criterion
- This fact was documented in ICRP Publications 1 (1959) and 9 (1966)
- It has also been documented by the tremendous success being achieved by the use of “tradable emission permits”

TRENDS IN CANCER RATES

- Data show that that, between 2002 and 2004, the overall death rate from cancer among members of the U.S. population was reduced by an average of 2.1% per year. This compares to a reduction of 1.1% per year between 1993 and 2001
- At the same time, the rate of reduction in colorectal cancer, the second leading (behind lung cancer) cause of cancer deaths in the United States was almost 5% for men, and almost 4.5% for women per year

TRENDS IN CANCER RATES

- Progress is also being made in the long-term reduction in the rates of lung cancer
- Also of interest, a poll of 6 leading U.S. cancer experts showed an almost unanimous consensus that, within the next 50 to 100 years, methods for the prevention and/or cure of the major cancers that afflict the U.S. population today will have been achieved

UNNECESSARY EPA RESTRICTIONS

- Restrictions imposed by EPA dictate that factors that could have a negative impact (i.e., geology, hydrology, and climate) on the repository thousands of years from now need to be examined in detail, while those that would have a positive impact (i.e., advances in methods for the cure and prevention of cancer) in 50 to 100 years cannot be considered
- In reality, the positive benefits of the continued improvement in cancer methodologies would overwhelm the negative impacts of any projected changes in geology, hydrology, and climate

POTENTIAL BENEFITS OF NEW STANDARDS

- Once the Standards are expressed in terms of risk, and if advances in methods for cancer prevention and/or cure continue as anticipated, it is quite probable that the time of maximum risk will occur at the time the wastes are being emplaced
- It is equally probable that the time of minimum risk will occur at the time of maximum dose, if not well before

RECOMMENDATION

- Nothing should be "locked-in-place"
- Every 25 to 50 years after the repository is closed, advances in all fields of science and technology should be evaluated, and applied wherever they hold promise of improving its operation and/or reducing its impacts on public health and the environment

CONCLUSIONS

- The YM repository is too important to the U.S. nuclear energy program to be impeded by inappropriate Standards and unnecessary restrictions
- Now is not the time to point fingers
- Let's concentrate on revising the EPA Standards, the USNRC Regulations, and the DOE License Application

FINAL COMMENTS

ADDRESSING CREDIBILITY

- A challenging attribute: difficult to establish; difficult to maintain; easy to destroy
- A challenging time: upcoming public hearings during review of License Application
- Necessity for effective responses: must anticipate questions and expressions of doubts
- Handouts: must be readily available
- Detailed backgrounds: should be provided for all speakers

National Cancer Institute

The Impact of Dosimetry Uncertainties on Dose-Response Analyses

Ethel S. Gilbert
National Cancer Institute

NCRP Annual Meeting
April 15, 2008

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Role of Doses in Epidemiology

- Explore and quantify dose-response relationships
  - Linear dose-response function plays important role
- Dose estimates subject to uncertainties
  - Dose estimation often retrospective
  - Complex systems often needed to estimate dose

“Errors” in doses

“Error” might be expressed as:

- **A difference:**

  estimated dose – true dose

Or

- **A ratio:**

  estimated dose/true dose

  log (*error*) = log (*estimated dose*) – log *(true dose*)

Some important distinctions

- **Classical errors versus Berkson errors**
- **Shared errors versus Errors that are independent for different subjects**
- **Impact on dose-response analyses depends on these distinctions**

Classical Error

- Error is independent of true dose
- Can be thought of as error that arises from imprecise measuring device
  - Example: film badge dosimeter
- Variance of measured doses larger than variance of true doses
- Adjustment needed to avoid distortion of dose-response

Examples

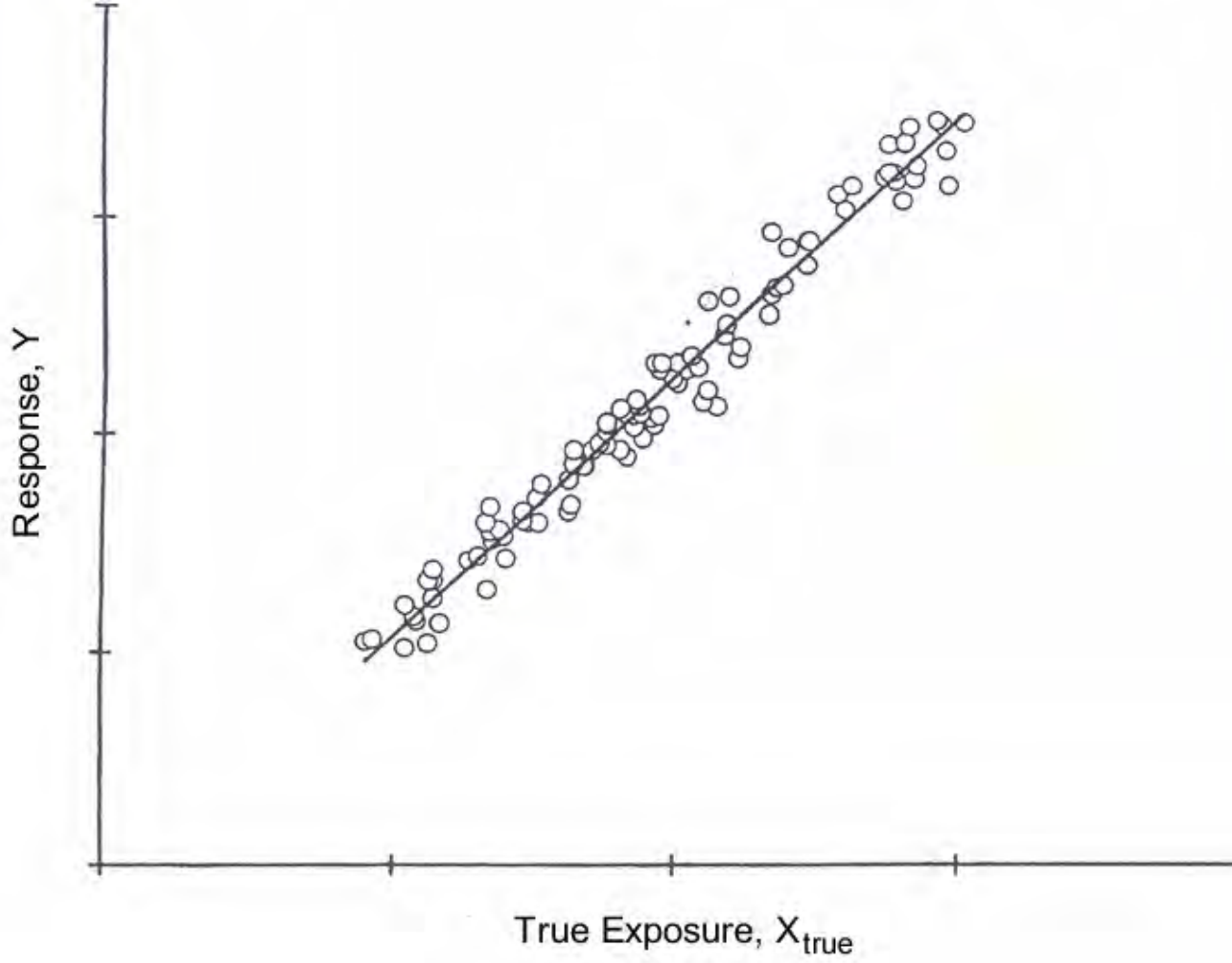
Taken from

DR Cox, SC Darby, GK Reeves, E Whitley,

“The Effects of Measurement Errors with Particular Reference to a Study of Exposure to Residential Radon”

National Cancer Institute, Publication No. 99-4541, 1999.

