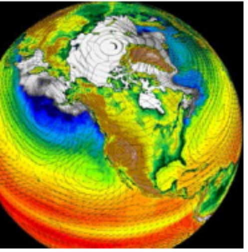
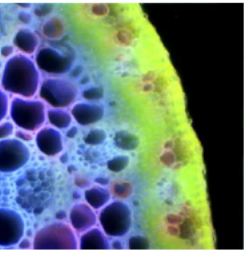
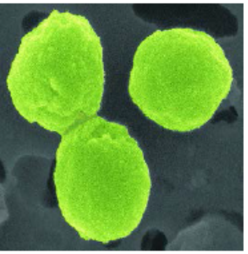


DOE's Low Dose Radiation Research Program

Overview and Update

NF Metting, Sc.D., Program Manager

16 October 2014

DOE's Low Dose Program:

Is the only program within the U.S. government focusing on low dose biological research

- **DOE** focuses on worker and public safety from very low dose x- and gamma-ray exposures encountered in energy production and environmental cleanup
- **DOE** low dose research is aimed at informing current and future national radiation risk policy for the public and the workplace

In contrast:

- **NASA** focuses on astronaut safety from high energy particulate radiation exposures encountered in space flight *(low doses, HZE particles)*
- **NCI** (National Cancer Institute) focuses on patient health from high dose clinically-relevant exposures *(200 rads and higher)*
- **NIOSH** Program Area: Radiation dose reconstruction for workers

DOE's Low Dose Program:

Supports basic research to decrease the uncertainties and shrink the confidence intervals around the central estimate of risk

- DOE uses <u>risk probability</u> as a basis for radiation protection, but it is not used directly to define radiation protection standards
- Regulatory standards are generally defined as a function of dose, or the directly measurable quantities of exposure, activity, or concentration
- Regulatory levels are consistent with US-NRC and EPA, and with recommendations from NCRP, ICRP
- The <u>risk uncertainty</u> rises drastically in the low dose regime (where we regulate)

Regulation at the upper confidence limit of risk is the current policy decision

Who is interested in Low Dose Program research?

- **Department of Energy**
  - Office of Nuclear Energy (nuclear power sustainability)
  - Office of Environment, Health, and Safety Security (AU) (setting implementation standards for DOE workers and public)
  - Office of Environmental Management (clean up levels; high cost)
  - National Nuclear Security Administration (emergency response)
  - General Council (GC-70) NEPA documentation
- **Environmental Protection Agency**
  - Setting of general regulatory standards
- **Nuclear Regulatory Commission**
  - Setting of regulatory standards for nuclear power industry
- **Departments of Labor, Transportation; NASA**
  - Worker safety
- **Department of Homeland Security**
  - Emergency response
- **Department of Defense**
  - Military action, emergency response

- **Citizenry of the U.S.** (fear levels: Fukushima, Chernobyl, TMI, …)

Outline

- **History:** *Research to develop a better scientific basis for understanding exposures and risks to humans*

- **Biology:** old assumptions, new paradigms

- **The Low Dose Program today**

- **Million U.S. Worker Study**

But first -- What is Low Dose?

X- or Gamma- rays:

One photon track/cell ~ 2 mSv = 200 mrem
~ 2 mGy = 0.20 rads

1 MeV γ-ray; $(20\mu m)^3$ cell volume; = 0.14 rads
500 keV x-ray; $(20\mu m)^3$ cell volume; = 0.19 rads

Alpha particles:

One particle track/cell ~ 200 mSv = 20,000 mrem
~ 200 mGy = 20 rads

Background radiation:

~ 15 ion pairs / cm^3 air / sec

Over land mass, approximately 10 to 20 ion pairs per cubic centimeter in air are formed every second.

This ionization rate decreases with altitude to 500 meters, after which it slowly rises with altitude, reaching the ground level rate at 1500 meters.

The Low Dose Program was initiated in 1999 with a workshop:

Bridging Radiation Policy and Science
An international meeting of experts
Airlie House Conference Center
1 – 5 December 1999

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

Other Programs are now supported:

- **MELODI** (**M***ultidisciplinary* **E***uropean* **Lo***w* **D***ose* **I***nitiative*)
- **Japan**
- **Other** (China, Korea, India,…)

The Low Dose Program was initiated :

- **To provide mechanistic data for the development of a scientific basis for radiation standards in the low dose region**
- **Possible in 1999 because of**
  - **Extensive biological advances associated with**
    - sequencing of the genome
    - the development of gene expression arrays
    - the expansion of information on cell-cell and cell matrix communication
  - **Technologies such as single cell irradiators**
    - (The first research program to emphasize whole tissue responses using these advances)

Historic Animal Studies

- Historic mega-mouse and -dog studies were conducted from1970s – ’90s (49,000 mice, 17,000 beagle dogs)
- Historic (and newer) studies have shown
  - A pronounced dose-rate effect for cancer
  - Strong low dose “sparing” effect
  - Data and tissue archives
- Animal studies help determine if cellular and molecular observations influence disease outcome
- Animal data still provide a link between cell and molecular mechanisms and human epidemiological data for risk assessment.

