

U.S. Low Dose Radiation Research Program

Update – November 2010

ISCORS

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U.S. DEPARTMENT OF
ENERGY

Office
of Science

Office of Biological
and Environmental Research

The Department of Energy

Office of Science (SC)

Biological and Environmental Research (BER)

Biological Systems Sciences Division

The Low Dose Radiation Research Program

DOE's Low Dose Program:

Is unique within the U.S. government in focusing on low dose biological research aimed at informing current and future national radiation risk policy for the public and the workplace (NASA focuses on high LET exposures)

Research with relevance to these DOE/BER missions:

“This research project supports the Department of Energy’s missions in energy production and environmental remediation. Relevance is demonstrated for the BER long term measure to provide sufficient scientific understanding such that DOE sites would be able to incorporate coupled physical, chemical and biological processes into decision making for environmental remediation and long-term stewardship by providing critical research into the biological effects of low dose radiation exposures.”

History– the Program was initiated in 1999

“The lowest dose at which a statistically significant radiation risk has been shown is ~ 100 mSv (10 rem) of x-rays.”

Bridging Radiation Policy and Science

An international meeting of experts, held
at Airlie House Conference Center

1 – 5 December 1999

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 USNRC and EPA, and with recommendations from NCRP, ICRP



-and-



Should we regulate at the upper confidence limit of risk?

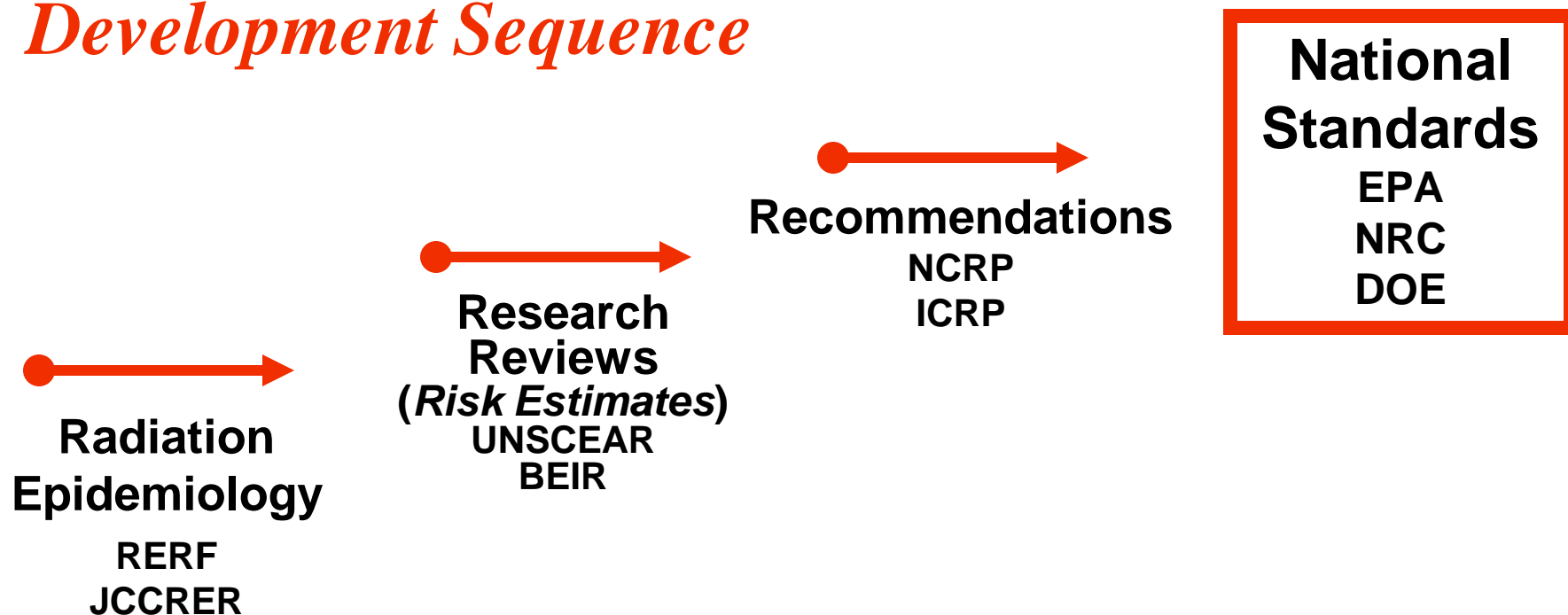
- **This is a policy decision** - (But biasing every risk factor to conservative values is not necessarily good safety policy, nor is it always in the best interest of the public welfare)
- **A better approach is to decrease the uncertainties and shrink the confidence intervals around the central estimate of risk**
- **DOE's Office of Science supports basic research to decrease these uncertainties**