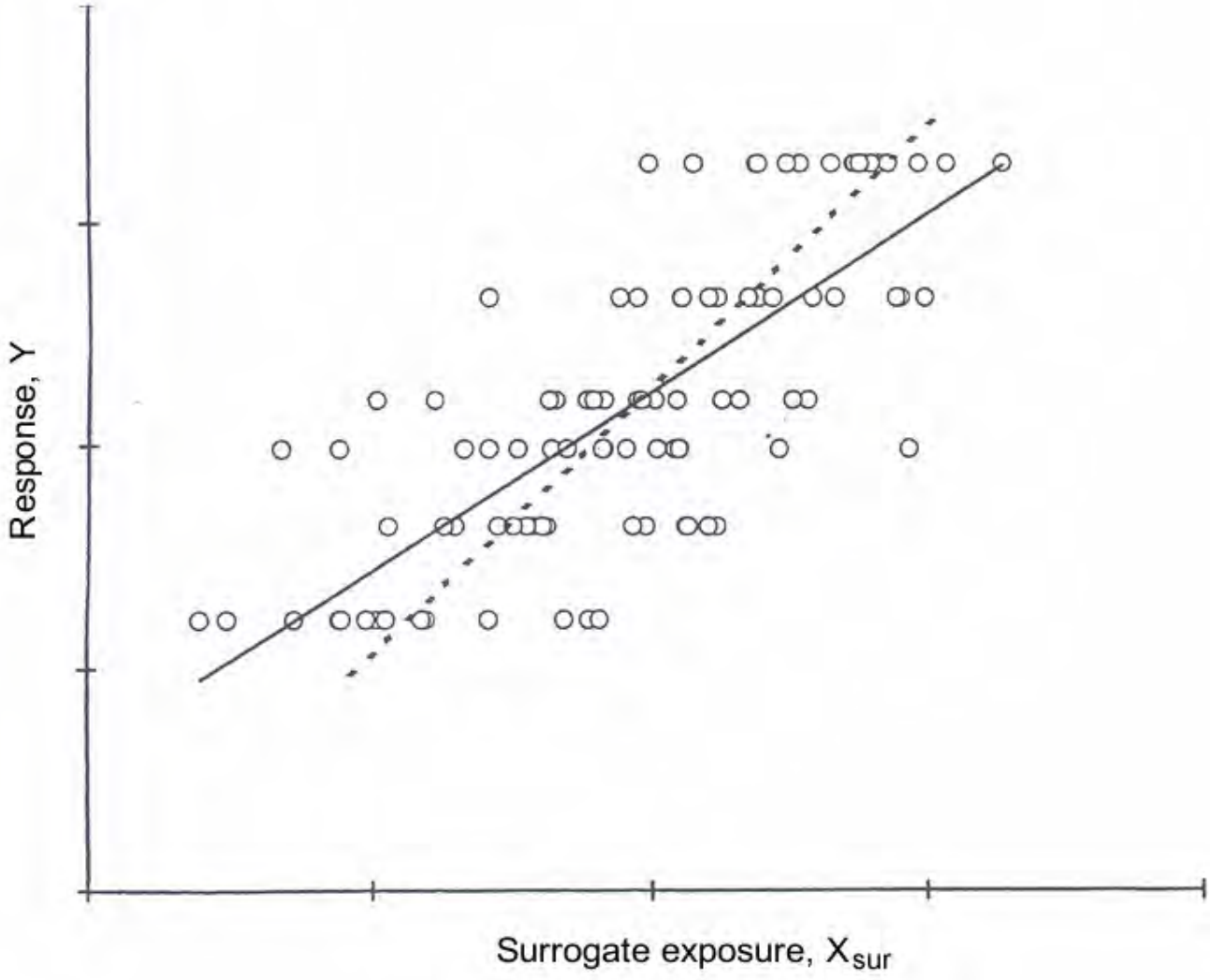
No error



Response versus true dose

Cox et al. 1999

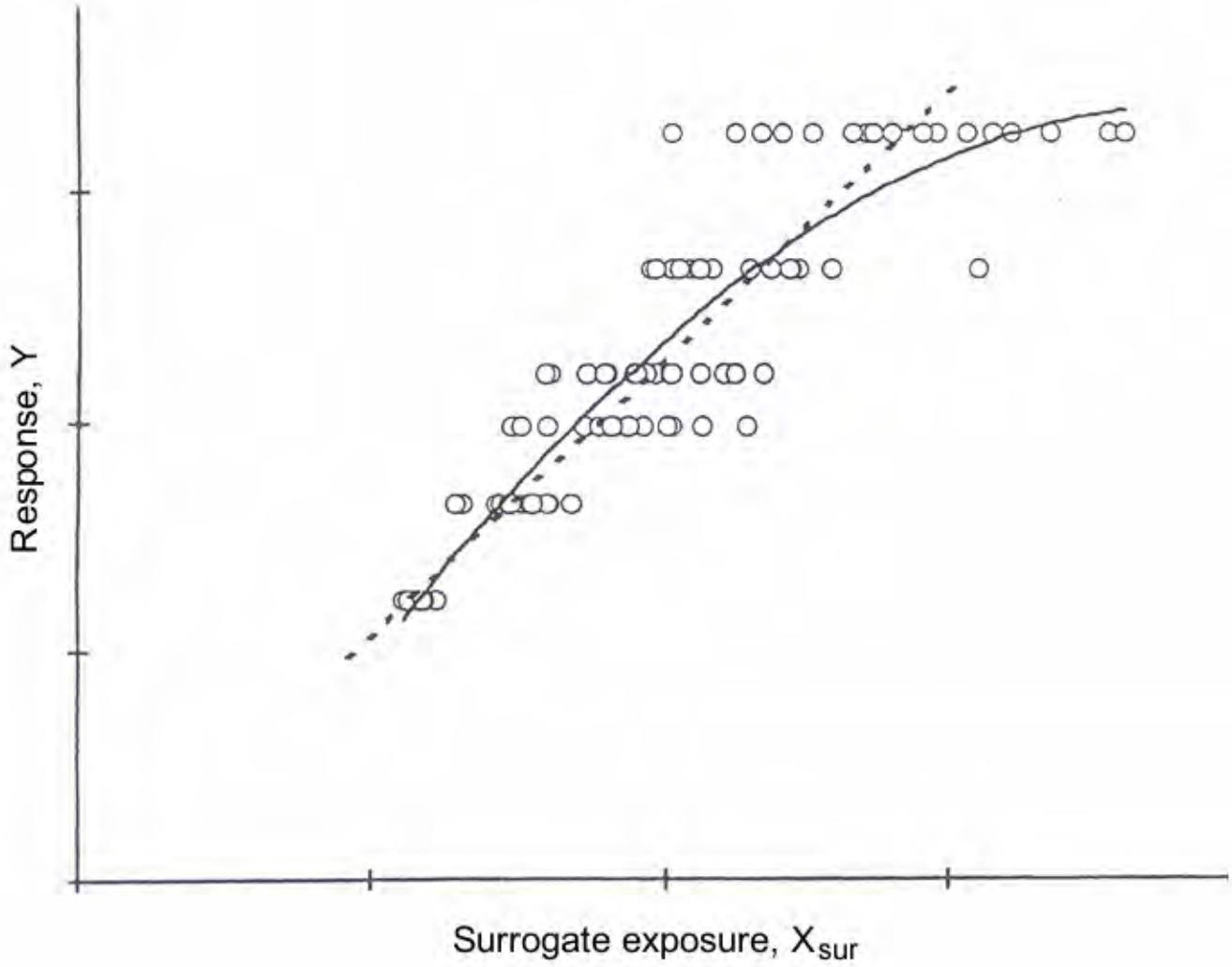
Classical error



Response versus estimated dose
True response

Cox et al. 1999

Classical error



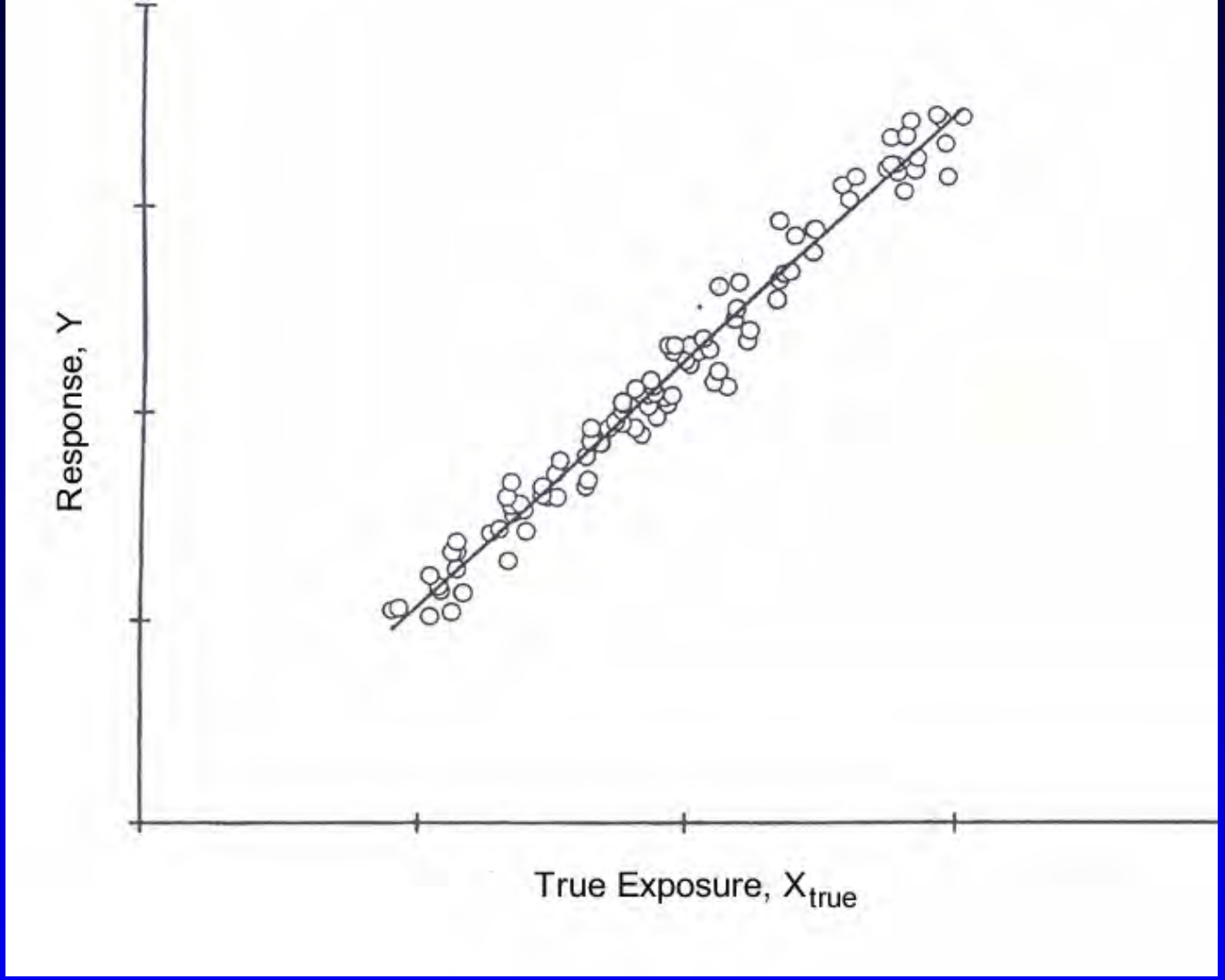
Response versus estimated dose

True response

Cox et al. 1999

Berkson error

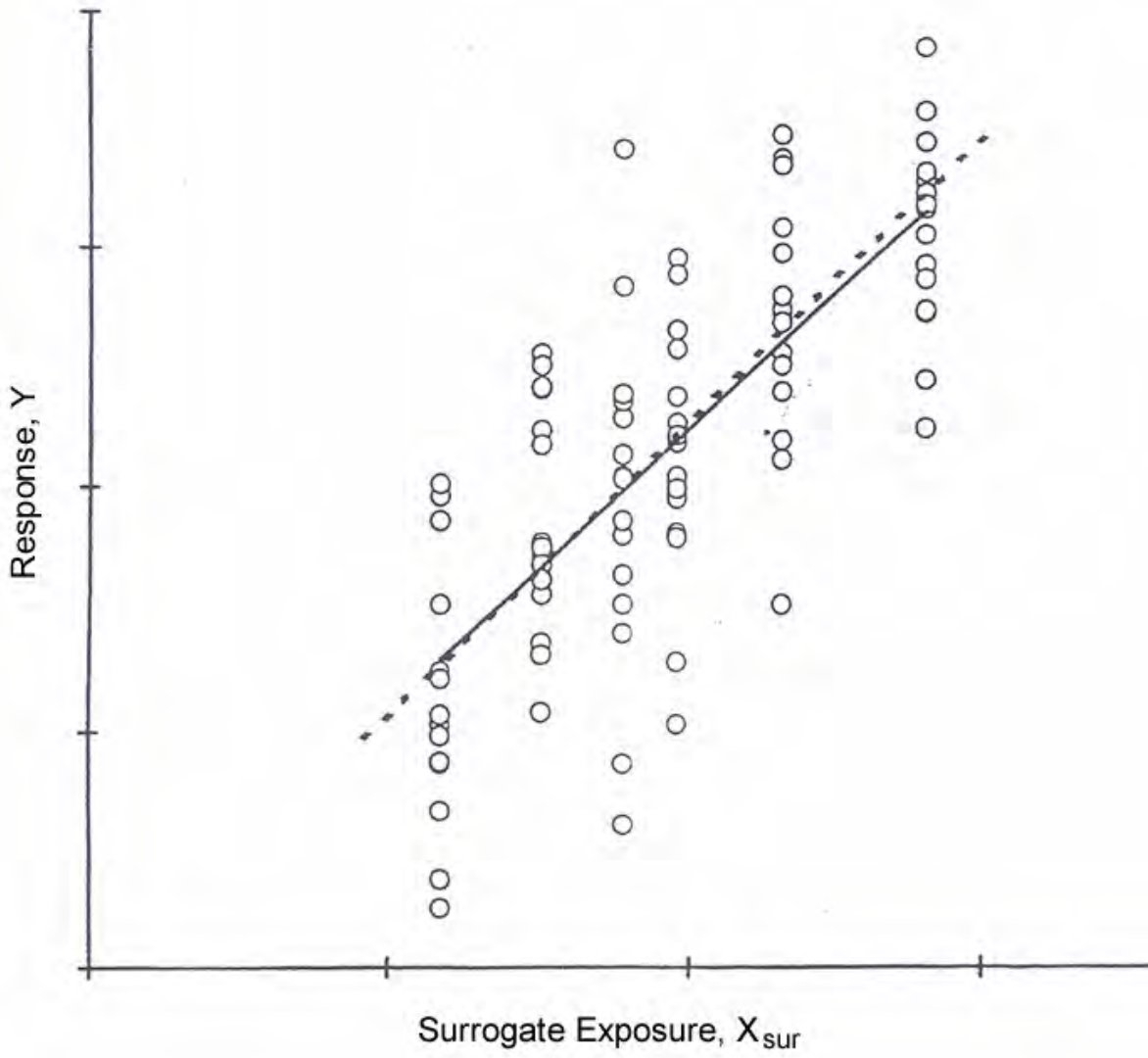
- Error is independent of observed dose
- Can be thought of as error that results when single dose used to represent group
  - Example: Same exposure assigned to all underground miners in particular location/time period
- Variance of true doses larger than variance of measured doses
- Little distortion in linear dose-response



Response versus true dose

Cox et al. 1999

Berkson error



Response versus estimated dose

True response

Cox et al. 1999

Some important distinctions

- **Classical errors versus Berkson errors**
- **Shared errors versus Errors that are independent for different subjects**
- **Impact on dose-response analyses depends on these distinctions**

Examples of Shared Errors

- **Errors in the yields of the Hiroshima or Nagasaki bombs**
- **Errors in factors used to convert “recorded doses” to organ doses in nuclear worker studies**

Impact of Shared Errors

Simplest situation:

- **Error shared by all subjects**
- **Expected value of the *estimated dose***

  = K x *true dose*

- **Estimates of linear risk coefficients biased by a factor K**
- **Desirable to include uncertainty in K in confidence intervals**

Impact of Shared Errors

More complex situations:

- **Expected value of the *estimated dose* depends in a complicated way on the *true dose* and several uncertainly estimated parameters**

- **Various subsets of subjects share different errors**

Possible Effects of Errors in Dose Estimates

- **Bias in estimates of risk per unit of exposure**
- **Distortion of the shape of the dose-response function**
- **Underestimation of uncertainty**
- **Reduction in statistical power for detecting dose-response relationships**

Possible Effects of Errors in Dose Estimates

- **Reduction in statistical power for detecting dose-response relationship**
  - **True for both classical and Berkson errors**
  - **Especially important in low dose studies since power may already be limited**
  - **Tests of significance based on imprecisely measured doses are usually valid**
  - **Dose uncertainties more likely to mask a true dose-response than to lead to a spurious one.**

What should we do about errors in dose estimates?

- Improve dose estimates if feasible, but will never be free from error

- Statistical approaches available
  - Often complex
  - Require good understanding of error structure

Error Structure

- Identify sources of error
- Nature of the error from each source
  - Classical or Berkson?
  - Shared or unshared?
- Magnitude of the error
  - Describe with distribution functions

A common mixture of errors

- Doses estimated for groups
- **Berkson error:** Variation among individual subjects within groups
- **Classical error:** Uncertainty in whether or not assigned doses are the correct average for the group
- Classical errors are **shared** by subjects in the same group

Error Structure

- Identify sources of error
- Nature of the error
  - Classical or Berkson?
  - Shared or unshared?
- Magnitude of the error
  - Describe with distribution functions

- Hard data on uncertainties not always available
- Subjective judgments often required

Tools for accounting for dosimetry uncertainties

- Maximum likelihood
- Replacement method
- Simulations
- Sensitivity analyses

Tools for accounting for dosimetry uncertainties

What they can't do

- **Improve power and precision of estimated risk coefficients**
- **Unlikely to modify statistical significance of dose-response**

What they can do

- **Avoid misleading results**
- **Correct biases in risk coefficients and confidence limits**

Examples where dose estimation errors have been taken into account

- **A-bomb survivors (Pierce et al. 1996)**
- **Residential radon exposure (Reeves et al. 1998)**
- **Utah fallout study (Thomas et al. 1999)**
- **Underground miners (Stram et al. 1999)**
- **Tinea capitis patients (Schafer et al. 2001; Lubin et al. 2004)**
- **Hanford fallout study (Stram and Kopecky 2003)**

Studies of persons exposed at low doses and dose-rates

Examples:

- **Nuclear workers**
- **A-bomb survivors with low doses**
- **Persons exposed to residential radon**

Objectives of studies of persons exposed at low doses

- **Direct assessment of risk at low doses and dose rates**
  - **Is there direct evidence of risk at low doses?**
  - **Are estimates of risk compatible with those obtained through extrapolation from high dose studies?**

Dosimetry for Nuclear Worker Studies

- Dose estimates based on dosimeters worn by the workers

Some sources of error --

- Laboratory measurement error in reading dosimeters

- Recorded doses are not unbiased estimates of dose to bone marrow and other organs (organ doses)

15-Country Nuclear Worker Study

- Coordinated by the International Agency for Research on Cancer (IARC)
- Cardis et al. (BMJ 2005; Radiat Res 2007)
- Largest worker study ever conducted
  - 400,000 workers
  - 6500 cancer deaths
- Extensive attention given to dosimetry

Dosimetry for 15-Country Nuclear Worker Study

- Dosimetry subcommittee
- Dosimetry questionnaires
  - Dosimetry practices
  - Radiation environments
- Special studies of representative
  - Nuclear power plant (Switzerland)
  - Mixed activities (France -- Saclay site)
- Testing of several representative dosimeters

Thierry-Chef et al. 2007

Dosimetry for 15-Country Nuclear Worker Study

Objectives

- **Develop factors for converting recorded doses to organ doses**
  - **Factors developed for groups of workers defined by time period and type of facility**

- **Evaluate uncertainties in these factors**
  - **Characterized by lognormal distributions**
  - **Based on work of dosimetry committee**
  - **Involved subjective judgments**

Thierry-Chef et al. 2007

Uncertainties in factors for converting recorded doses to organ doses

- **Berkson error:** Variation among individual workers within the groups for which factors developed
- **Classical error:** Uncertainty in whether or not factor was correct average for group
- Classical errors are **shared** by subjects in the same group

Limitations of Low Dose Studies (aside from dose errors)

- **Increase in risk likely to be at most a few percent**
- **Low statistical power and imprecisely estimated risks**
- **Strong potential for confounding**

Predicted relative risks* for adult male exposed at low dose rate

Dose	Solid cancers	Leukemia
1 Gy	1.2	2.4
0.5 Gy	1.1	1.7
0.2 Gy	1.03	1.3
0.1 Gy	1.02	1.1
0.01 Gy	1.002	1.01

*Based on BEIR VII models developed from A-bomb survivor data

Most Important Effects of Dose Uncertainties in Low Dose Studies

- **Increase potential for bias in risk estimates**

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- **Increase potential for bias in risk estimates**
- **Reduce the already limited statistical power for detecting dose-response relationships**

Most Important Effects of Dose Uncertainties in Low Dose Studies

- **Increase potential for bias in risk estimates**
- **Reduce the already limited statistical power for detecting dose-response relationships**
- **Dose uncertainties much more likely to mask a true dose-response than lead to a spurious one**

General Summary

- **Increasingly, errors are being evaluated and considered in dose-response analyses**
- **Requires detailed understanding of error structure**
- **Requires lots of communication between dosimetrists and statisticians**

2000 Annual NCRP Meeting
" Low dose and low dose-rate radiation effects and models"
April 14-15, 2008 in Washington

Does scientific evidence support a change from the LNT model for low dose radiation risk extrapolation?

Affirmative Response

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Introduction (1)

- The linear no-threshold concept (LNT) has been widely used to establish international rules and standards in radiation protection(ICRP).
- It is based on the notion that the physical energy deposition of ionizing radiation (IR) increases carcinogenic risk linearly with increasing dose, i.e. the carcinogenic effectiveness remains constant irrespective of dose or dose-rate.
- However, recent findings have strongly put into question the LNT concept and its scientific validity, especially, for very low doses and dose rates *(see report of the French National Academies of Science and Medicine 2005).*

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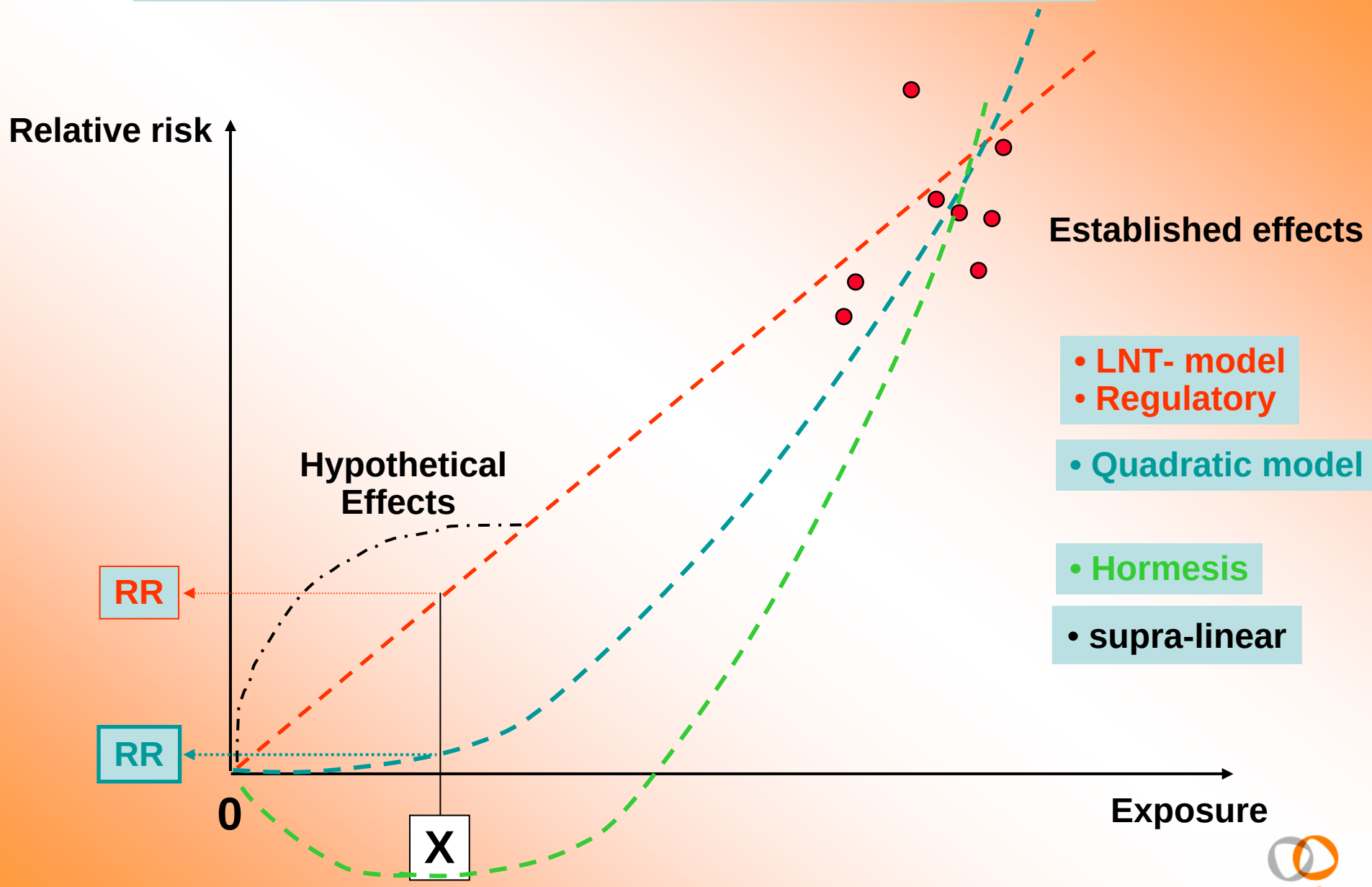
Risk evaluation for ionizing radiation