In 1999, five research needs were identified:

- **Understanding biological responses to low dose radiation exposures**
- **Low dose radiation versus endogenous oxidative damage**
- **Thresholds for low dose radiation**
- **Genetic factors affecting individual susceptibility**
- **Communication of research results**

The real challenge: to do research at 10 rads or less

Fourteen years later – 2014

Radiation physics ***(energy deposition)*** *dictates a linear induction of <u>initial</u> events as a function of dose*

Radiation biology *shows us that the <u>subsequent</u> biological response is much more complex*

DNA repair

Cell apoptotic death

Cell/tissue growth and replacement

Immune system surveillance

★ ***Metabolic shift after low (but not high) dose exposure is protective — very new…***

Fourteen years later – 2014

Program Research Results

- Biological systems detect and respond to very low doses of radiation
- Cells not directly exposed can show a biological response to the low dose radiation exposure of neighboring cells
- Cell-cell and cell-matrix communication are critical in the total response to radiation, resulting in whole tissue or organism responses as compared to individual cell responses
- Qualitatively different molecular-level responses result after low doses of radiation vs. high doses of radiation
- Many cellular and tissue-level responses demonstrate non-linear responses with respect to radiation dose
- In addition to radiation-induced DNA damage, other processes are induced by low dose radiation that participate in either increasing or deterring carcinogenesis

Fourteen years later – 2014

Old Assumptions

New Paradigms

Qualitatively similar radiation effects occur at high and low dose exposures → Qualitatively different processes are induced by high vs. low doses/dose-rates

All radiation effects contribute to the process of carcinogenesis → Many radiation effects do not contribute to the process of carcinogenesis

DNA damage is the only mechanism responsible for increasing cancer risk → In addition to DNA damage, cancer risk is highly dependent on the cell microenvironment

These assumptions have been prevalent since World War II

We now know much more about biology and radiobiology

2000-2012 – Evolution of the Program:

- **NASA joint-funded research**
- **Strong appreciation for cell microenvironment**
- **Added mouse systems genetics**
- **Additional low dose / low dose-rate effects:**
  - Proteomic responses
  - Immune system
  - Epigenetic regulation
  - Aging effects – cell/molecular endpoints
- **Mathematical/risk modeling projects** incorporating new radiobiology
- **Funding of integrated program projects**

2000-2012 – Evolving Research 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 scientific consensus
- **Adaptive responses**
  - Small "priming" dose can stimulate protective effects that are seen in response to a subsequent stress
- **Epigenetic regulation**
  - Heritable changes in gene expression or cell phenotype caused by mechanisms other than changes in the DNA sequence
- **Mouse systems genetics**
- **Low dose epidemiology**

The Low Dose Program in 2012 (1)

- **12th year of Program**

- **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)

- **Re-analysis of Radiobiology Tissue Archive data at Northwestern University**
  - The Woloschak laboratory hosts several radiobiology archives containing data and tissues from radiobiology very large (mouse, dog) studies conducted in the second half of the 20th century

- **Research to enable mechanism-based models that incorporate both radiobiology and epidemiology**

The Low Dose Program in 2012 (2)

- **Currently funded projects:**
  - **<u>University-based</u>**
    - Three 5-yr Program Projects in 5th year
    - 21 radiobiology projects in 3rd (last) year or no-cost extensions–
      - 7 of these are joint NASA-DOE projects
    - **Million U.S. Worker Study**
  - **<u>National Lab</u> SFAs: LBNL, PNNL**

- **Communication links with the public; science to inform public debate**
  - Website
  - Workshops
  - Dose ranges charts

- **>700 peer-reviewed publications (*www.lowdose.doe.gov*)**

- **<u>New public awareness:</u>**
  - **Medical diagnostic doses (CT scans)**
  - **Fukushima – evacuation/relocation**

The Low Dose Program Today - 2014

- **Currently funded projects:**
  - **University-based**
    - Two 5-yr Program Projects in no-cost extension
    - 9 radiobiology projects in last-year or no-cost extensions–
      - 3 of these are joint NASA-DOE projects
    - **Million U.S. Worker Study (in nce; supplemented by NASA, NRC, and EPA interagency transfers)**
  - **National Lab SFAs: LBNL, PNNL (less than $ 1M/yr)**