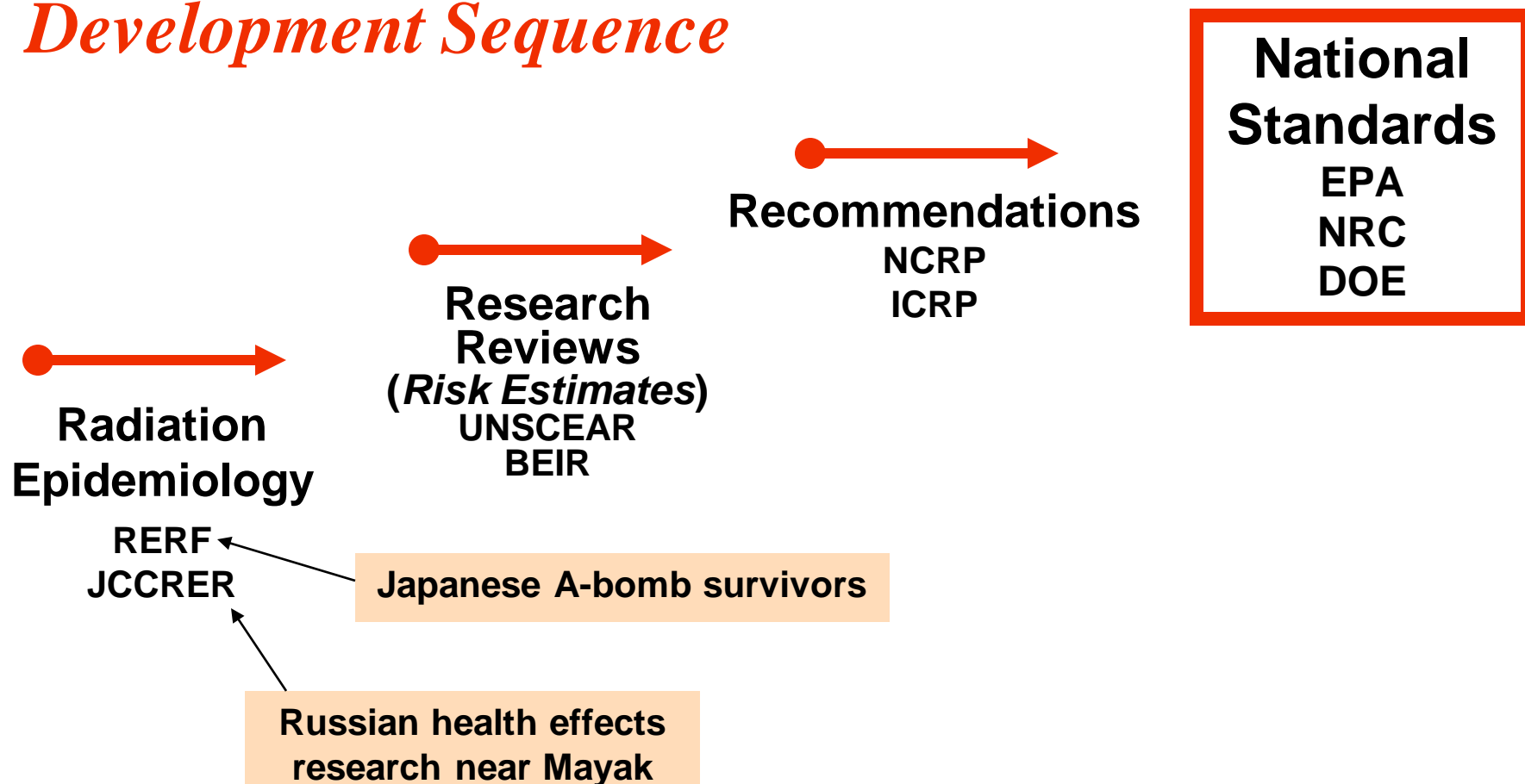
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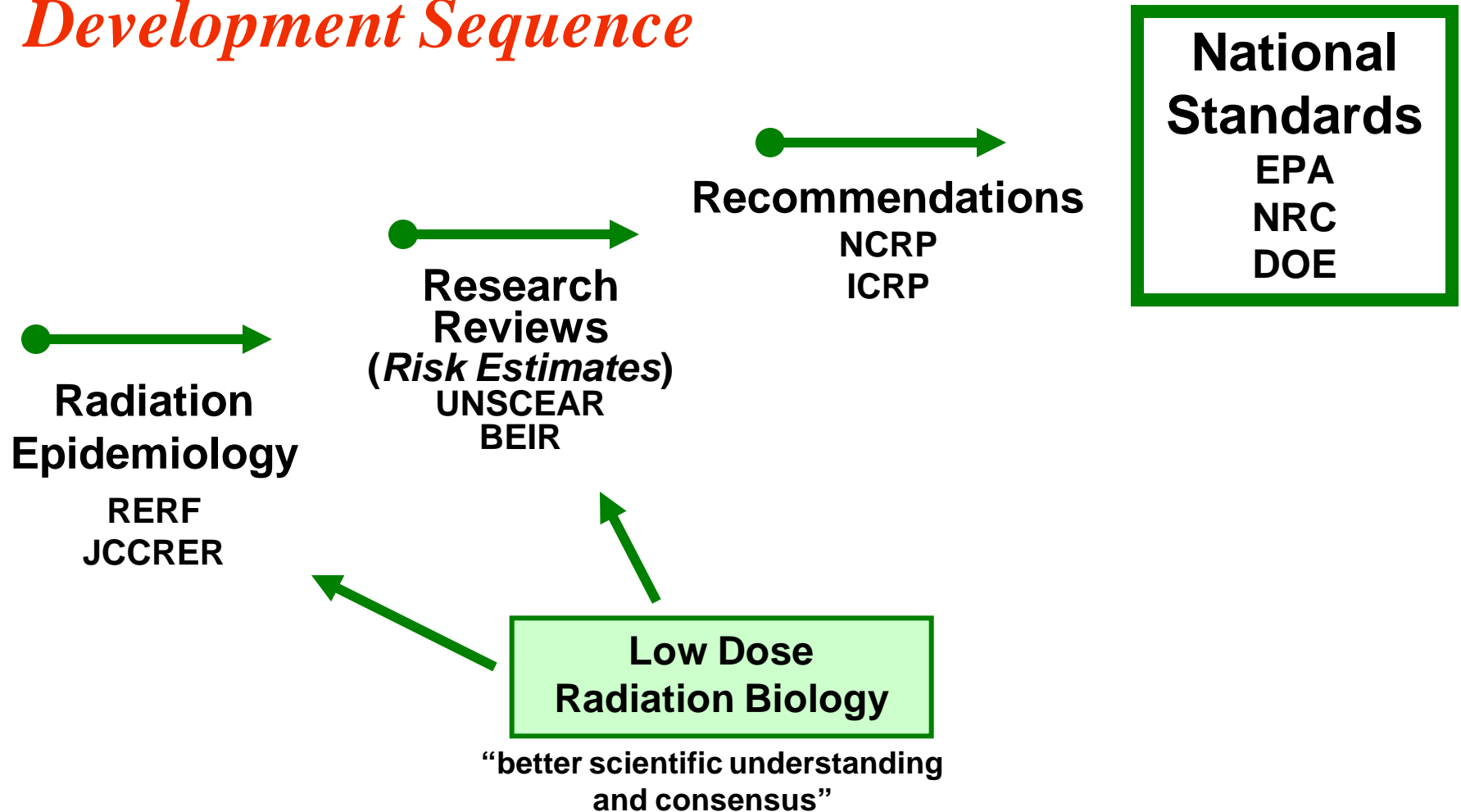
Radiation Protection Standards: Development Sequence