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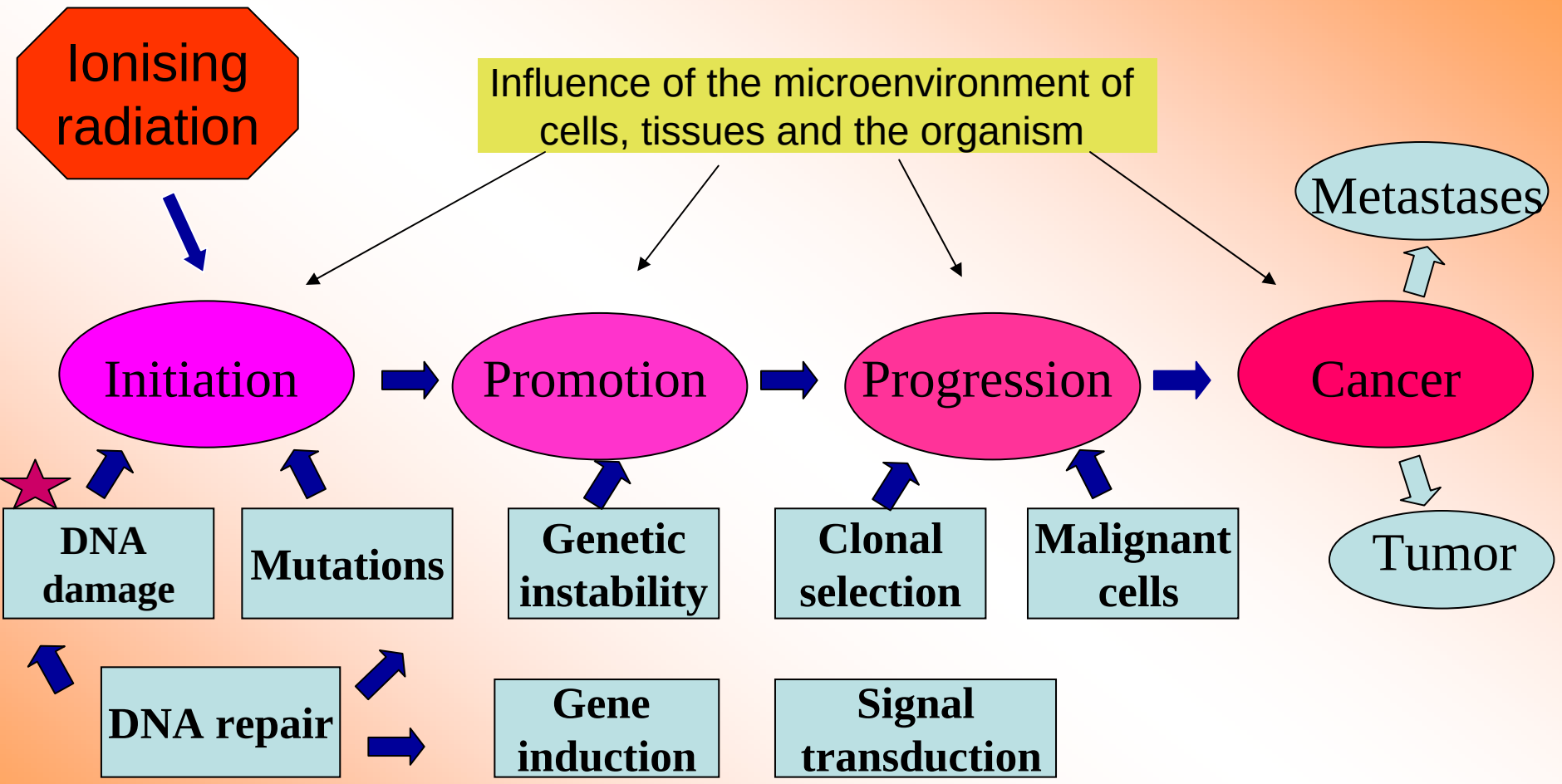
Introduction (2)

- Low dose effects are more difficult to ascertain than high dose effects. Epidemiological studies usually lack sufficient statistical power to determine health risks from very low dose exposures.
- In this situation, studies of the fundamental mechanisms involved can help to understand and assess short and long term effects of low dose IR and to evaluate low dose radiation risks.

IR effects on human health

- Radiation risk evaluations are concerned with radiation effects that lead to long term genotoxic effects such as genetic alterations (mutations), genomic instability, malignant transformation and cancer.
- Radiation-induced carcinogenesis is considered a multistep process, initiated by DNA damage and genetic alterations in somatic cells, which after stepwise promotion and progression will cause cell transformation and the development of cancer. It is strongly dependent on the cell and tissue microenvironment.

Multi-stage Radiocarcinogenesis



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Dose response relationship for radiocarcinogenesis

•There is a general consensus from epidemiological studies (A-bomb survivors, accidental exposures) that the **cancer risk increases above doses of 100-200 mGy.**

We would like to know more about the effects at

- **low doses (< 100 mGy)** and
- **very low doses (< 10 mGy)**

  of ionizing radiation

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Molecular studies

- Using recent molecular approaches radiation impacts , *e.g.* the induction of DNA lesions in cells and tissus has been measured down to very low doses (<1mGy).
- This allowed to get important new insights in the effects on cells and tissus in this formerly inaccessible dose range.
- It is not surprizing that some results obtained changed our understanding of IR-induced effects at low and very low doses.

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Importance of radiolesions induced at low doses *versus* endogenous lesions and their repair

- High amounts of DNA damage are already endogenously produced during normal cellular metabolism. Most of them are oxidatively generated lesions (single strand breaks (SSBs) and modified bases), very few are DNA double strand breaks(DSBs).
- Low IR doses add relatively few lesions of the same type (mostly oxidative damage).
- Specific types of complex IR lesions *(DSBs, locally multiply damaged sites(LMDS))* are induced as well but are likely to promote cell death rather than mutations.

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Response to ionizing radiation (IR)

- ***Signalling***
- *Gene induction*
- ***Cell cycle arrest***

Cell death

DNA repair

Error-prone

Error-free

Mutation

Survival

Genetic instability

Cell transformation

Carcinogenesis

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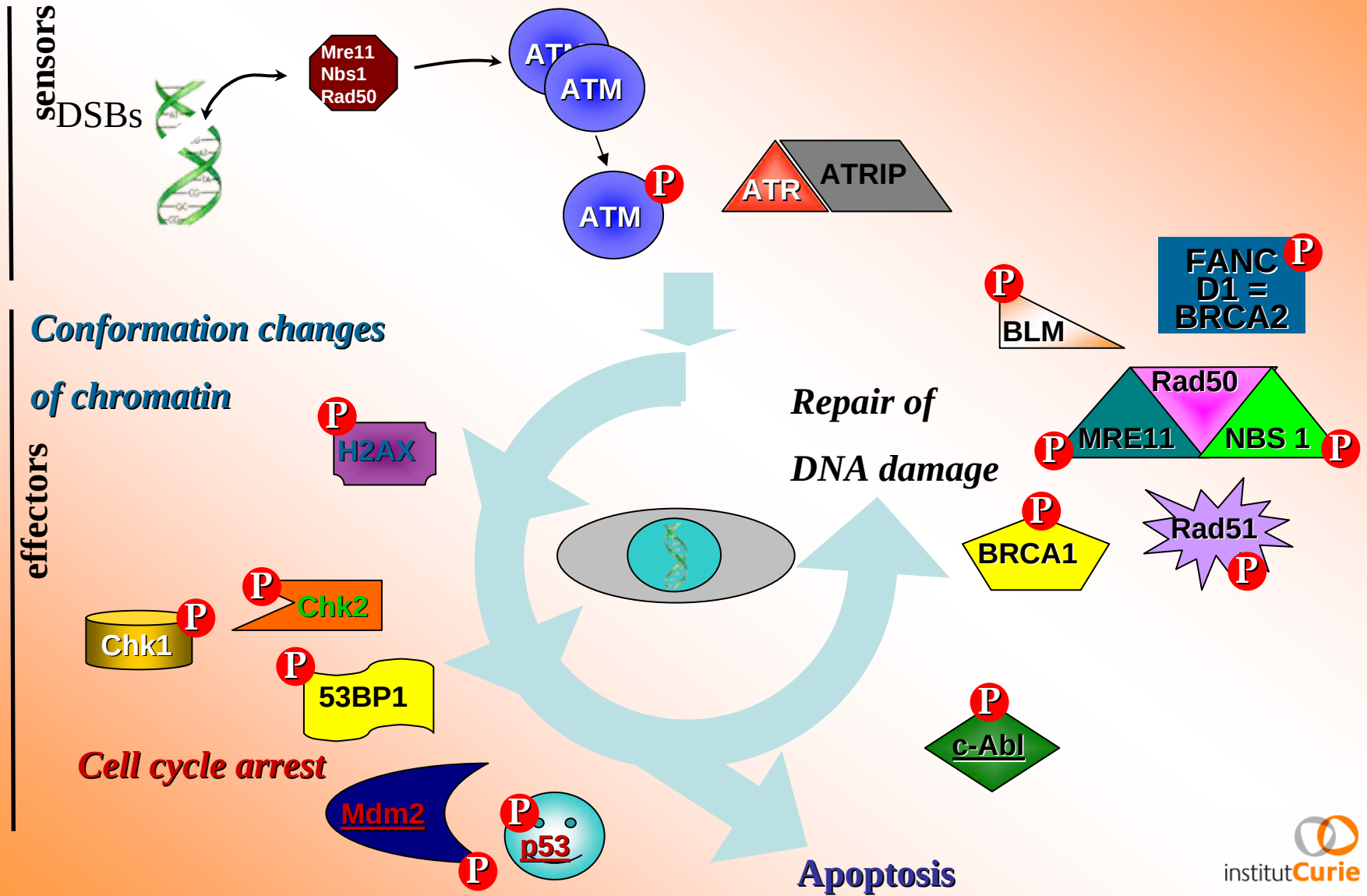
Genetically controlled signalling of IR-induced DSBs

(see Bakkenist CJ and Kastan MB, Cell 2004;118:9-17)



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Scientific facts contradicting LNT (1)

- Physical energy deposition and DNA damage are produced linearly with IR dose but cells and tissues show mostly non linear radiation responses (mostly threshold, linear-quadratic and, very rarely, supralinear responses).
- During evolution effective cellular protection mechanisms have evolved that are especially active at low doses (and clearly insufficient or not operative) at high doses,

  (for example, activation of cellular antioxidant defenses (glutathion, superoxide dismutase..) providing protection against DNA damage produced by reactive oxygen species (ROS), adaptive responses, elimination of damaged cells by cell death (low dose hypersensitivity) etc.)

  DNA damage induced at very low doses appears to have relatively less harmful consequences than that induced by high doses of IR (Feinendegen LE et al. Br J Radiol 2005;78:3-7).
- In fact, several lines of evidence demonstrate that living cells and tissus react differently (qualitatively and quantitatively) to radiation insults from high and low dose IR exposures with an evident impact on cellular fate and long term outcomes.

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Scientific facts contradicting LNT (2)

The dose-dependent cellular responses involve intra- and extracellular signalling towards cell cycle arrest, DNA repair and/or apoptosis, and the respective induction (repression) and activation (suppression) of genes and proteins.In particular, there are data on

---> DNA damage signalling at low doses and low dose rates (*Bakkenist CJ and Kastan MB, Cell 2004;118:9-17*, *Rothkamm K and Löbrich M , PNAS 2003;100:5057-62, Collis et al. JBC 2004; 279:49624-49632*)

---> Transcriptomic and proteomic changes *(Amundson SA et al. Mol Cancer Res 2003;1:445-52; Franco N et al. Radiat Res 2005;163:623-35; Yang F et al. J Proteome Res 2006;5:1252-60)*

---> Signalling involving membrane receptors and inter-cellular communication (*e.g.* bystander effect..) *(Little JB, Carcinogenesis 2000;21:397-404, Mothersill C and Seymour CB Mutat Res 2006;597:5-10)*

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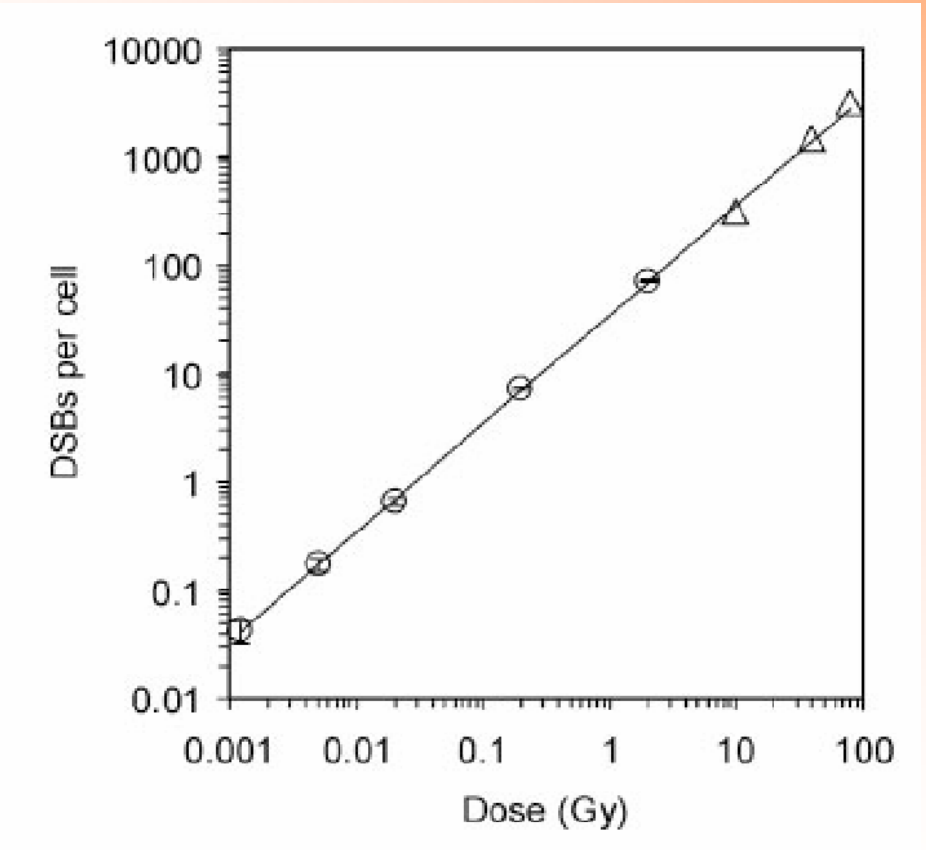
Induction of DSBs in mammalian cells is linear with IR dose

(Rothkamm and Löbrich , PNAS 2003;100:5057-5062)



⇨**IR-induced DSBs directly correlate with formation of γ-H2AX foci**
(Sedelnikova OA et al. Radiat. Res. 2002;158:486-492)

⇨**In primary human fibroblasts the induction of DSBs is linear with IR-dose down to 1.2 mGy .**