- **Communication links with the public; science to inform public debate**
  - Website (no longer fully funded, but still accessed by public)
  - Workshops (last one in 2010) http://lowdose.energy.gov/workshops.aspx
  - Dose ranges charts (still requested; ~28,000 given out to date)

Program Evolution /Planning

1999

- Endogenous oxidative damage
- DNA damage and repair
- Adaptive responses
- Bystander effects
- Genetic susceptibility
- Genomic instability
- Risk Communication

Current

- Endogenous oxidative damage
- DNA damage and repair
- Adaptive responses
- Bystander effects
- Genetic susceptibility
- Genomic instability
- Epigenetics (2006)
- Aging endpoints/ homeostasis (2008)
- Tissue-emergent carcinogenesis
- Molecular epidemiology
- Risk Communication (website, Dose Ranges chart)

2010+

- Adaptive responses
- Genetic susceptibility
- Epigenetics
- Tissue-emergent carcinogenesis*
- U.S. workers epidemiology
- Risk Communication (website, Dose Ranges chart)

* Includes endogenous oxidative damage, bystander effects, genomic instability, and aging endpoints/homeostasis

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 Worker Study**
  - *"Epidemiological Study of One Million U.S. Workers and Military Veterans Exposed to Ionizing Radiation"*
    - **Established cohort studies will be updated to the present**
    - **Dosimetry will be validated**
    - **Cohorts will be integrated into one large study for analysis**

Q: Is the science community in agreement that these are the proper levels for Protective Actions?

A: The community is largely unaware of these guidelines..!

Protective Action Guides for RDD or IND Incidents
Federal Register—August 2008

Table 1 – Protective Action Guides for RDD and IND Incidents

Phase	Protective action recommendation	Protective action guide
Early	**Sheltering or evacuation of public**	**1- 5 rem (.01-.05 Sv) projected dose**
Intermediate	**Relocation of public**	**2 rem (.02 Sv) projected dose 1st year, subsequent 0.5 rem/yr (.005 Sv/yr)**

[a] Should normally begin at 1 *rem* (0.01 *Sv*); take whichever action (or combination of actions) that results in the lowest exposure for the majority of the population. Sheltering may begin at lower levels if advantageous.
[b] Total Effective Dose Equivalent (TEDE)—the sum of the effective dose equivalent from external radiation exposure and the committed effective dose equivalent from inhaled radioactive material.
[c] Provides thyroid protection from radioactive iodine only.
[d] For other information on other radiological prophylactics and medical countermeasures, refer to *http://www.fda.gov/cder/drugprepare/default.htm*, *http:/www.bt.cdc.gov/radiation*, or *http://www.orau.gov/reacts*.
[e] Committed Dose Equivalent (CDE). FDA understands that a KI administration program that sets different projected thyroid radioactive dose thresholds for treatment of different population groups may be logistically impractical to implement during a radiological emergency. If emergency planners reach this conclusion, FDA recommends that KI be administered to both children and adults at the lowest intervention threshold (*i.e.*, >5 *rem* (0.05 *Sv*) projected internal thyroid dose in children) (FDA 2001).