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At the beginning, research needs were identified in five interrelated areas:

1. Low dose radiation vs. endogenous oxidative damage -- the same or different?
2. Understanding biological responses to radiation and endogenous damage.
3. Thresholds for low dose radiation -- fact or fiction?
4. Genetic factors that affect individual susceptibility to low dose radiation.
5. Communication of research results.

The challenge: Do research at 10 rad or less

Ten years later-- 2010

What has currently been determined:

- Biological systems can detect and respond to very low doses of radiation -- in the dose range below where a single alpha particle or electron track traverses the cell
- In the low dose region, cells that do not have energy deposited in them can elicit a biological response to the radiation exposure of their neighboring cells
- This suggests that cell/cell and cell/matrix communication are critical in the total response to radiation
- This communication results in whole tissue responses as compared to individual cell responses

Ten years later-- 2010

What has currently been determined (2):

- At the molecular level, most responses to low doses of radiation are different than the responses seen following high doses of radiation, suggesting different mechanisms of action
- Many cellular responses thought in the past to increase as a linear function of radiation dose, have fine structure in their low dose-response relationships, involving many non-linear responses

Ten years later-- 2010

What has currently been determined (3):

- The mechanistic basis for non-linear responses in the low dose region is being studied:
 - changes in gene and protein expression
 - redirection of many biological pathways
 - alteration of the concentration of molecules that serve to protect against radiation damage
 - induction of apoptosis in transformed cells
 - changes in the ROS status of the cells toward a radio-protective state

Ten years later-- 2010

What has currently been determined (4):

- Exposure in the low dose region decreases the frequency of many biological changes below the spontaneous frequency, suggesting protective mechanisms
- In addition to radiation-induced DNA damage, other processes are induced by radiation that participate in the prevention of the development of cancer
- These different processes change as a function of radiation exposure parameters including dose, dose-rate and dose-distribution.

[The website -- http://www.lowdose.energy.gov](http://www.lowdose.energy.gov)

Ten years later-- 2010

New Biological Paradigms:

- Different processes are induced:
 - By high vs. low dose,
 - By high vs. low dose-rates
 - Dependent on the cell microenvironment, tissue type, health,...
- This raises the question of whether health consequences at very low doses can be extrapolated from high-dose cancer rates

Radiation physics (*energy deposition*) dictates a linear induction of initial effects as a function of dose

Radiation biology shows us that the subsequent biological response is much more complex

The challenge going forward:

Linking cellular and molecular changes induced by radiation to important biological endpoints is the critical challenge for research in the low dose region

Major Focus Areas

- **Systems biology / tissue microenvironment**
 - Regard the tissue / organ / organism as the primary responder
 - Allows rational study of homeostatic mechanisms
 - Will resolve issues and bring about consensus
- **Human inter-individual variability**
 - **Adaptive responses**
 - Mechanisms (protein complexes, signaling, networks, ...)
 - Modes of action (immune function, etc)
 - **Epigenetic regulation**
 - The interface between environment and the genome
 - Cell differentiation / Imprinting / Tissue specificity
 - Molecular and cellular hallmarks of aging
 - **Systems genetics – mouse**
- **Intersection of biology with epidemiology**
 - The human population as the system