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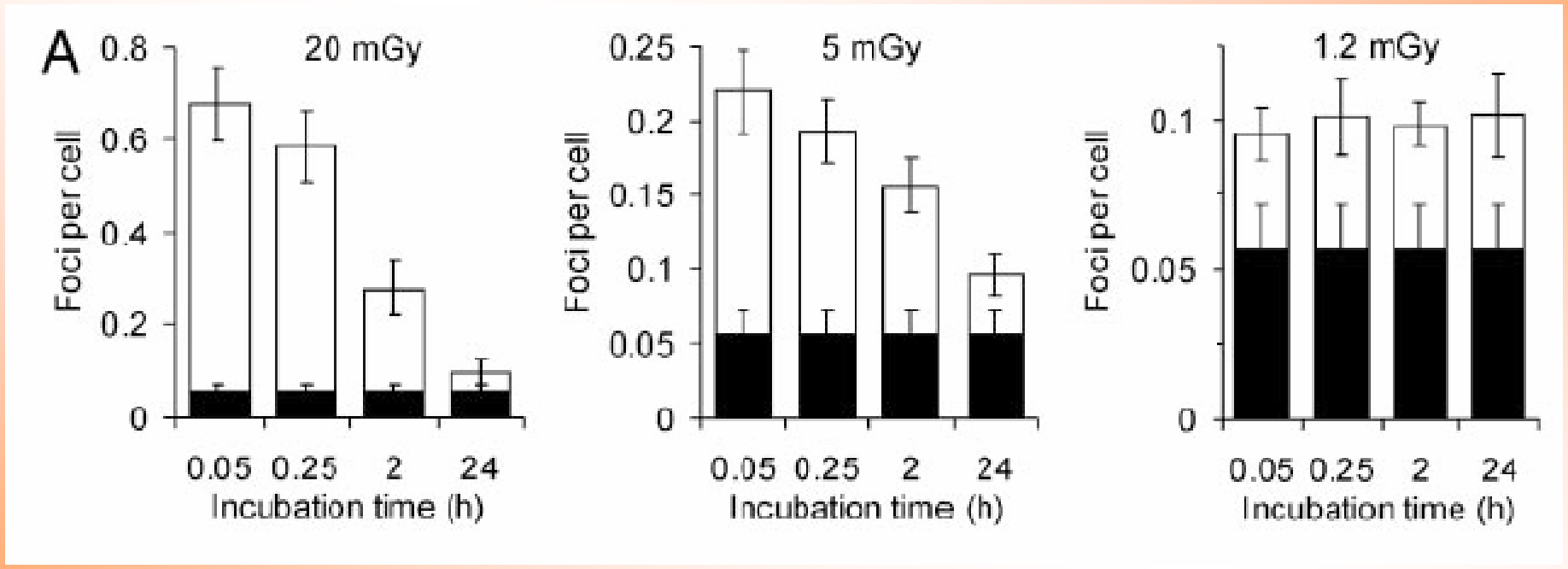
Repair of DSBs in human fibroblasts depends on IR dose

(Rothkamm and Löbrich , PNAS 2003;100:5057-5062)



⇨**Absence of repair at 1.2 mGy**

⇨ **Presence of repair at 5 mGy and 20 mGy**

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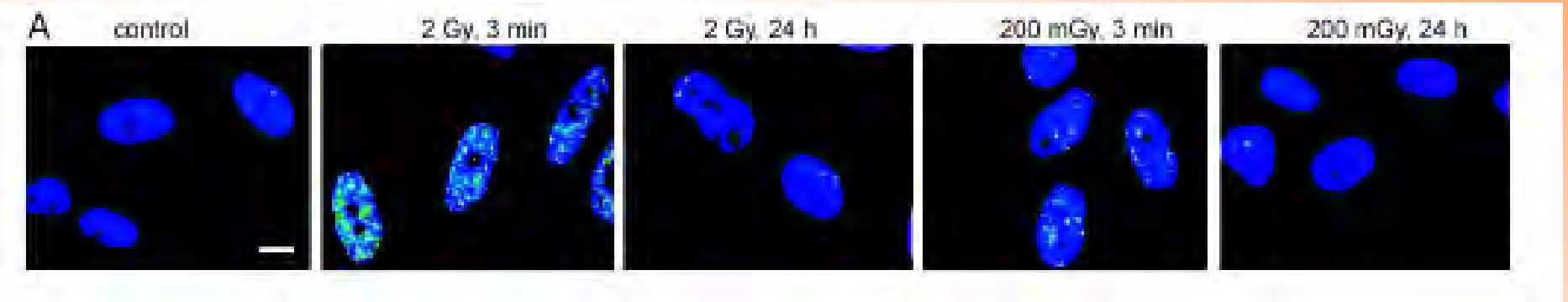
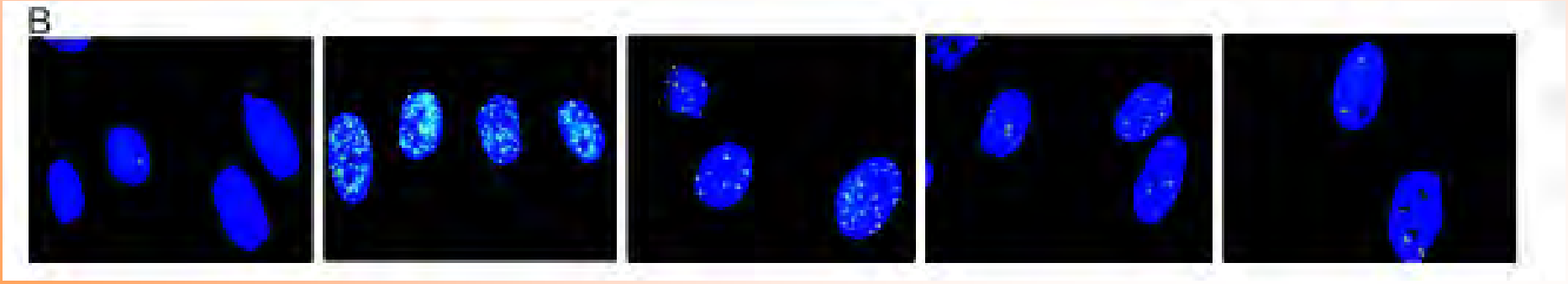
Induction and repair of DSBs as visualized by γ-H2AX in human cells

(Rothkamm K, Löbrich M, Proc Natl Acad Sci USA 2003,100:5057-5062).

MRC5 cells



180BR cells



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Cellular reactions and DNA repair depend on the dose level of IR

(Rothkamm and Löbrich , PNAS 2003;100:5057-5062)

- At very low dose (1 mGy), cells are going to die (probably absence of proper DNA signalling), and there is no initiation of DNA repair of DSBs (or other complex lesions)
- At slightly higher doses (5-20 mGy), DNA repair is initiated *(5 mGy: 1 electron track/cell ⇨ 5-10 damaged bases, 2.5-5 SSBs and 0.25 DSBs, see BEIR VII report)*
- At higher doses, DNA repair may start to be counteracted by apoptosis but also **repair may be error-prone and mutagenic and thus enhance the risk of cancer.**

--->Thus, extrapolations from high to low dose effects do not correspond to the actual reactions of living cells to IR-exposure.
----->This is in contradiction with the LNT hypothesis.

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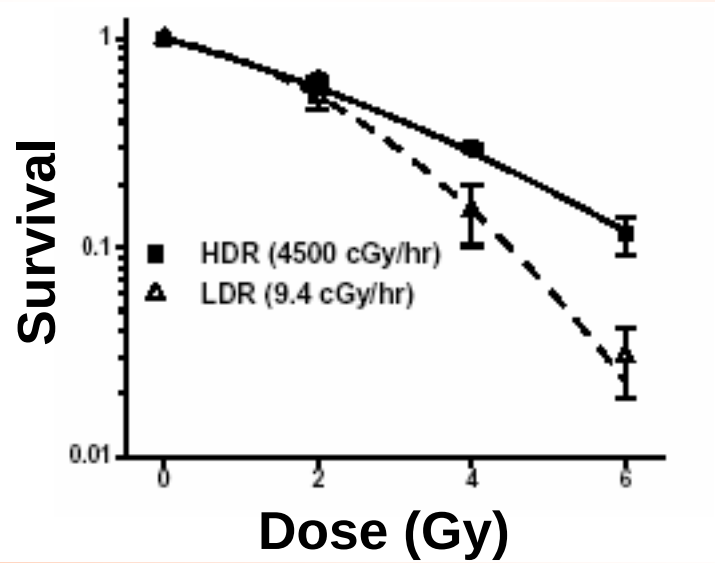
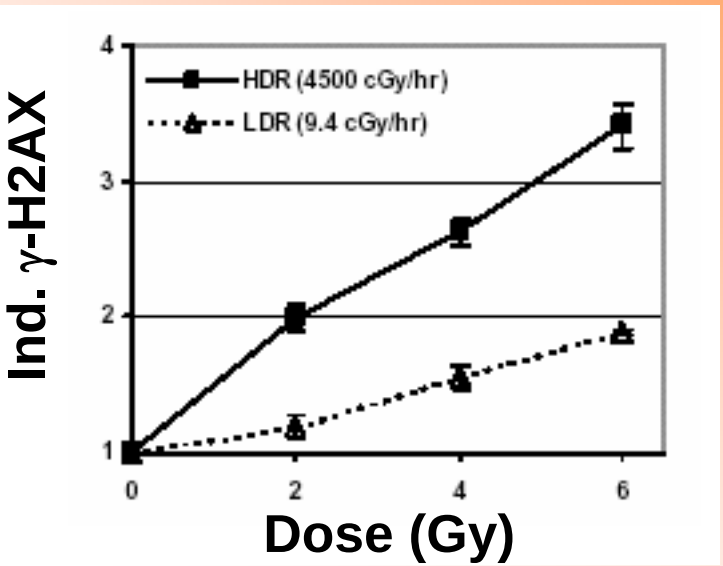
DSB signalling and repair depends on dose-rate

(Collis et al. JBC 2004; 279:49624-49632)





DSBs signalling via ATM and H2AX phosphorylation **was found to be absent at a very low dose-rate** (1.5 mGy/min) **- and associated with lethality – but present at slightly higher dose-rate** (4.16 mGy/min) **and at high dose-rate** (750 mGy/min) *(Collis et al. JBC 2004; 279:49624-49632)*

There appears to be a threshold for ATM dependent signalling and DNA repair. ---> This is in contradiction with the LNT hypothesis.

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Gene expression at low IR doses (1)

- In accord with differences in DNA damage signalling and repair at low and very low doses, data from transcriptome and proteomic analyses demonstrate that different gene and protein families are activated or repressed when comparing low (10-20 mGy and high doses (Gy).
- This reflects clear differences in signalling and processing of IR-induced damage, and is likely to determine the final outcome (mutagenesis and carcinogenesis).

---> *These data showing clear differences in gene expression at different dose levels contradict the LNT hypothesis.*

Extrapolations from high to low dose effects appear to be illegitimate.

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Gene expression at low IR doses (2)

- Cells react very sensitively to all environmental insults including ionizing radiation (IR).

  Molecular analysis of the induction or repression, up- or downregulation of genes indicates that already very low IR doses (< 1 mGy) induce significant changes of transcriptomic and proteomic profiles in living cells.

---> modifications at very low doses mostly concern general (energy) metabolism and antioxidant defenses but not

DNA repair or pro-apoptotic genes.

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Gene expression at low IR doses (3)

At very low doses (1 mGy) genes involved in DNA repair are not yet induced. However, **genes of energy metabolism and oxidative stress** are induced at doses 1000 times lower than those needed for the induction of mutations (in yeast).

(Mercier G. et al. 2004 Nucleic Acids Res. 2004 Jan 13;32(1):e12.).

Low doses of gamma irradiation (10 mGy) elicit different gene sets than high doses (2 Gy) in normal human skin cells.
(Franco N. et al. Radiat. Res. 2005; 163: 623-635)

Phosphoproteomic profiles in human fibroblasts differ at low and high IR-doses *(Yang F et al. J Proteome Res. 2006;5:1252-1260).*

--->Induction of genes involved in cellular IR-responses is highly dose dependent

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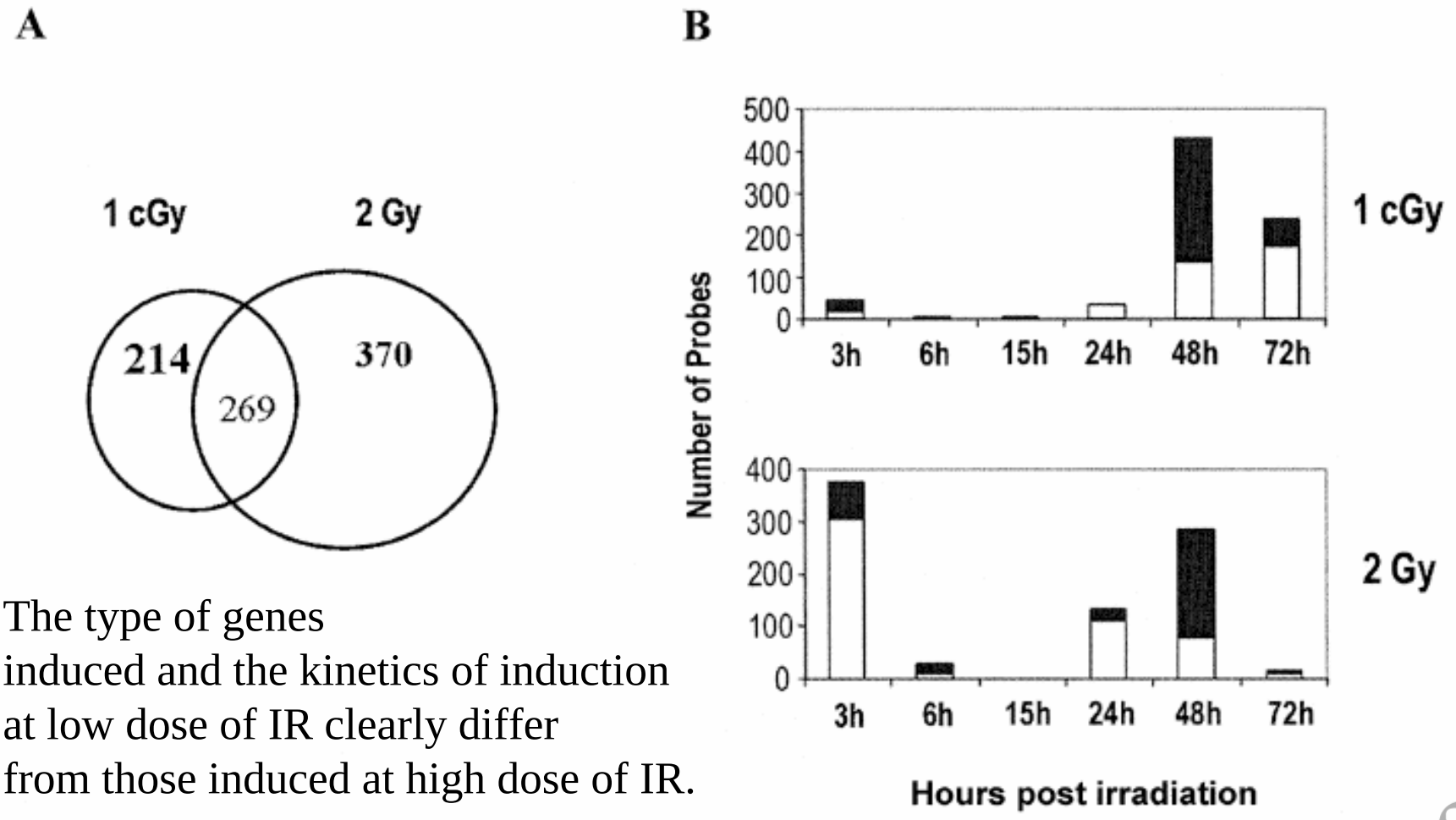
Induction of specific genes at low dose

(Franco N et al. Radiat. Res. 163, 2005)



The type of genes induced and the kinetics of induction at low dose of IR clearly differ from those induced at high dose of IR.

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Different phosphoproteomic profiles in human fibroblasts after low- and high-dose X-irradiation

(Yang F et al. J Proteome Res. 2006;5:1252-1260)

Ionizing radiation activates (by phosphorylation) important proteins involved in **cell cycle checkpoint** control, **DNA damage signalling**, **DNA repair and apoptosis**.

⇨ This is specific to high dose radiation (4 Gy)

⇨ At low dose (20 mGy), a more general spectrum of proteins is phosphorylated.

A **low dose (20 mGy) activates global metabolism** (such as cyclin dependent kinase, 6-fold) and not specific genotoxicity-related proteins.

A **high dose (4 Gy) activates 3-phosphoinositide-dependent protein kinase-1** (PDK1) and AKT/RSK motifs 8.5 and 5.5 fold, respectively.

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Expression of genes involved in cellular IR-responses is dose-rate dependent

Dose-rates affect expression of genes involved in different cellular functions:
---> Genes of IR-induced apoptosis (APO-1,TRAIOL,TRID etc.) but
not genes of cell proliferation (MDM2,BTG2,ELK4, SNK, etc.).
DNA repair genes such as XPC, and DDB2, but not ERCC1 and MDM2
(Amundson et al. Mol Cancer Res.2003; 1:445-452).