Protective Action Guides for RDD or IND Incidents Federal Register—August 2008

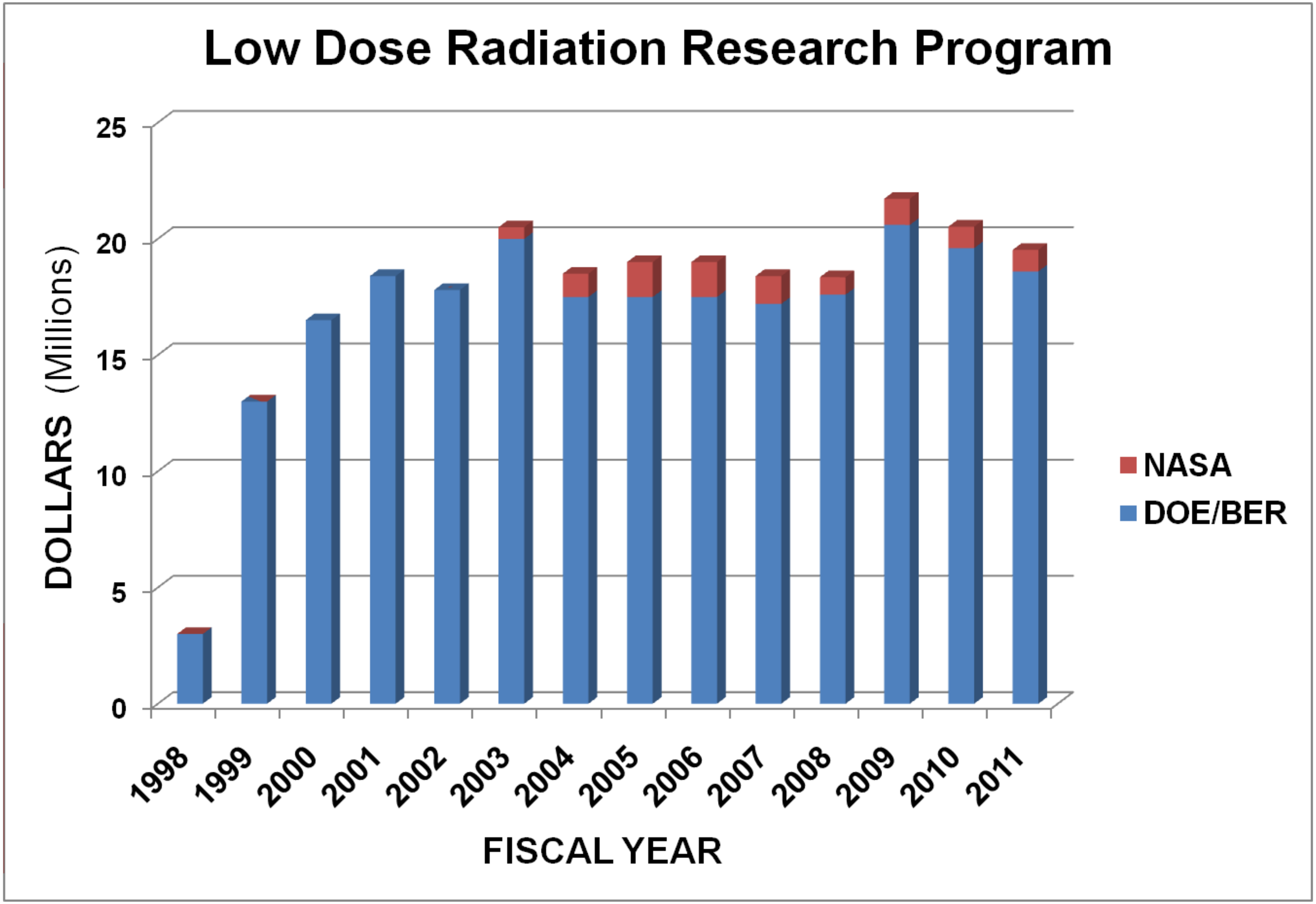
Federal Register / Vol. 73, No. 149 / Friday, August 1, 2008 / Notices **45035**

TABLE 1—PROTECTIVE ACTION GUIDES FOR RDD AND IND INCIDENTS

Phase	Protective action recommendation	Protective action guide
Early	Sheltering-in-place or evacuation of the public[a].	1 to 5 *rem* (0.01–0.05 *Sv*) projected dose.[b]
	Administration of prophylactic drugs—potassium iodide[c,e] Administration of other prophylactic or decorporation agents[d].	5 *rem* (0.05 *Sv*) projected dose to child thyroid.[c,e]
Intermediate	Relocation of the public	2 *rem* (0.02 *Sv*) projected dose first year. Subsequent years, 0.5 *rem*/y (0.005 *Sv*/y) projected dose.[b]
	Food interdiction	0.5 *rem* (0.005 *Sv*) projected dose, or 5 *rem* (0.05 *Sv*) to any individual organ or tissue in the first year, whichever is limiting.
	Drinking water interdiction	0.5 *rem* (0.005 *Sv*) projected dose in the first year.

[a] Should normally begin at 1 *rem* (0.01 *Sv*); take whichever action (or combination of actions) that results in the lowest exposure for the majority of the population. Sheltering may begin at lower levels if advantageous.
[b] Total Effective Dose Equivalent (TEDE)—the sum of the effective dose equivalent from external radiation exposure and the committed effective dose equivalent from inhaled radioactive material.
[c] Provides thyroid protection from radioactive iodine only.
[d] For other information on other radiological prophylactics and medical countermeasures, refer to *http://www.fda.gov/cder/drugprepare/default.htm*, *http:/www.bt.cdc.gov/radiation*, or *http://www.orau.gov/reacts*.
[e] Committed Dose Equivalent (CDE). FDA understands that a KI administration program that sets different projected thyroid radioactive dose thresholds for treatment of different population groups may be logistically impractical to implement during a radiological emergency. If emergency planners reach this conclusion, FDA recommends that KI be administered to both children and adults at the lowest intervention threshold (*i.e.*, >5 *rem* (0.05 *Sv*) projected internal thyroid dose in children) (FDA 2001).

PAG= Protective Action Guides


Low Dose Radiation Research Program
DOLLARS (Millions)
25
20
15
10
5
0
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
FISCAL YEAR
NASA
DOE/BER