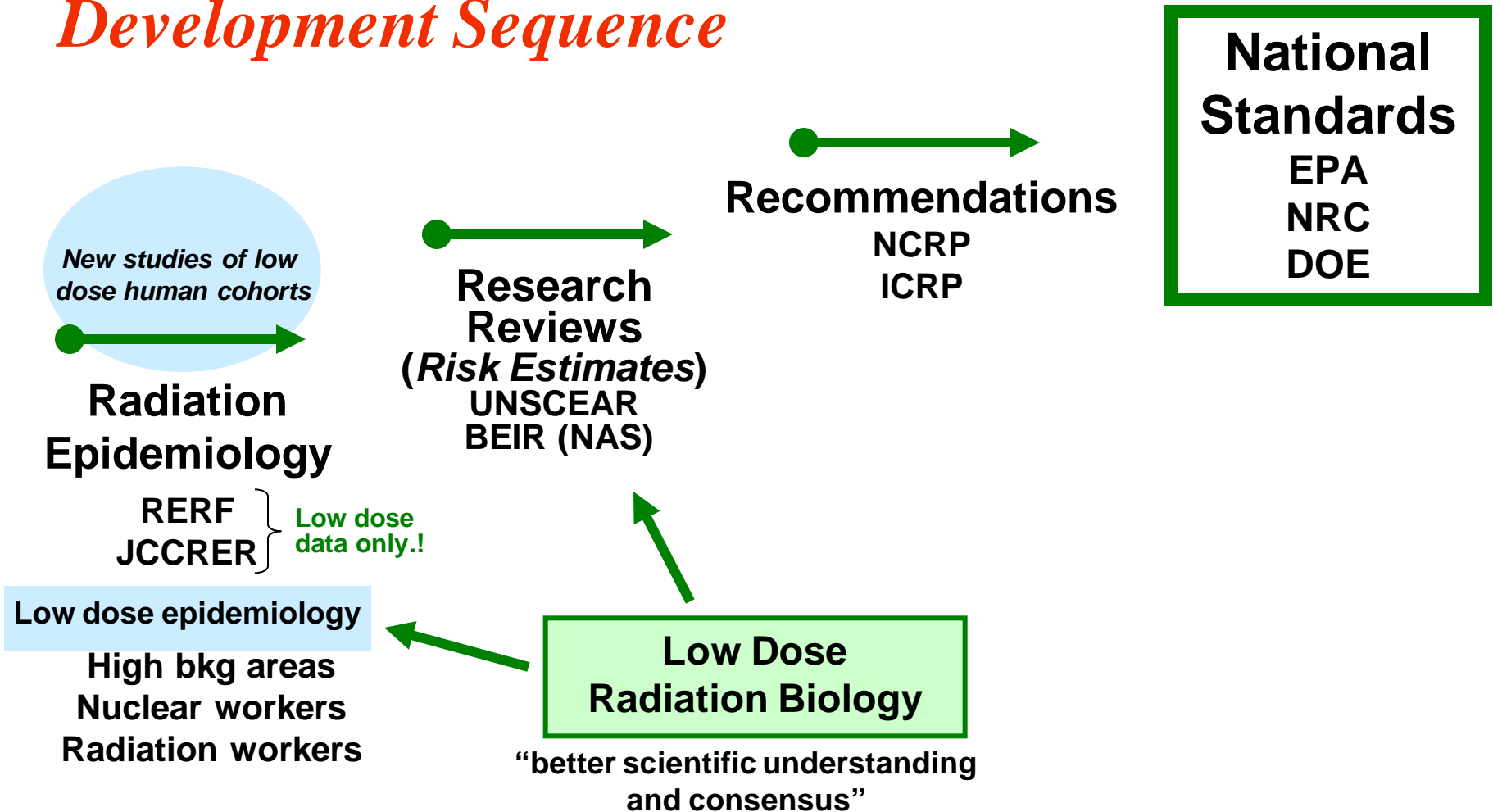
Why Adaptive Responses?

- The adaptive response is initiated by very low dose, and a beneficial effect is seen most clearly in normal healthy organisms
- This response is the strongest argument for not extrapolating from high dose effects to low dose risk
- Therefore, we need to know the mechanisms
 - **Protection by Selective Deletion of Aberrant Cells**
 - Low doses suppress transformation in vitro (Redpath, 2008)
 - Transformed cells are selectively deleted by signals from normal cells and low dose irradiation augments the efficacy of normal cells (Bauer, 1996; Portess et al. 2007)
 - Radiation-induced TGF β mediates surveillance of genomically unstable cells in vitro and in vivo (Maxwell et al, 2008)
 - Low dose radiation suppresses recombination in vivo (Sykes and colleagues, 2008)

Why Epidemiology?