• Gene expression in normal human lung fibroblasts was found to depend on the dose-rate:
---> 1/3 of the genes showed modified expression after 1 Gy of γ -irradiation at HDR (1 Gy/min) versus LDR (0.7 mGy/min)
(Skolov MV et al. Gene 2006;382:47-56)

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Other radiobiological phenomena which contradict the LNT hypothesis (1)

Bystander effects: irradiated cells communicate with unirradiated cells either through intercellular gap junctions or through the relase of mediators into the medium. This changes radiation target size and gives rise to non linear responses in cell populations and tissues.

- *Little JB Carcinogenesis 2000; 21: 397-404; Mothersill and Seymour Nature 2004; 4: 256-63; Mutat Res. 2006 May 11;597(1-2):5-10; Belyakov OV et al. Mutat Res. 2006: 597 (1-2) 43-9.*

Low dose hypersensitivity: increased lethality is observed at low doses (a few hundred mGy) followed by radioresistance at doses over 500mGy.

- *Chalmers et al. IJROBP, 2004;58:410-419, Marples et al. Rad. Res. 2004;161:247-55*

Radioadaptive responses: a small conditioning dose (20 mGy) gives rise to resistance to a high challenging dose of IR.

- *Rigaud and Moustacchi, Mutat Res.1996; 435(2):127-34*

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Bystander effects

Effects of radiation on single cells influence the responses of adjacent nonirradiated cells

- Often cell-to-cell contacts are required but in some cells bystander effects are obtained without cellular contacts. The bystander effect can be beneficial or detrimental depending on the cell type and the range of doses analysed.

- Low doses (30 -60 mGy) of low LET IR may cause cell killing (apoptosis).
- Low doses of alpha particles may cause increased mutations of the spontaneous type and very few deletions (intercellular gap junctions were required).

  (*Little JB Carcinogenesis 2000; 21: 397-404)*

- In whole organisms abscopal effects may be observed

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Non-targeted effects of ionizing radiation may have positive consequences *in vivo*

(Belyakov OV et al. Mutat Res. 2006: 597 (1-2) 43-9)

- **Non-targeted effects** of ionizing radiation might be interrelated and possibly have a **protective role** under *in vivo* conditions by promoting differentiation.

- These effects might relate to **adaptive responses** because of increased non-targeted differentiation in irradiated samples.

- Based on these experimental data the authors proposed as the main function of non-targeted effects, the **decrease of the risk of carcinogenesis** in a multicellular organism exposed to oxidative damage (including IR-induced damage)

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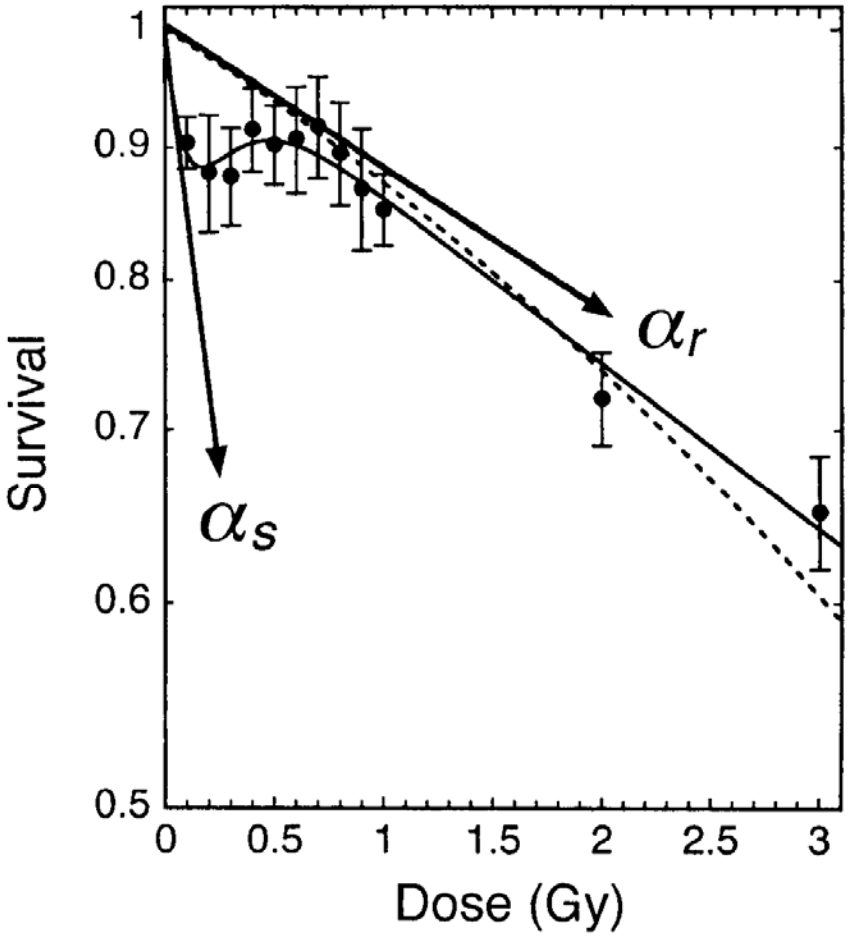
Low dose radiation hypersensitivity

(Joiner MC et al. Int J Radiat Oncol Biol Phys 2001;49-379-389)



Low dose hypersensitivity is observed in many cell types *(Joiner MC et al. Int J Radiat Oncol Biol Phys 2001;49:379-389; Marples et al. Radiat Res 2004;160: 543-548).*

---> high lethality at a few hundred mGy followed by radioresistance at doses > 0.5 Gy

It involves poly(ADP-phosphoribosyl)transferase (PARP 1), ineffective cell cycle arrest in G2-phase cells and DNA repair *(Wykes SM et al. Radiat Res. 2006;165:516-24).*

The exact role of hyper-radiosensitivity responses in radiocarcinogenesis (0-100 mGy) is not yet elucidated.

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Radioadaptive responses (1)

Adaptive responses have been shown to reduce DNA damage, mutation induction, chromosomal aberrations, micronuclei and cell transformation (*Rigaud and Moustacchi, Mutat Res.1996; 435(2):127-34*).

- Priming doses of less than 5 mGy or greater than 200 mGy yield very little adaptation (*Wolff S.* Environ Health Perspect 1998;106:277-28).

- Adaptive response on micronuclei production in human fibroblasts after a priming dose of 1 mGy and a 2 Gy challenging dose has been observed (*Broome et al. Radiat Res. 2002;158:181-186*) (needs to be confirmed).

- Induction of adaptive responses in human lymphocytes appears to be quite variable in different individuals. Occupational exposures of 2.5 mGy/year for up to 21 years resulted in variable adaptive responses in lymphocytes challenged with 2 Gy *(Barquinero et al. IJRB 1995;67(2):187-191).*

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Radioadaptive responses (2)

Adaptive radiation response in human lymphocytes *in vitro*:
Conditioning of cells with 20 mGy X-rays renders them more resistant to SSB and DSB produced by 1 Gy challenging dose. Persistent DNA strand discontinuities are thought to trigger the signal for adaptation against IR
(Stoilov *LM et al. Mutagenesis 2007;22(2):117-122)*

An *in vivo* adaptive response for chromosomal inversions was observed in pKZI mouse prostate by low doses of X-irradiation delivered at high dose.
(Day T. et al. Radiat. Res. 167: 682-692)

An *in vivo* adaptive response of γ-irradiation on the induction of DNA strand breakage in the spleen of mice:

clear adaptive effect on the induction of DNA strand breaks *in vivo* with a significant significant increase in gene expression of catalase and Mn-SOD by low dose-rate exposure (0.5 Gy over 23 days)

(Otsuka K et al. Radiat Res 2006;166(3)474-478)

----> adaptive responses involve the activation of cellular antiradical defenses

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Other radiobiological phenomena which contradict the LNT hypothesis (2)

Low dose and dose-rate effects observed on cell transformation *in vitro*

Neoplastic cell transformation *in vitro* in C3H 10T1/2 cells was shown to decrease at low dose rate below the spontaneous frequency *(Redpath JL et al. Radiat. Res 2003;159:433-436).*

In human non tumor cells CGL1 exposed to 30 keV photons (125I) neoplastic transformation is found to be lower than background at dose-rates of 0.19 and 0.47 mGy/min and radiation doses up to 1 Gy *(Elmore E et al. Radiat Res 2006;166:832-838).*

---> Thus, there is no linear dose-response relationship at these low dose-rates (contradiction with LNT-hypothesis)

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Protective processes induced by low doses of low LET radiation

- Recent work showed that low doses selectively remove transformed cells in coculture by stimulating intercellular induction of a protective pro-apoptotic process mediated by reactive oxygen and nitrogen species and TGFbeta that eliminates cells with genomic instability (*Portess DI et al. Cancer Res. 2007; 67(3):1246--1253; Bauer G. 2007 Int. J. Radiat. Biol. 83: 873-888*)
- This may be related to positive effects of low dose IR (radiation hormesis) showing a reduction in transformation frequency after low doses *(Redpath et al. Radiat. Res Radiat Res*, *2003; 159*: 433-436.Ko et al. *2006; Mutat.Res. 597:11-17;Azzam EI et al. Radiat. Res. 1996; 146:369-373).*

- The low-dose saturation of radiation-induced apoptosis in pretransformed cells has potential implications for the effect of low doses of ionizing radiation on a naturally occurring anticancer defense mechanism.

--->These effects are not compatible with the linear-no-threshold model !

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Low-dose radiation-induced selective removal of precancerous cells via intercellular induction of apoptosis

(D.I. Portess et al. Cancer Res. 2007; 67(3):1246-1253)

Table 1. Comparison of percent apoptosis scored in nonirradiated *src* transformed cells following 65-h coculture with irradiated 208F cells

Experimental conditions	Dose (Gy)	% Apoptosis (±SD)
LET comparison	Negative control*	14.52 (±0.90)
γ-Rays	0 †	26.70 (±1.54)
	0.5	47.15 (±1.66)
α-Particles	0 †	27.24 (±2.47)
	0.5	48.69 (±2.24)

---> Radiation of nontransformed cells 208F leads to increased levels of apoptosis in unirradiated transformed 208F*src3* cells in coculture.

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Hormesis

- Evidence for beneficial low level radiation effects and radiation hormesis i.e. protection against spontaneous genomic damage *(Feinendegen L., Br. J. Radiol. 78:3-7 (2005)*
- Protection against spontaneous neoplastic transformation in vitro via a low dose induced adaptive response (*Redpath J et al. 2001 Radiat. Res. 156,700-707)*
- *After low dose rate exposure (0.19 and 0.47 mGy/min) in vitro cell transformation in the very low dose rage 10 mGy was below or close to background (Elmore E. et al. Radiat. Res. 166: 832-838)*

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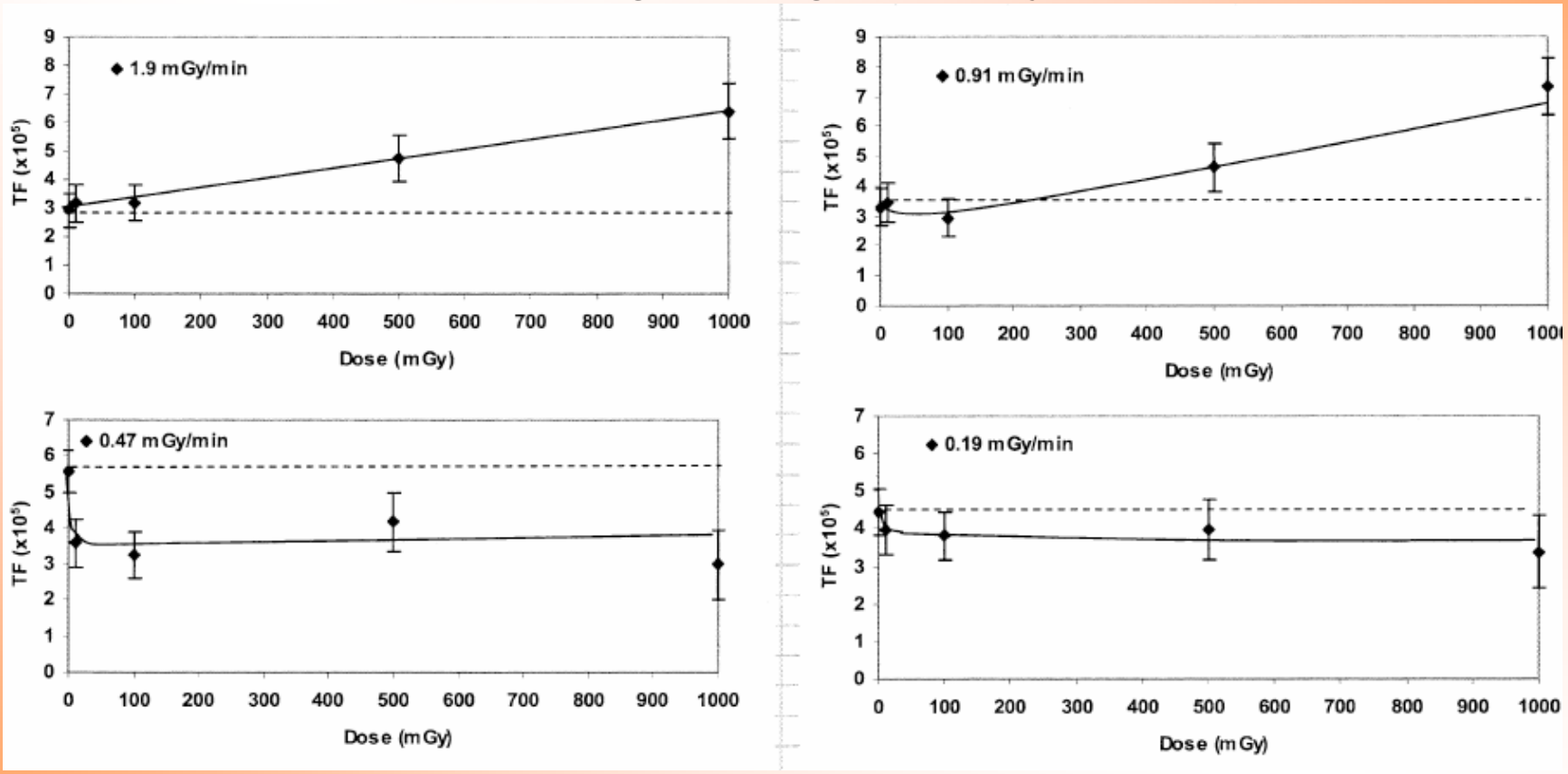
Dose-rate effects observed on different biological endpoints : cell transformation in HeLa x Skin fibroblast hybrid cells *in vitro*

(Elmore E et al. Radiat Res 2006;166:832-838).

Low to high dose range of ^{125}I decays



----> at a dose of 1 Gy at dose-rates 1.9 and 0.91 mGy/min neoplastic transformation is significantly different from background.

---> IR-induced cell transformation appears to be lower than spontaneous background at very low dose rates (0.47mGy/min and 0.19 mGy/min of ^{125}I) (36 keV X rays +31 keV electrons)

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Dose dependency of immune responses

- Low doses of low LET-radiation induce immunity against cancer cells

  (Liu S Nonlin. Biol. Toxicol.Med.1(1):71-92(2003)

  Liu S (2007) Dose response 5: 39-47)

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Animal data

Most animal data show an absence of harmful effects of low dose IR exposures.

- A meta-analysis of experimental tumour data revealed the existence of a practical threshold in nearly all experimental tumour studies *(Tanooka H. Int J. Radiat. Biol. 2001;77:541-551.*
- 40% of animal studies showed a hormesis-like response, *i.e.* a decrease in spontaneous cancer incidence at low radiation doses *(Duport P. Int J Low Radiation 2003;1:120-131)*
- Moreover, at continuous very low IR dose (10cGy/year) no adverse effects were observed on life span and incidence of lymphoma in SJL female mice *(Lacoste-Collin L. et al. Radiat. Res. 168, 725-732,2007)*

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Epidemiological surveys (1)

Large epidemiological studies are important to assess low dose health risks for humans. Most studies are unable to determine excessive risks at low doses. Most data can be fitted either to a linear or a linear-quadratic relationship.

•Data from A-bomb survivors (high dose rate) showed at low doses:
- a threshold at about 150 mSv for leukemias *(Little MP et al. IJRB 2000;76:939-953)*
- a curvi-linear relationship for solid tumours *(PrestonDL et al. Radiat Res 2004:162:377-389)*
- a non significant increase but a similar excess relative risk if the group of 5 to 125 mSv was taken as homogenous (*Brenner DJ et al. PNAS 2003;100:13761-13766*).

---->However, this can be due to increased statistical power due to sample size.