- Major radiation biology paradigm shifts have not yet affected regulatory principles
- Debate on whether the 'new' effects are positive or negative, big or small
- Therefore, there is a need to tie experimental data and modeling to epidemiology
 - **Increased interaction with epidemiologists will be needed**
 - **Big effects seen in humans (age and gender) should be the focus for mechanistic studies**
 - **Clearer understanding of the biological assumptions underlying epidemiological analysis (dose lagging, time lagging, binning by dose, cancer type)**

Radiation Protection Standards: Development Sequence



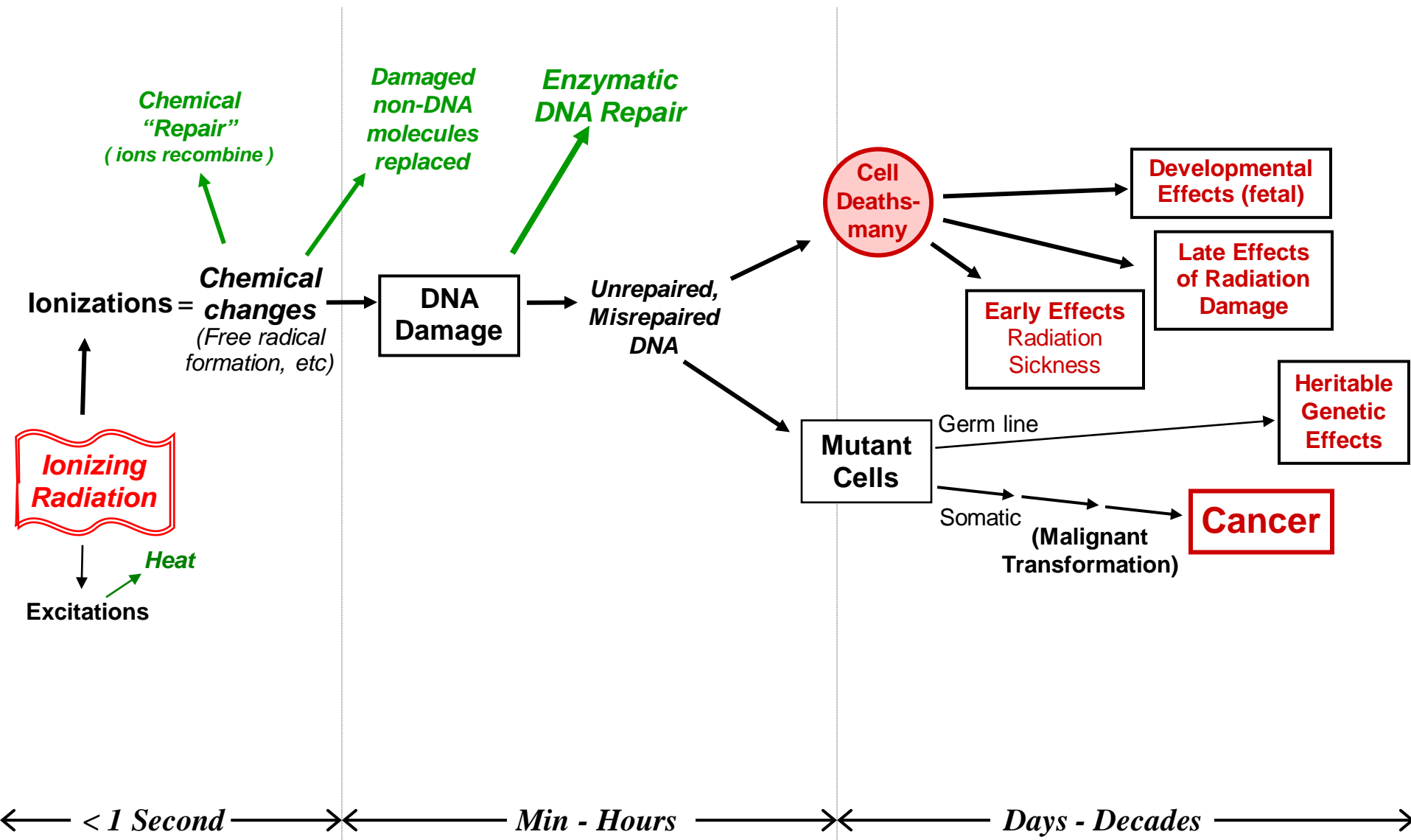
Low Dose Epidemiology

- **Low Dose Epidemiology Workshop**
 - “...There is a pressing need, and a golden opportunity , to obtain more information on the long-term effects of relatively low doses, delivered over protracted periods by pooling and updating the data for the various groups of occupationally exposed U.S. nuclear workers...” (Hall, *et al.*, Rad. Res., 2009)
- **Million U.S. Worker Study**
 - ***“Epidemiological Study of One Million U.S. Workers and Military Veterans Exposed to Ionizing Radiation” (Boice)***
 - Established cohort studies to be updated to the present
 - Dosimetry to be validated
 - Cohorts to be integrated into one large study for analysis
 - Currently funding a “pilot” study...

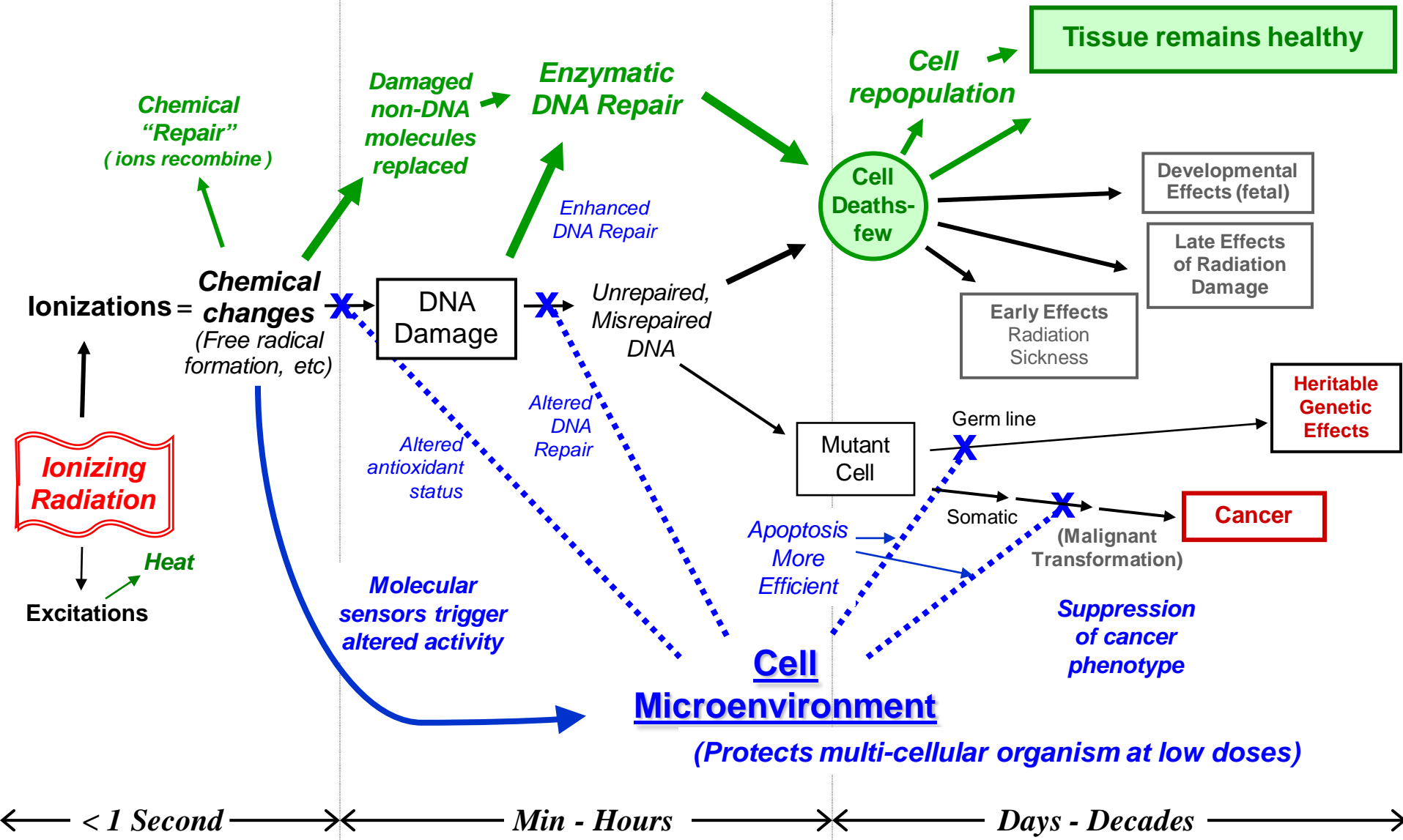
Research funded by the Program has motivated a paradigm shift in radiation biology

- Adaptive Response vs. LNTH
- Bystander Effects vs. Hit Theory
- Genomic Instability vs. Mutation
- Tissue Response vs. Single Cell Action

Classic Paradigm of Radiation Injury (High Dose)



Low Doses show other pathways....



Low Dose Program today:

- **11th year of Program**
- **Currently funded projects:**
 - University-based: 25
 - 3 new University-based 5-year Program Projects
 - National Lab Program Projects: LBNL, ORNL, PNNL
 - 10 projects are joint NASA-DOE funded
 - ~ 500 peer-reviewed publications, ~80 in the last year
- **Next Investigator Workshop -- May 2011**
- Anticipated Funding Opportunity in the next year, for FY2012 funding

DOE Low Dose Program Today:

- **Research focused on –**
 - **Cellular and molecular responses in normal tissues**
 - **After x- or gamma- radiation exposures**
 - **For doses at or near current workplace exposure limits**
- **Research to enable mechanism-based models that incorporate both radiobiology and epidemiology –**
 - **From cellular and molecular actions within tissues**
 - **To the evolution of cancer as a multi-cellular disease**
 - **In human populations**
- **Improved models that will facilitate incorporation of biological paradigms into the regulatory process**

DOE Low Dose Program Today (2):

- **Joint funding of research with NASA's Space Radiation Research Program**
 - Cellular and molecular responses in normal tissues
 - After high LET radiation exposures
 - At fluences approximating the space environment (high single-cell doses but low tissue doses)
 - Ten projects currently supported
- **Re-analysis of Radiobiology Archive data at Northwestern University** The Woloschak laboratory hosts several radiobiology archives containing data and tissues from radiobiology mega (mouse, dog) studies conducted in the second half of the 20th century
- **Communication links with the public, science to inform public debate** –website, Workshop, dose range charts, ...