--->Cancer incidence compatible with LNT but also with an up to 60 mSv threshold or a quadratic relationship *(Pierce and Preston DL Radiat. Res. 2000;154:178-186)*

•Mayak workers 21500: excess relative risk of death is lower than expected from A-bomb survivors, however, plutonium dosimetry causes problems.
(Shilnikova NS et al. Radiat Res.2003;159:787-798)

•Chernobyl 8600 individuals (mean dose >50 mSv): incidence of all cancers 12% lower than in general Russian population *(Ivanov V et al. JRadiat Res 2004;45:41-44.)*

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Epidemiological surveys (2)

- IARC's meta-analysis of 96000 nuclear workers showed a risk for leukemia > 400 mSv *(Cardis E et al. Radiat Res. 1995;142:117-132)*

- Radiologists and technicians receiving doses 10-50 mSv (and cumulative doses > 50mSv) showed no excesss risk for sensitive organs (breast, thyroid, hematopoietic tissue)

- Residential exposure to radon in Japan showed no excessive risk at low exposure *(Sobue T et al.J Radiat Res 2000;41:81-92)*

- Air crew members 44000 receiving doses 1.5-6 mSv/year did not show particular excess in cancers except of melanoma

(Zeeb H et al. Am J Epidemiol 2003; 158: 35-46)

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Epidemiological surveys (3)

- Several studies did not find an increase in leukemia risk after medical diagnostic doses below 100 mSv

- Fractionated doses 10 mGy for high cumulative doses (1 Gy) are apparently carcinogenic for the breast (*ICRP committee I, Dec 10,2004)*

- In an IGR study on breast cancer cases, no carcinogenic efect was observed for dose fractions < 160 mGy and cumulative dose up to 5 Gy) *(Rubino C et al. Br J Cancer 2003;89: 840-846)*

- Among 2000 thyroid cancers observed after Chernobyl 80% of patients were less than 5 years old. No excess in thyroid cancers outside of former USSR.

- Medical irradiation *in utero* (Oxford study) *(Doll R BrJ Radiol 1997;70:130-139)* concluded to an increased risk at 10 mSv. (weaknesses:excess risk is the same for all cancer sites: this is unusual; rat and mouse studies do not indicate a particular susceptibility to cancer of embryonic tissu except nerves and ovary, respectively; no excess of cancers in twins (*Inksip PD et al. Cancer Cause Contr 1991, 2: 315-324; the cumulative dose of women was mostly > 500 mSv)* *(Howe HL et al. Cancer Control 1995 2; 113-120*)

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Epidemiological surveys (4)

- Studies on painters of luminous dials contamined with radium-226 and 228.

There was an excess in osteosarcomas but not at doses < 10 Gy *(Carnes E et al. Radiat Res. 1997;147: 707-714*):

Also studies in patients receiving thorotrast (thorium based). A threshold of about 2 Gy was observed for hepatomas *(Travis LB et al. Radiat Res. 2003;160:691-706)*

- Radon in homes: 7148 people/14208 controls (13 European case-control studies) showed a proportionate increase in lung cancer risk for radon using fitting to LNT *(S. Darby et al.BMJ 2004, 330, 233-240)*

- Cancer mortality of 4000 000 nuclear workers of 15 countries. There was no excess of leukemia but following LNT there was a small excess of cancers attributable to IR. 196 death by leukemia with an EER/Sv of 1.93, a value that is not statistically significant in the light of important range of uncertainties. Smoking as a confounding factor could not be totally excluded. *(Cardis E. et al. BMJ Online First 29 June 2005)*

--->Most epidemiological studies adopted the LNT model for data fitting. However, all low dose epidemiological data can be fitted as accurately to linear-quadratic or threshold type models contrasting LNT.

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Conclusions (1)

- The above arguments are in favour of lower than expected biological effects (practical threshold type responses) at low doses and low dose-rates of IR.
- Most data contradict the LNT hypothesis and show that simple extrapolations from high to low dose IR exposures are not possible because at low doses other biological processes are operating than at high doses.
- The complexity of the response is higher at low than at high IR doses. This his also true for epidemiological data where the number of possible confounding factors is greater at low than at high radiation doses.
- More parameters have to be taken into account for low dose risk evaluations and a different type of modeling is needed. Obviously, the LNT-hypothesis cannot fulfill this role. System biology modelling might provide a solution.

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Conclusions (2)

It seems scientifically sound, and wise from the practical and economical point of view,

- to recognize the limits of the LNT-hypothesis for low dose risk evaluations and
- to decrease existing uncertainties at low doses and dose-rates by taking into account the available scientific findings.

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Future research needs

- Radiation specific signatures: lésions (Role of LMDS), mutagenesis, carcinogenesis. Molecular epidemiology.
- Radiation-induced intra-and intercellular signalling
- Radiation sensitivity: stem cells, young and adult cells, differentiation,children *versus* adults, individual radiation sensitivity
- Ageing and Radiation-induced carcinogenesis
- Radio-immune responses
- Adaptive responses and Hormesis
- Interaction of radiation with other genotoxic insults
- Impact of epigenetic effects and chromatin modifications
- System biology modeling of radiation-induced responses (stepwise or continuous modification of responses at different dose and dose-rate levels)

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U.S.NRC

United States Nuclear Regulatory Commission

Protecting People and the Environment

LOW DOSE RADIATION EFFECTS, REGULATORY POLICY AND IMPACTS ON THE PUBLIC - NRC PERSPECTIVE

Martin J. Virgilio

Deputy Executive Director for Materials, Waste, Research, State, Tribal, and Compliance Programs

April 15, 2008

U.S.NRC
United States Nuclear Regulatory Commission
Protecting People and the Environment

System of Radiological Protection

- Three basic fundamentals
- Dose based system
- Assumptions
  - Linear- no threshold (LNT) for stochastic health effects
  - Gender/Age averaged
  - Protect the most exposed individual

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Protecting People and the Environment

Technical Developments That May Influence NRC Regulations

- Developments in basic science (e.g., Department of Energy low dose research program, JCCRER)
- UNSCEAR Reports (2000 – 2007)
- BEIR V and VII
- ICRP Reports 60 – 103
- New Respiratory and Human Alimentary Tract Model
- New derived air concentrations (DACs) and annual limits on intake (ALIs)

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United States Nuclear Regulatory Commission
Protecting People and the Environment

Issues That Might Increase Regulatory Control

- Reduced threshold for lens opacification
- Significant difference in gender sensitivity to radiation
- Protect the most sensitive vs the most exposed individual
- Other

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United States Nuclear Regulatory Commission
Protecting People and the Environment

Issues That Might Decrease Regulatory Control

- Existence of a dose response threshold
- Efficient DNA repair at low dose and low dose rates
- Issues that arise in constructing an alternative regulatory program
- Other?

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Protecting People and the Environment

Path Forward

- Review basic research and ICRP recommendations
- Coordinate with Interagency Steering Committee on Radiation Standards
- Options for Commission consideration (late 2008)
- Slow, deliberate process

The DOE Perspective

NCRP Annual Meeting

13-14 April 2008

Noelle F Metting, Sc.D.
Office of Science

U.S. Department of Energy

Preparation of this presentation was a joint effort:

Noelle Metting

Senior Radiation Biologist

Office of Biological and Environmental Research

Office of Science

Andrew Wallo

Deputy Director

Office of Nuclear Safety and Environment

Office of Health, Safety, and Security

Office of Science
U.S. DEPARTMENT OF ENERGY

HSS
Office of Health, Safety and Security

What are the tipping points for radiation protection standards revision?

- Significant safety issues
  - ***Highest priority—quick response***
  - Discovery of a new issue not previously addressed
  - Discovery of a flaw in a current standard
- Implementation issues
  - ***High priority—timely measured response***
  - A standard is not clear or is inefficient
  - Requirements are not implementable as written
- Consistency—Best practice—Current science
  - ***Of lesser priority if there is no safety issue attached***
  - Addressed as time and resources permit

What constitutes compelling evidence that it is time to change a standard?

- A consensus on better scientific understanding, tools, or approaches indicates the **need for a change**

- But the **pace of change** has been driven by the associated component of human health risk
  - If a large increase in safety is indicated, this benefit alone will drive the action quickly
  - If a small or zero increase in safety is indicated, then decisions on change will also be based on resources and costs

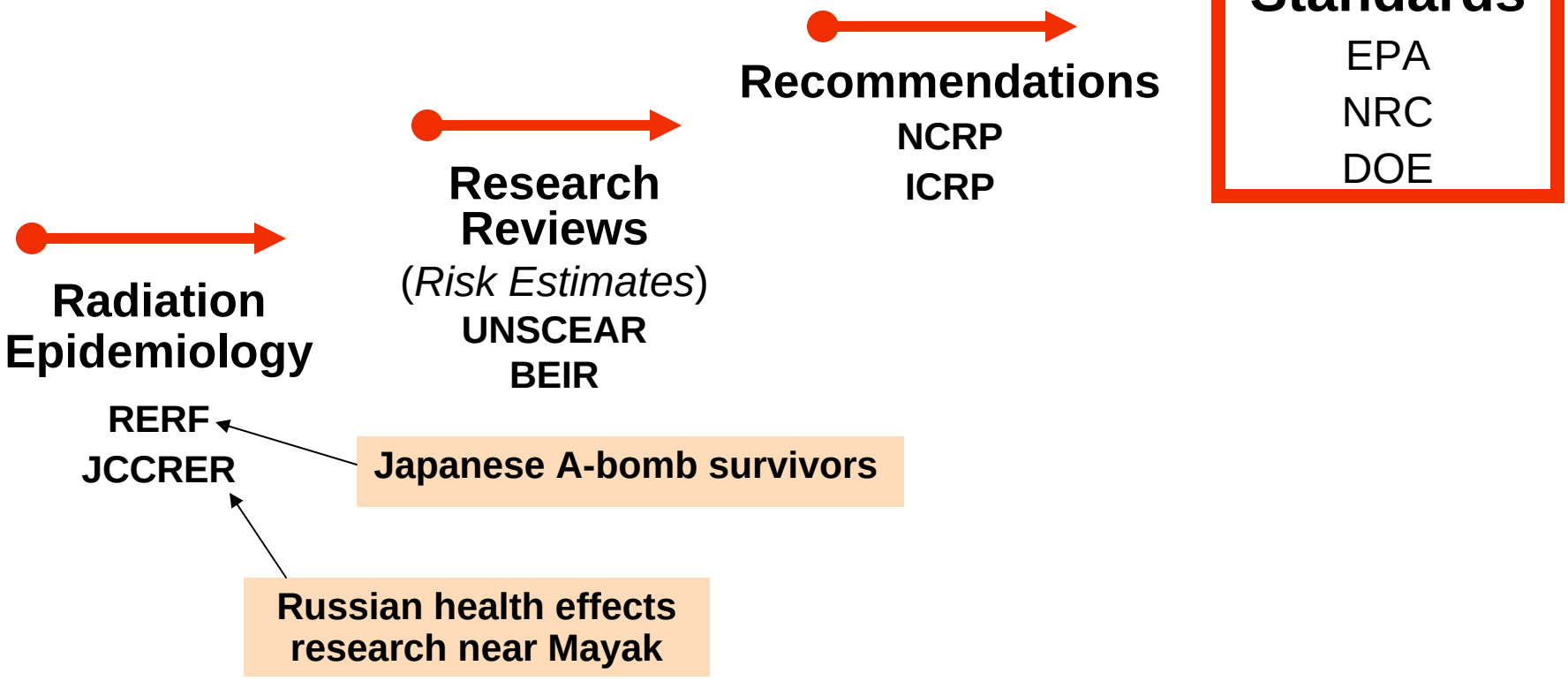
What is DOE's perspective on establishing a radiation protection system based on risk?

- **DOE's radiation protection system uses risk as a basis, but it is not used directly for radiation protection standards**
  - This is because the risk uncertainty rises drastically in the low dose regime (where we regulate)
  - Standards are generally defined as a function of dose, or the directly measurable quantities of exposure, activity, or concentration
  - Levels are consistent with NRC, and with recommendations from NCRP, ICRP

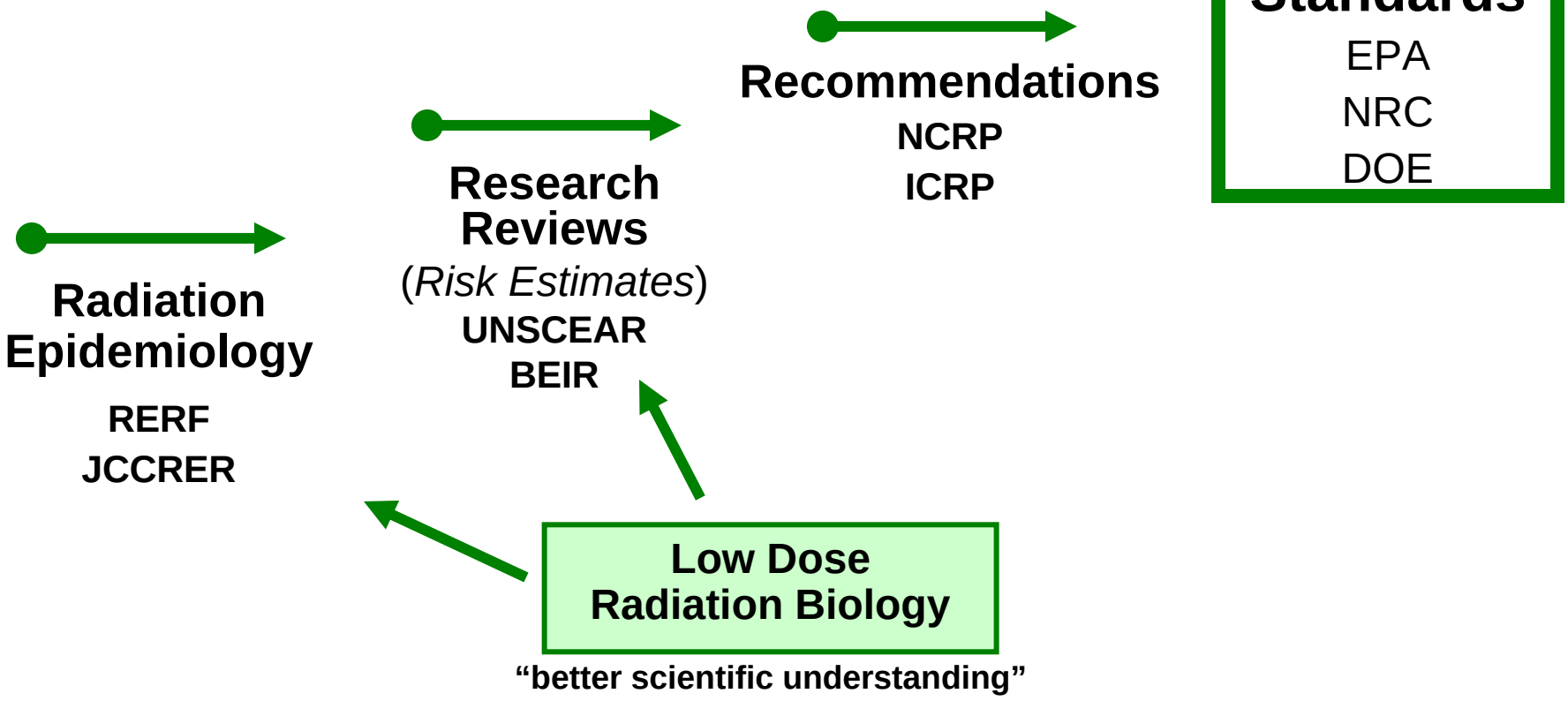
Should we regulate at the upper confidence limit of risk?

- **This is a policy decision** - (But biasing every risk factor to conservative values is not necessarily good safety policy, nor is it always in the best interest of the public welfare)
- **A better approach is to decrease the uncertainties and shrink the confidence intervals around the central estimate of risk**
- **DOE's Office of Science supports basic research to decrease these uncertainties**

Radiation Protection Standards: Development Sequence



Radiation Protection Standards: Development Sequence



Radiation physics ***(energy deposition)*** *dictates a linear induction of initial biological effects as a function of dose*

Radiation biology *now shows us that the ultimate biological response is much more complex:*

- Different types of genes are activated after low dose versus high dose exposure (gene expression studies, DNA repair)
- Cells irradiated within tissues respond very differently than do cells irradiated in culture (comparative gene expression and apoptosis studies)
- Cells communicate, and normal cells in tissue act as an integrated unit to protect the tissue from cancer (bystander studies, epigenetics)
- After low dose exposure, damaged cells within a normal intact tissue are efficiently suppressed, or stimulated to die, and tissue survives with its functionality intact (microenvironment studies, mouse immune function studies)

Considerations:

- **Homeostasis** --- Just because biological responses occur after very low dose exposure does not mean they are detrimental to the organism.
- **Systems Biology** --- Understanding response in the intact organism will bring about scientific consensus.
- **Human Genetic Variation** --- “There are an estimated 15 million places in our genome where one base can differ from one person or population to the next.”