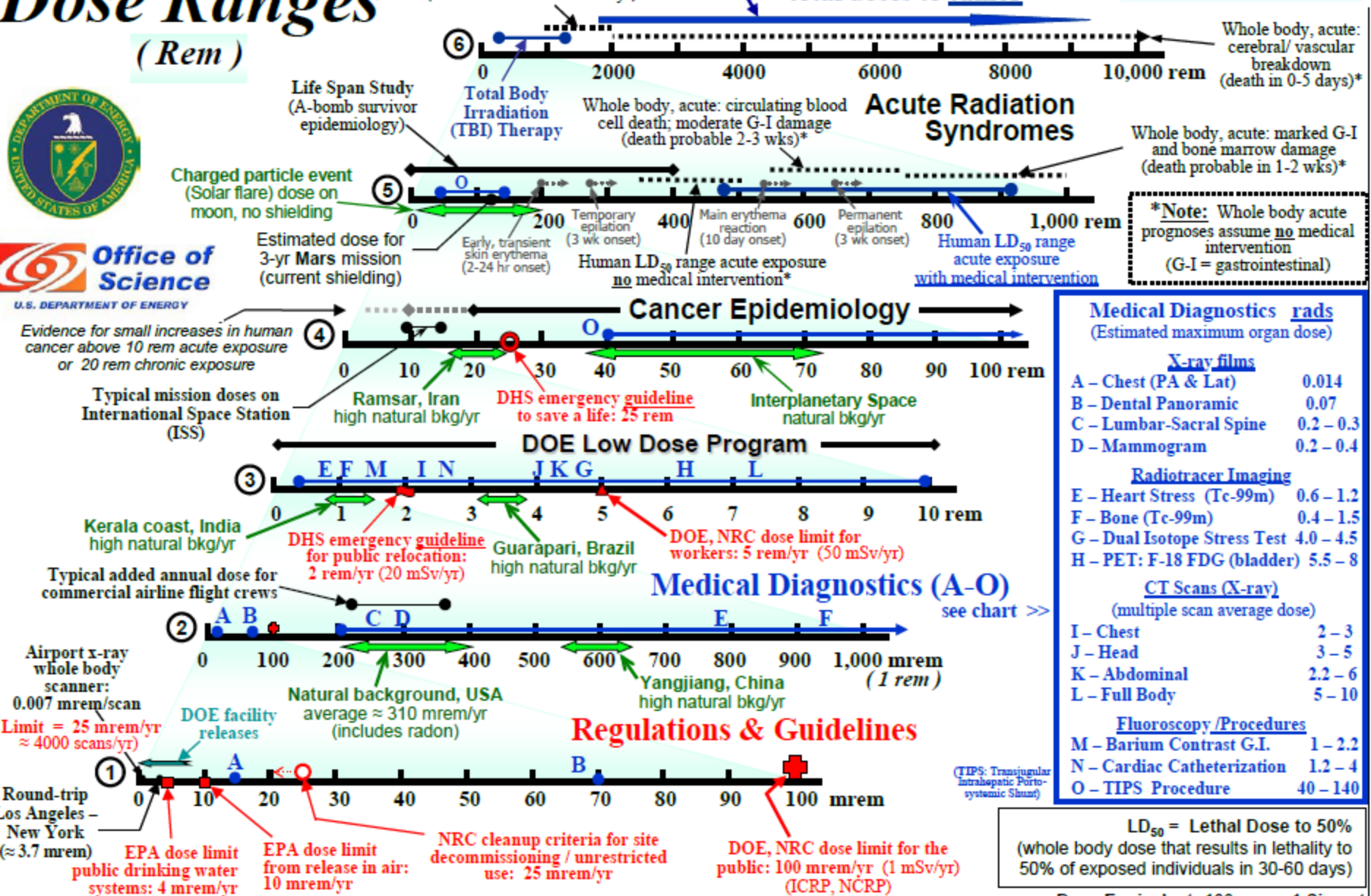
Ionizing Radiation Dose Ranges (Rem)



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

Cancer Radiotherapy
total doses to tumor

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



Medical Diagnostics (Estimated maximum organ dose)

X-ray films

| | |
|-------------------------|-----------|
| A - Chest (PA & Lat) | 0.014 |
| B - Dental Panoramic | 0.07 |
| C - Lumbar-Sacral Spine | 0.2 - 0.3 |
| D - Mammogram | 0.2 - 0.4 |

Radiotracer Imaging

| | |
|------------------------------|-----------|
| E - Heart Stress (Tc-99m) | 0.6 - 1.2 |
| F - Bone (Tc-99m) | 0.4 - 1.5 |
| G - Dual Isotope Stress Test | 4.0 - 4.5 |
| H - PET: F-18 FDG (bladder) | 5.5 - 8 |