(SCIENCE - Breakthrough of the Year, 2007)

Radiation Protection Standards: Development Sequence

Radiation Epidemiology

New studies of low dose human cohorts

RERF
JCCRER
} Low dose data only

Research Reviews
(*Risk Estimates*)
UNSCEAR
BEIR

If the risk is judged to be lower …

Recommendations
NCRP
ICRP

Recommendations may be modified …

National Standards
EPA
NRC
DOE

And standards may change.

Low Dose Radiation Biology

"better scientific understanding and consensus"

Low dose epidemiology

High bkg areas
Nuclear workers
Radiation workers

Ionizing Radiation

Dose Ranges

(Rem)

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

Cancer Radiotherapy
total dose to tumor

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

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

6 — 0 — 2000 — 4000 — 6000 — 8000 — 10,000 rem

Total Body Irradiation (TBI) Therapy

Acute Radiation Syndromes

Life Span Study (A-bomb survivor epidemiology)

Solar flare dose on moon, no shielding

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

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

5 — 0 — 200 — 400 — 600 — 800 — 1,000 rem

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

Human LD_{50} range, acute exposure with no medical intervention (50% death in 3-6 weeks)*

Human LD_{50} range, acute exposure with medical intervention

*Note: Whole body acute prognoses assume no medical intervention.)

Office of Science
U.S. DEPARTMENT OF ENERGY

Cancer Epidemiology

Evidence for small increases in human cancer above 10 rem acute exposure, 20 rem chronic exposure

4 — 0 — 10 — 20 — 30 — 40 — 50 — 60 — 70 — 80 — 90 — 100 rem

Typical mission doses on Intl. Space Station (ISS)

Natural bkg /yr Ramsar, Iran

EPA guideline for lifesaving: 25 rem

DOE Low Dose Program

EPA radiological emergency guideline for public relocation: 2 rem/yr

3 — 0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10 rem

H — I — J

Natural bkg /yr Kerala coast, India

DOE administrative control: 2 rem/yr = 20 mSv/yr

Natural bkg /yr Guarapari, Brazil

DOE, NRC Dose Limit for Workers: 5 rem/yr = 50 mSv/yr

Medical Diagnostics (A-J)

Typical annual doses for commercial airline flight crews

2 — A — B — F — G — 0 — 100 — 200 C — D E 400 — 500 — 600 — 700 — 800 — 900 — 1,000 mrem = 1 rem

Natural background, U.S.A average ≅ 300 mrem/yr (includes radon)

Natural bkg /yr Yangjiang, China

Regulations & Guidelines

NRC cleanup criteria for site decommissioning / unrestricted use: 25 mrem/yr

DOE facility releases

1 — 0 — 10 — 20 — 30 — 40 — 50 — 60 — 70 — 80 — 90 — 100 mrem

EPA dose limit applicable to public drinking water systems: 4 mrem/yr

Round-trip NY to London

EPA dose limit from releases in air: 10 mrem/yr

ANSI standard N43.17 Personnel scans max dose for total scans in 1 yr: 25 mrem

DOE, NRC Dose Limit for Public: 100 mrem/yr = 1 mSv/yr (ICRP, NCRP)

Medical Diagnostics, rem

A- Chest x-ray (1 film)	0.01
B- Full dental series	0.16
C- Mammogram	0.25
D- Lumbosacral spine	0.32
E- PET	0.37
F- Bone (Tc-99m)	0.44
G- Cardiac (Tc-99m)	1
H- Cranial CT (MSAD) (multiple scan average dose)	5
I- Fluoroscopy- 2 min scan (barium contrast-G.I.)	8.5
J- Spiral CT- full body	1.5- 10

LD_{50} = Lethal Dose to 50% (the acute whole body dose that results in lethality to 50% of the exposed individuals)

Absorbed dose: 100 rad = 1 Gray
Dose equivalent: 100 rem = 1 Sievert
100 mrem = 1 mSv
(1 rem = 1 rad for x- and gamma-rays)

Note: This chart was constructed with the intention of providing a simple, user-friendly, "order-of-magnitude" reference for radiation quantities of interest to scientists, managers, and the general public. In that spirit, most quantities were expressed in the more commonly used radiation protection unit, the rem (or Sievert, 2nd page), and medical doses are not an "effective" dose. It is acknowledged that the decision to use one set of units does not address everyone's needs. (NRC—US Nuclear Regulatory Commission; EPA—US Environmental Protection Agency)
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Chart compiled by NF Metting, Office of Science, DOE/BER
"Orders of Magnitude" revised April 2008
http://www.science.doe.gov/ober/

Ionizing Radiation

Dose Ranges

(Sievert)

Office of Science
U.S. DEPARTMENT OF ENERGY

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

Cancer Radiotherapy
total dose to tumor

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

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

⑥ 0 10 20 30 40 50 60 70 80 90 100 Sv

Total Body Irradiation (TBI) Therapy

Life Span Study (A-bomb survivor epidemiology)

Solar flare dose on moon, no shielding

Acute Radiation Syndromes

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

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

⑤ 0 1 2 3 4 5 6 7 8 9 10 Sv

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

Human LD_{50} range, acute exposure with no medical intervention (50% death in 3-6 weeks)*

Human LD_{50} range, acute exposure with medical intervention

*Note: Whole body acute prognoses assume no medical intervention.)

Cancer Epidemiology

Evidence for small increases in human cancer above 0.1 Sv acute exposures, 0.2 Sv chronic exposure

④ 0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1 Sv

Typical mission doses on Intl. Space Station (ISS)

Natural bkg /yr Ramsar, Iran

EPA guideline for lifesaving: 0.25 Sv

DOE Low Dose Program

EPA radiological emergency guideline for public relocation: 20 mSv/yr

③ 0 10 20 30 40 50 60 70 80 90 100 mSv

H I J

Natural bkg /yr Kerala coast, India

DOE administrative control: 20 mSv/yr = 2 rem/yr

Natural bkg /yr Guarapari, Brazil

DOE, NRC Dose Limit for Workers: 50 mSv/yr = 5 rem/yr

Medical Diagnostics (A-J)

Typical annual doses for commercial airline flight crews

② A B F G 0 1 2 C 3 D E 4 5 6 7 8 9 10 mSv

Natural background, U.S.A average ≅ 3 mSv/yr (includes radon)

Natural bkg /yr Yangjiang, China

Regulations & Guidelines

NRC cleanup criteria for site decommissioning / unrestricted use: 0.25 mSv/yr

DOE facility releases

① 0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1 mSv

EPA dose limit applicable to public drinking water systems: 0.04 mSv/yr

Round-trip NY to London

EPA dose limit from releases in air: 0.1 mSv/yr

ANSI standard N43.17 Personnel scans max dose for total scans in 1 yr: 0.25 mSv

DOE, NRC Dose Limit for Public: 1 mSv/yr = 100 mrem/yr (ICRP, NCRP)

Medical Diagnostics, mSv

A- Chest x-ray (1 film)	0.1
B- Full dental series	1.6
C- Mammogram	2.5
D- Lumbosacral spine	3.2
E- PET	3.7
F- Bone (Tc-99m)	4.4
G- Cardiac (Tc-99m)	10
H- Cranial CT (MSAD) (multiple scan average dose)	50
I- Fluoroscopy- 2 min scan (barium contrast-G.I.)	85
J- Spiral CT- full body	15-100

LD_{50} = Lethal Dose to 50% (the acute whole body dose that results in lethality to 50% of the exposed individuals)

Absorbed dose: 1 Gray = 100 rad
Dose equivalent: 1 Sievert = 100 rem
1 mSv = 100 mrem
(1 Sv = 1 Gy for x- and gamma-rays)

Note: This chart was constructed with the intention of providing a simple, user-friendly, "order-of-magnitude" reference for radiation quantities of interest to scientists, managers, and the general public. In that spirit, most quantities were expressed in the more commonly used radiation protection unit, the rem (or Sievert, 2nd page), and medical doses are not in "effective" dose. It is acknowledged that the decision to use one set of units does not address everyone's needs. (NRC—US Nuclear Regulatory Commission; EPA—US Environmental Protection Agency)
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"Orders of Magnitude" revised April 2008
http://www.science.doe.gov/ober/

What it would take to change radiation protection regulations – EPA's Perspective

April 15, 2008

Presented by:
Juan Reyes, Director

US EPA/ Radiation Protection Division

Why change a regulation?

Statutory mandate

Litigation

Public or special interest groups petition for change

New scientific information compels a change

Regulation becomes obsolete

Risk Principles Applied to Standards

Radiation protection standards need to account for uncertainty

- Cancer risk estimates have large uncertainties
- Reasonable conservatism in setting risk-based standards reduces the chance that we are under-regulating

Scientific weight of evidence:

- If evidence shows regulations are too lax, rules likely get strengthened
- If evidence shows the opposite, rules *may* be relaxed (if statute permits; if there is a compelling need; …)

Why we use LNT

Epidemiological studies have insufficient statistical strength to test LNT at low doses

So far, biological research has not filled the gap left by epidemiology at low doses

According to BEIR VII (NAS), scientific weight of evidence still favors LNT

Before rejecting LNT, EPA would want –

Scientific consensus (as reflected in reports from NAS, UNSCEAR, NCRP, ICRP, etc.)

Concurrence from EPA's Science Advisory Board

Acceptance among Federal agencies

A transparent public process for considering scientific evidence

What is a threshold?

A threshold might be strictly defined as a radiation dose (or dose rate) below which no harm to any individual in a population would occur

For regulatory purposes, however, a “practical threshold” might be adopted if there were compelling evidence that, below this level, the risk is much lower than predicted by LNT, but not necessarily zero

Regulating with a threshold

A threshold below the level of unavoidable dose would have no impact on current regulations

A practical threshold substantially above background might mean certain regulations could be relaxed or reinterpreted, including:

- Drinking water MCLs
- Derived soil cleanup levels

Issues in setting threshold-based standards

Magnitude of threshold dose or dose rate

Uncertainty in threshold dose

Consideration of sensitive subpopulations

Contribution of multiple sources

- Example: If threshold = 10 mSv/y, then an individual source limit might be set at 1 mSv/y

Summary

Radiation protection is currently based on LNT, consistent with recent NAS recommendations

Before adopting a threshold, EPA would need a scientific consensus

Compelling evidence for a threshold might influence environmental standards

A change in standards would require statutory authority and need to consider safety factors (multiple sources, sensitive subgroups, etc.)

Beliefs about Radiation: Scientists, the Public and Public Policy

Hank C. Jenkins-Smith
Carol L Silva
Christopher Murray

University of Oklahoma
Department of Political Science

Research Questions

- To what extent (and in what ways) do human radiation dose-response relationships influence scientists' perspectives on radiation risks?
- Do scientists' ideological dispositions independently influence assessed radiation risks?
- How do perceived risks influence scientists' nuclear energy policy preferences?
- In what ways do scientists' and the mass publics' beliefs about radiation risk (and benefits) differ?
- Are public preferences concerning nuclear policy constructed in a *meaningfully different manner* than scientists' preferences?

Figure 1: Hypothesized Radiation Dose-Response Relationships

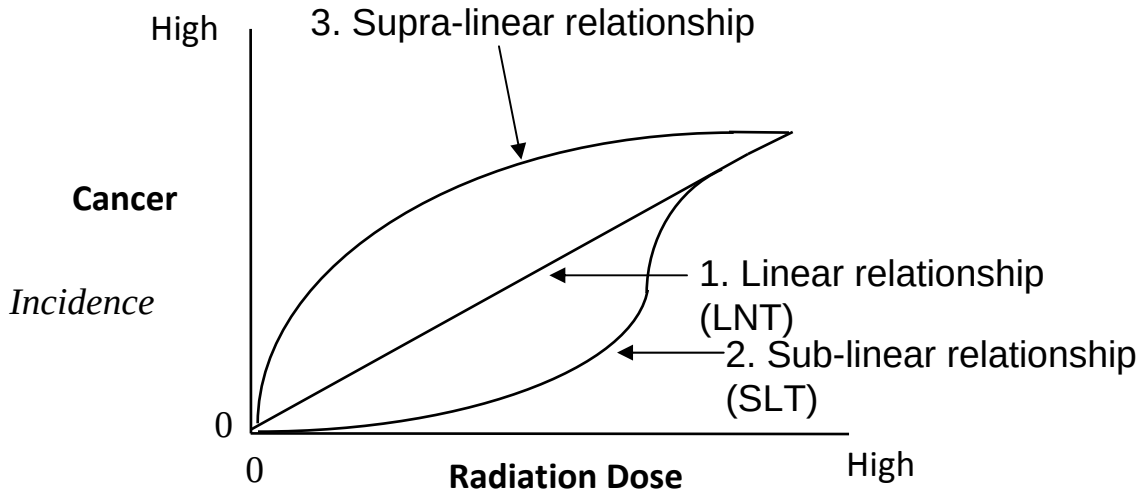

Table 1: Scientists' Beliefs about Radiation Dose Response Function

	USA Scientists	UK Scientists	French Scientists	German Scientists	Other EU Scientists
Believed Dose-Response					
Linear No-Threshold	19.2%	20.9%	17.6%	22.5%	23.2%
Sub-linear Threshold	75.0%	70.6%	69.7%	64.2%	68.6%
Supralinear	5.8%	8.5%	12.6%	13.4%	8.1%
Certainty (0-10)	5.65	5.16	5.42	6.25	5.96

Table 2: Perceived Risk Comparisons of Scientists and the Public

Scientists 2002 Multination Survey
Public 2006 Telephone/Web Survey

Variable	USA Public	USA Scientists	UK Scientists	France Scientists	Germany Scientists	Other EU Scientists
Dependent Variables						
Risk from Reactor Accident (0=no risk, 10=extreme risk)	6.12	4.49	4.72	4.41	5.16	4.73
Risk from Spent Fuel (0=no risk, 10=extreme risk)	6.28	5.45	5.37	4.81	5.51	4.98
Support for New Nuclear Reactors (1=strongly oppose, 7=strongly support)	4.20	4.36	3.86	4.14	3.14	3.77
Policy Core Variables						
Political Ideology (1=strong lib/left, 7=strong cons/right)	4.26	3.41	3.58	3.73	3.79	3.65
Egalitarian Disposition (1=strongly disagree, 7=strongly agree)	4.41	4.08	4.55	5.13	4.82	5.12

Table 2 (continued):Perceived Risk Comparisons of Scientists and the Public

Scientists 2002 Multination Survey
Public 2006 Telephone/Web Survey

Variable	USA Public	USA Scientists	UK Scientists	France Scientists	Germany Scientists	Other EU Scientists
Energy Domain Postures						
Rad. Dose-Response Scale (-10=certain LNT, 10=certain SLT)	NA	3.28	2.09	2.09	2.33	2.29
Nuclear Benefit: No GHG (0=no benefit, 10=extremely beneficial)	7.09	7.45	7.30	7.91	7.06	7.24
Nuclear Benefit: Domestic Supply (0=no benefit, 10=extremely beneficial)	7.37	7.35	6.74	7.69	6.62	6.88
Individual Demographic Controls						
Percent Bio/Med/Ag	NA	58.5%	55.3%	62.0%	62.4%	60.8%
Age (average years)	47.45	54.67	53.82	56.25	50.99	53.79
Percent Male	46.30%	79.7%	88.3%	80.8%	88.0%	89.4%
Percent Ph.D.	2.56%	77.3%	70.0%	93.4%	87.2%	82.7%
Sub-sample size	3012	824	247	151	244	568