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

| | |
|---------------|---------|
| I - Chest | 2 - 3 |
| J - Head | 3 - 5 |
| K - Abdominal | 2.2 - 6 |
| L - Full Body | 5 - 10 |

Fluoroscopy /Procedures

| | |
|-----------------------------|----------|
| M - Barium Contrast G.I. | 1 - 2.2 |
| N - Cardiac Catheterization | 1.2 - 4 |
| O - TIPS Procedure | 40 - 140 |

LD₅₀ = Lethal Dose to 50% (whole body dose that results in lethality to 50% of exposed individuals in 30-60 days)

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

Chart compiled by NF Metting, Office of Science, DOE/BER. "Orders of Magnitude" revised June 2010 1 rem ≈ 1 rad for x- and gamma-rays (\approx stands for "approximately equal to")

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

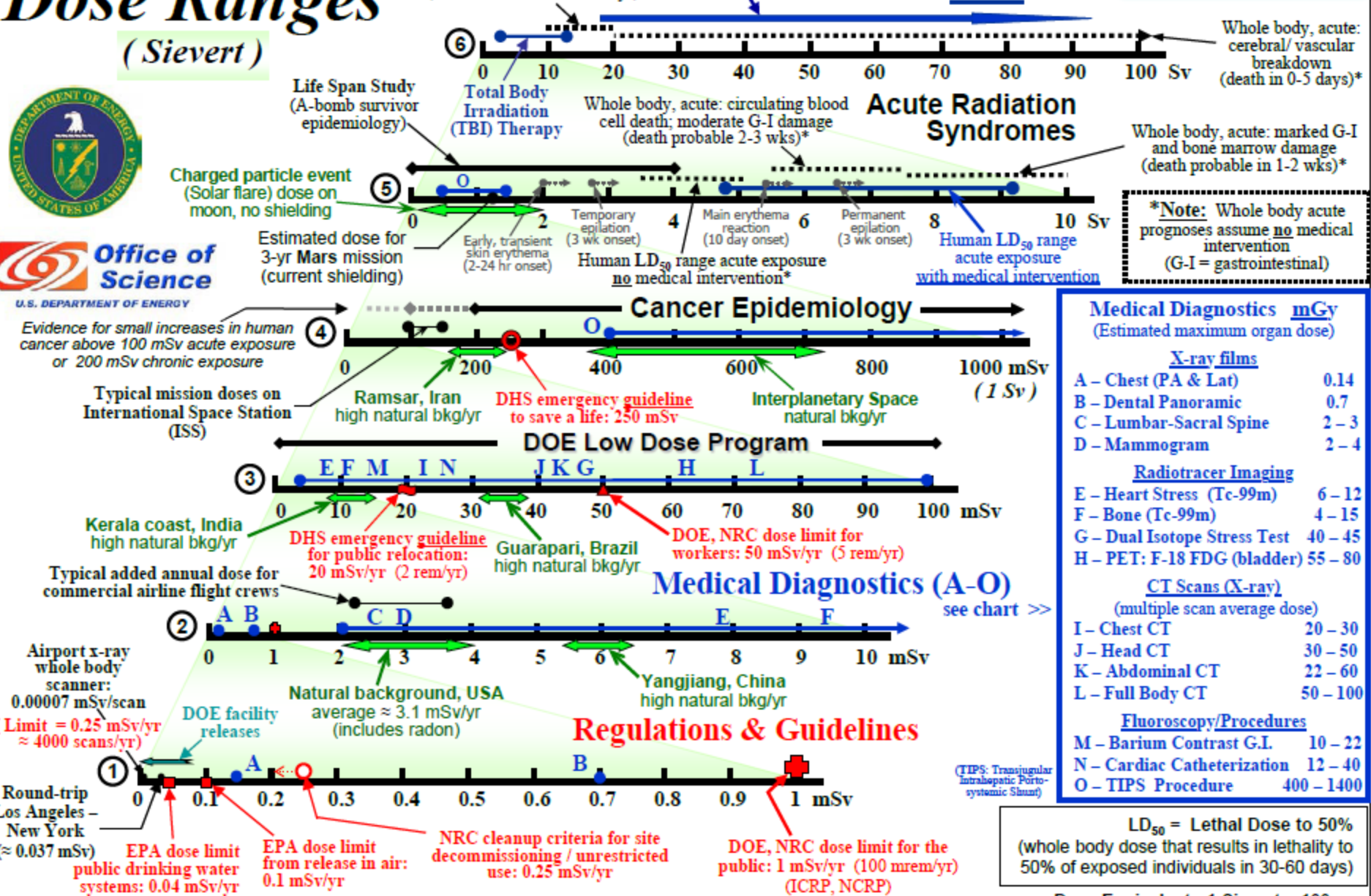
Ionizing Radiation Dose Ranges (Sievert)



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

Cancer Radiotherapy
total doses to tumor

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



LD₅₀ = Lethal Dose to 50%
(whole body dose that results in lethality to 50% of exposed individuals in 30-60 days)

Dose Equivalent: 1 Sievert = 100 rem = (absorbed dose x radiation quality)
Absorbed Dose: 1 Gray = 100 rad
1 Sv \approx 1 Gy for x- and gamma-rays

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