Figure 2: Comparing US and EU Scientists D-R Certainty

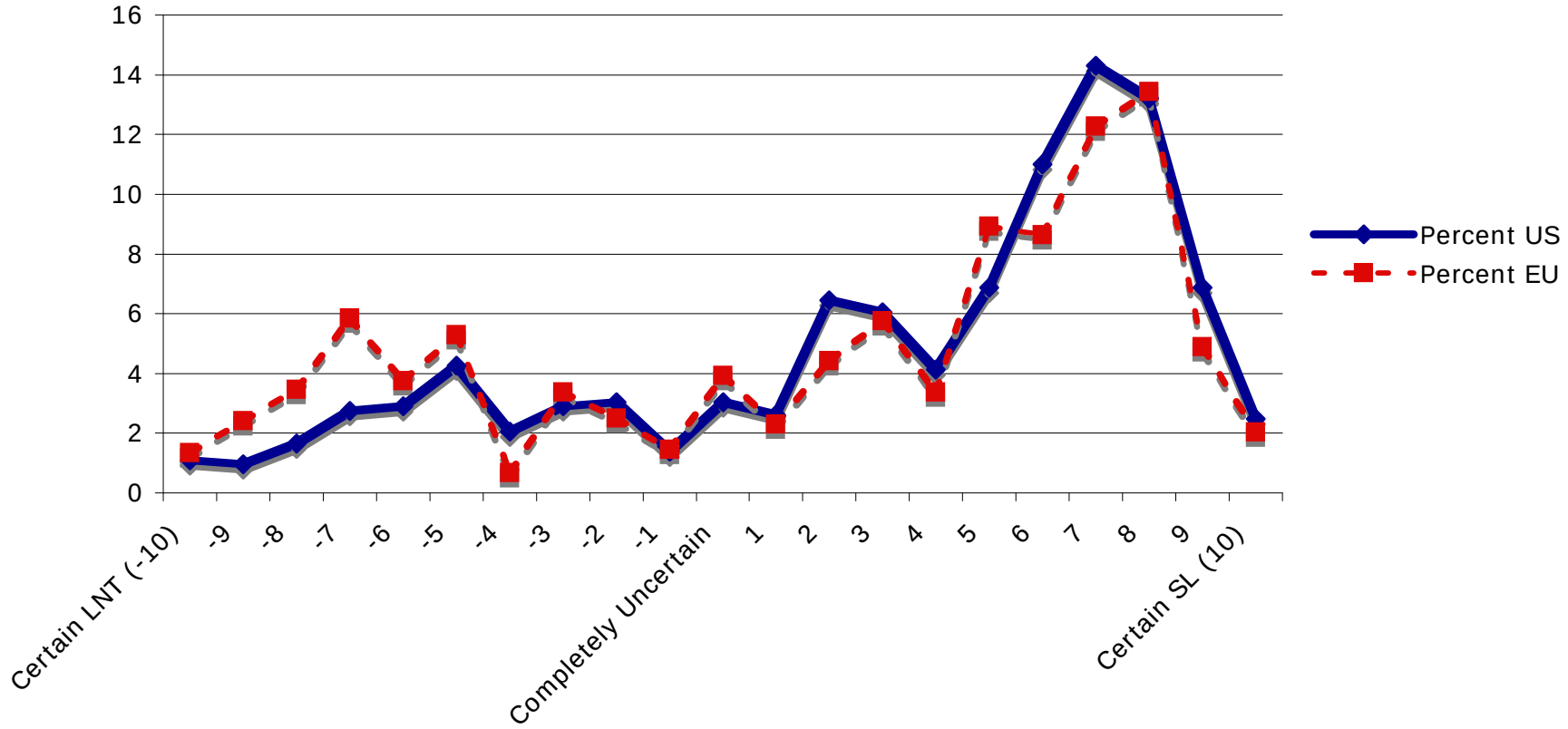

Table 3: Perceived Risks of Nuclear Reactor Accidents: Modeling Scientists and Mass Publics

Independent Variable	US and EU Scientists	US Public
Political Ideology	-0.172**	0.011
Egalitarian Disposition	0.309**	0.617**
Dose-Response Scale	-0.030**	NA
Age	-0.035**	-0.011**
Gender (Male=1)	-0.512**	-1.473**
USA	0.210	NA
United Kingdon	0.430	NA
Germany	0.575**	NA
Rest of EU	0.259	NA
Bio/Medical/Ag Specialist	0.356**	NA
Education Level	NA	-0.132**
Intercept	5.676**	5.063**
Sample Size	1449	2442
Model Adj. R^2	0.10	0.20

Table 4: Perceived Risks of Spent Nuclear Fuel Management: Modeling Scientists and Mass Publics

Independent Variable	US and EU Scientists	US Public
Political Ideology	-0.273**	0.031
Egalitarian Disposition	0.303**	0.569**
Dose-Response Scale	-0.029**	NA
Age	-0.043**	-0.011**
Gender (Male=1)	-0.593**	-1.452**
USA	0.636**	NA
United Kingdom	0.579*	NA
Germany	0.506*	NA
Rest of EU	-0.009	NA
Bio/Medical/Ag Specialist	0.361**	NA
Education Level	NA	-0.113**
Intercept	7.092**	5.239**
Sample Size	1447	2441
Model Adj. R^2	0.12	0.194

Table 5: Support for Additional Nuclear Reactors: Modeling Scientists and Mass Publics

Independent Variable	US and EU Scientists	US Public
Political Ideology	0.206**	0.130**
Egalitarian Disposition	-0.144**	-0.001
Nuc Benefit: No GHG	-0.063	0.126**
Nuc Benefit: Domestic Supply	0.659**	0.220**
Risk of Reactor Accident	-0.230**	-0.106**
Risk of Spent Nuclear Fuel	-0.233**	-0.133**
Age	0.005	0.010**
Gender (Male=1)	0.425**	0.313**
USA	-0.446**	NA
United Kingdom	-0.492*	NA
Germany	-1.454**	NA
Rest of EU	-0.741**	NA
Bio/Medical/Ag Specialist	-0.210*	NA
Education Level	NA	0.020
Intercept	4.216**	1.946
Sample Size	1634	2383
Model Adj. R^2	0.555	0.437

Discussion

- Scientists use dual modes in arriving at risk perceptions
  - DR beliefs
  - Ideological dispositions, personal demographics
    - National differences are striking
- Mass public perceptions derived in a remarkably similar manner
  - Ideological dispositions vary
    - Political ideology more consistent among scientists
    - Understood risks and benefits very influential
      - The puzzling place of GHGs
    - Demographics play a role for both
      - Scientists tend to mute gender effect, amplify age
- Risk perception heuristics transcend the divide between the public and scientists

Federal Programs to Reimburse the Public for Environmental and Occupational Exposures

Paul L. Ziemer, Ph.D., CHP
Chairman, Advisory Board on Radiation and Worker Health

NCRP Annual Meeting, April 2008

Radiation Compensation Programs

- Veterans Dioxin and Radiation Exposure Compensation Act (1984)
- Radiation-Exposed Veterans Compensation Act of 1988
- Radiation Exposure Compensation Act (1990)
- Energy Employees Occupational Illness Compensation Program Act (2000)

Veterans Dioxin and Radiation Exposure Compensation Act (1984)

(Public Law 98-542)

- Administered by the VA
- Focus on veterans exposed during atmospheric testing or in occupation of Hiroshima or Nagasaki
- Defense Threat Reduction Agency determines participation and dose status
- 1,000,000 potential claimants

Veterans Dioxin and Radiation Exposure Compensation Act (1984)

- Compensation based on verification that
  - the individual was in a specified participant group
  - has medical proof of a qualifying disease
  - has a dose estimate for which probability of causation (PC) shows that the disease was “at least as likely as not” caused by the radiation
- No lump-sum awards; complex award formula

Radiation-Exposed Veterans Compensation Act of 1988
(Public Law 100-321)

- Also administered by VA
- Grew out of dissatisfaction of vets and public on dose reconstruction process and payout rates for the 1984 program
- Claimant needs only show proof of being in specified group and medical proof of eligible disease (i.e., it is a “presumptive” compensation program)
- 400,000 potential claimants
- Complex awards formula

Establishment of Veterans' Advisory Board on Dose Reconstruction

- Established in accordance with Section 601 of Public Law 108-183
- Based on recommendation of the National Research Council report, entitled "Review of the Dose Reconstruction Program of the Defense Threat Reduction Agency"
- Chartered November 24, 2004
- NCRP provides technical and administrative support

Radiation Exposure Compensation Act (1990)

(Public Law 101- 426/510)

- Arose from political pressure by nuclear test site worker advocates, and civilians who lived downwind from atmospheric test locations
- Administered by the Department of Justice, with support from the Defense Threat Reduction Agency
- Compensation is based on proof that claimant falls into a defined participant group and medical proof that the claimant has a qualifying disease ("presumptive" compensation program)

Radiation Exposure Compensation Act (1990)

- 50,000 potential claimants
- Lump sum awards for successful claimants:
  - $75,000 for on-site participants
  - $50,000 for downwinders
  - $100,000 for uranium workers (miners, millers, and ore transporters)

CLAIMS TO DATE SUMMARY OF RECA
(As of 2/14/2008)

Claim Type	Approved	Denied	Pending	Total	% Approved	$ Approved (1000s)
Down-winder	11,815	3,360	410	15,585	77.9	590,720
Onsite	1,175	1,461	72	2,708	44.6	83,896
U Miner	4,749	2,788	177	7,714	63.0	474,174
U Miller	1,067	274	51	1,392	79.6	106,700
Ore Trans-porter	223	29	17	319	73.8	22,300
Total	**19,029**	**7,962**	**727**	**27,718**	**70.5**	**1,277,790**

Energy Employees Occupational Illness Compensation Program Act (EEOICPA)

- Public Law 106-398, enacted by Congress in 2000
- Became effective July 1, 2001
- Is intended to provide timely, uniform, and adequate compensation of covered employees (or survivors) who have suffered from illnesses incurred in the performance of duty for the Dept. of Energy and certain of its contractors and subcontractors

Energy Employees Occupational Illness Compensation Program Act (EEOICPA)

Provides for $150,000 in lump-sum compensation to workers who contracted certain diseases as a result of such exposures while working for the Department of Energy (DOE), its contractors, or subcontractors in the nuclear weapons industry.

Legislative Authority for the Advisory Board

- Part B of the Energy Employees Occupational Illness and Compensation Program Act (EEOICPA) authorizes the President to establish and appoint an Advisory Board on Radiation and Worker Health
- By Executive Order 13179 (December, 2000) the President designated responsibility of the Advisory Board to the Secretary of HHS

Benefits of Having An Independent Advisory Board

- Increased public confidence that the process is open and fair
- Opportunities to introduce alternate scientific and practical issues and views
- Increased transparency that brings increased accountability
- Opportunity for views of various interest groups (stakeholders) to surface and be considered openly

ROLE OF THE ADVISORY BOARD

The Board shall advise the Secretary of HHS

1. On the development of guidelines
   - for providing reasonable estimates of radiation doses received by individuals who seek assistance under the program (*dose reconstructions)*
   - for assessing the likelihood that an individual sustained cancer in the performance of duty at a DOE or weapons facility (*probability of causation*)

ROLE OF THE ADVISORY BOARD
(continued)

The Board shall advise the Secretary of HHS

2. On the scientific validity and quality of dose reconstruction efforts

3. On whether there is a class of DOE employees for whom it is not feasible to estimate dose and whether there is a likelihood such dose may have endangered their health

Composition of the Advisory Board on Radiation and Worker Health

- Consists of no more than 20 members appointed by the President, who also designates the Chair

- Members shall include affected workers and their representatives, and representatives of the scientific and medical communities.

How does NIOSH Carry Out Dose Reconstructions ?

- Individual worker monitoring data: If complete and adequate, individual dosimeter readings and bioassay are given highest priority
  - Default values based on reasonable scientific assumptions used if individual data inadequate
  - Worst case assumptions may be used to provide benefit of a doubt (claimant favorable)

How does NIOSH Carry Out Dose Reconstructions ?

- Workplace area monitoring data: Used if individual monitoring data not available
  - May use monitoring results for groups of workers with comparable activities and relationships
- Process description information: Quantity and composition of radioactive material, chemical form, particle size distribution, containment

The Role of the Site Profile

Site Profiles are documents that describe a specific work site. A Site Profile includes:

- the physical appearance and layout of the work site,
- the work processes used there,
- the types of materials used, potential sources of radiation, and
- other details important at that work site.

Site Profiles may be used to assist NIOSH in the completion of the individual work required for each dose reconstruction.

What are the Components of the Reconstructed Dose?

1. The measured doses
2. Missed dose (resulting from null readings)
3. Missing dose (periods where dosimetry is missing)
4. Occupational medical exposures (i.e. mandatory x-rays as condition of employment)

Use of Probability of Causation

- PC is an estimate of the percentage of cases caused by a health hazard among a group of persons exposed to the hazard
- PC is used in compensation programs as an estimate of the likelihood that the illness of an individual member of the group was caused by exposure to the hazard
- PC = (RadRisk) / (RadRisk +Base Risk) x 100%

What Value from the PC Distribution is Used?

- The NIOSH guidelines, as required by the EEOICPA Law, use the upper 99 percent credibility limit to determine whether the cancer of an employee is as likely as not caused by the radiation exposure.
- This is intended to minimize the possibility of denying compensation to claimants with cancer that may have been caused by ionizing radiation.

Development and Use of Radio-epidemiological Tables

- In 1985, NIH developed a set of radio-epidemiological tables for estimating probability of causation for individuals with cancer who were exposed to ionizing radiation,
- The tables were intended for use by the Department of Veterans Affairs to make compensation decisions for veterans who had cancer.
- The primary source for the tables is cancer deaths among the Japanese A-bomb survivors

Development and Use of Radio-epidemiological Tables

- The tables have been updated and incorporated into an interactive computer program called IREP (Interactive RadioEpidemiological Program).
- The IREP program allows the user to take into account uncertainties in the dose information as well as uncertainties in relating dose to risks.
- Uncertainty is very important in that it can have a large effect on probability of causation estimates.

Status of NIOSH Program

Overall Claim Information (as of 12/31/07)

- 26,108 cases have been referred to NIOSH from DOL for dose reconstruction
- 19,255 (74 %) have been return to DOL
  - Cases submitted with a DR report 17,074
  - Cases currently pulled from DR by DOL 670
  - Cases pulled from DR for SEC 1,511
- 312 Cases have been administratively closed
- 6,541 (25 %) cases remain at NIOSH for dose reconstruction

Summary of Completed Dose Reconstructions
(as of September 27, 2007)

Of the 17,074 dose reconstructions sent back to DOL for final adjudication:

- 5,474 (32 %) cases had a PC $\geq$ 50%
- 11, 600 (68 %) cases had a PC < 50%

EEOICPA NIOSH Case Related Compensation Paid
(As of December 25, 2007)

Note: These are DOL statistics

- $917 Million in compensation
  - $ 748 million on dose reconstructed cases
  - $169 million on added SEC cases

What is the Special Exposure Cohort?

- The SEC was established by the Act and allows eligible claims to be compensated without the completion of a radiation dose reconstruction or determination of the probability of causation.
- To qualify for compensation under the SEC, a covered employee must have at least one of 22 “specified cancers" and worked for a specified period of time at one of the SEC work sites.
- Initially the SEC included the Paducah, Portsmouth, and Oak Ridge gaseous diffusion plants and the Amchitka Island Nuclear Explosion Site.

Adding Additional Classes to the SEC

- In addition to establishing the SEC, Congress allowed for additional classes of employees to be added to the SEC.
- The responsibility for developing a process for adding classes of employees to the SEC was assigned to the Secretary of Health and Human Services (HHS).
- NIOSH/OCAS is responsible for collecting and evaluating petitions for consideration by the Secretary of HHS when determining whether or not to add groups of employees (classes) to the SEC.

Requirements for Adding a Class to the SEC

1. HHS finds that it is not feasible to estimate the radiation doses of a class of employees with sufficient accuracy
2. There is a reasonable likelihood that such radiation doses may have endangered the health of members of the class

What is Sufficient Accuracy?

- Radiation doses can be estimated with sufficient accuracy if NIOSH has established that it has access to sufficient information to estimate the maximum radiation dose, for every type of cancer for which radiation doses are reconstructed, that could have been incurred in plausible circumstances by any member of the class, or
- NIOSH has established that it has access to sufficient information to estimate doses to members of the class more precisely than an estimate of maximum radiation dose.

Adding Additional Classes to the SEC

- NIOSH/OCAS prepares an Evaluation Report on the SEC petition
- The ABRWH is required to review the NIOSH/OCAS Evaluation Report and provide a recommendation to the Secretary of HHS
- The Secretary makes a recommendation to Congress on adding a class to the SEC

Cancers Included in the SEC Rules

- Bone cancer
- Renal cancers
- Leukemia (other than chronic lymphocytic leukemia) provided the onset of the disease was at least two years after first exposure
- Lung cancer
- The following diseases provided onset was at least five years after first exposure:
  - Multiple myeloma
  - Lymphomas (other than Hodgkin's disease)
  - Primary cancer of the bile ducts, brain, breast, colon, esophagus, gall bladder, liver, ovary, pancreas, pharynx, salivary gland, small intestine, stomach, thyroid, urinary bladder

Successful SEC Petitions
(as of December 31, 2007)

- 25 SEC classes have been added since May 2005
  - 16 (59%) through the regular petition process
  - 9 (41%) through process whereby NIOSH identifies inability to do dose reconstruction
- Represents classes of workers from 19 sites
- Represents 1,519 potential claims