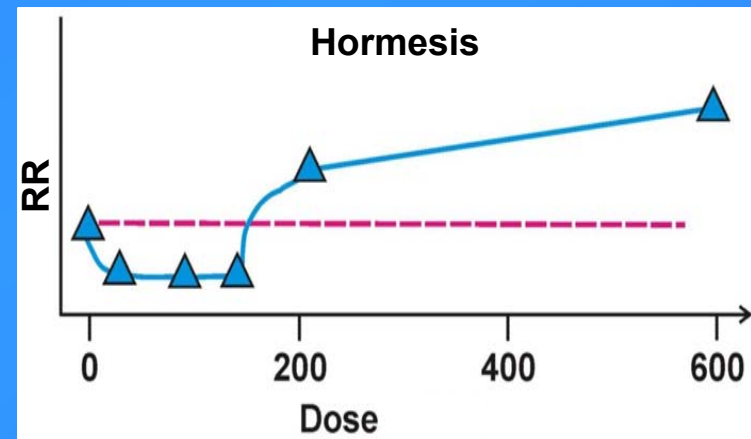
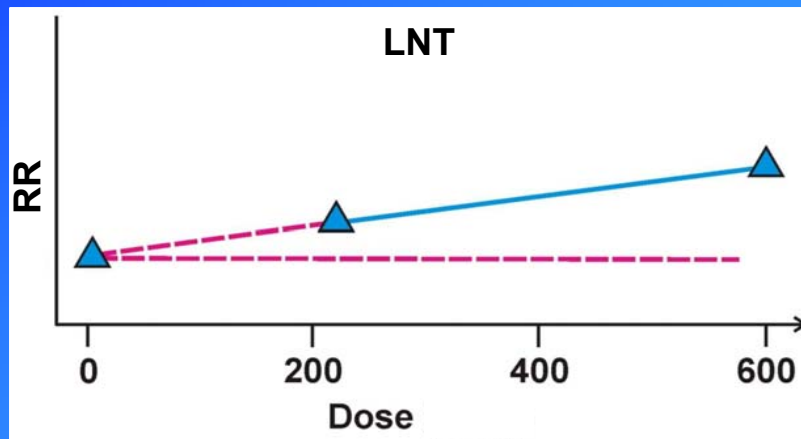


# The LNT Hypothesis vs. Radiation Hormesis: Implications for Managing Radiological Terrorism Events



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**Seminar, NIH/NIAID, Bethesda, MD**

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**<http://www.radiation-scott.org>**

# Contents

- **Background information on residual radiation exposure.**
- **BEIR VII vs. French Academies on LNT and radiation hormesis.**
- **Biological basis for radiation hormesis (NEOTRANS<sub>3</sub> model).**
- **New hormetic relative risk (HRR) model.**
- **Radiological terrorism exposure scenarios and protecting from stochastic biological effects.**
- **Different implications of LNT and radiation hormesis for managing radiological terrorism events.**
- **Need for new multiagency hormesis research program.**

## **Residual Radiation Exposure**

- **Radiation exposure associated with residual radioactivity (e.g., after terrorists detonate a dirty bomb).**
- **Residual radiation exposure includes radiation exposure after application of radioprotector drugs (e.g., chelating agents) or bronchopulmonary lavage.**

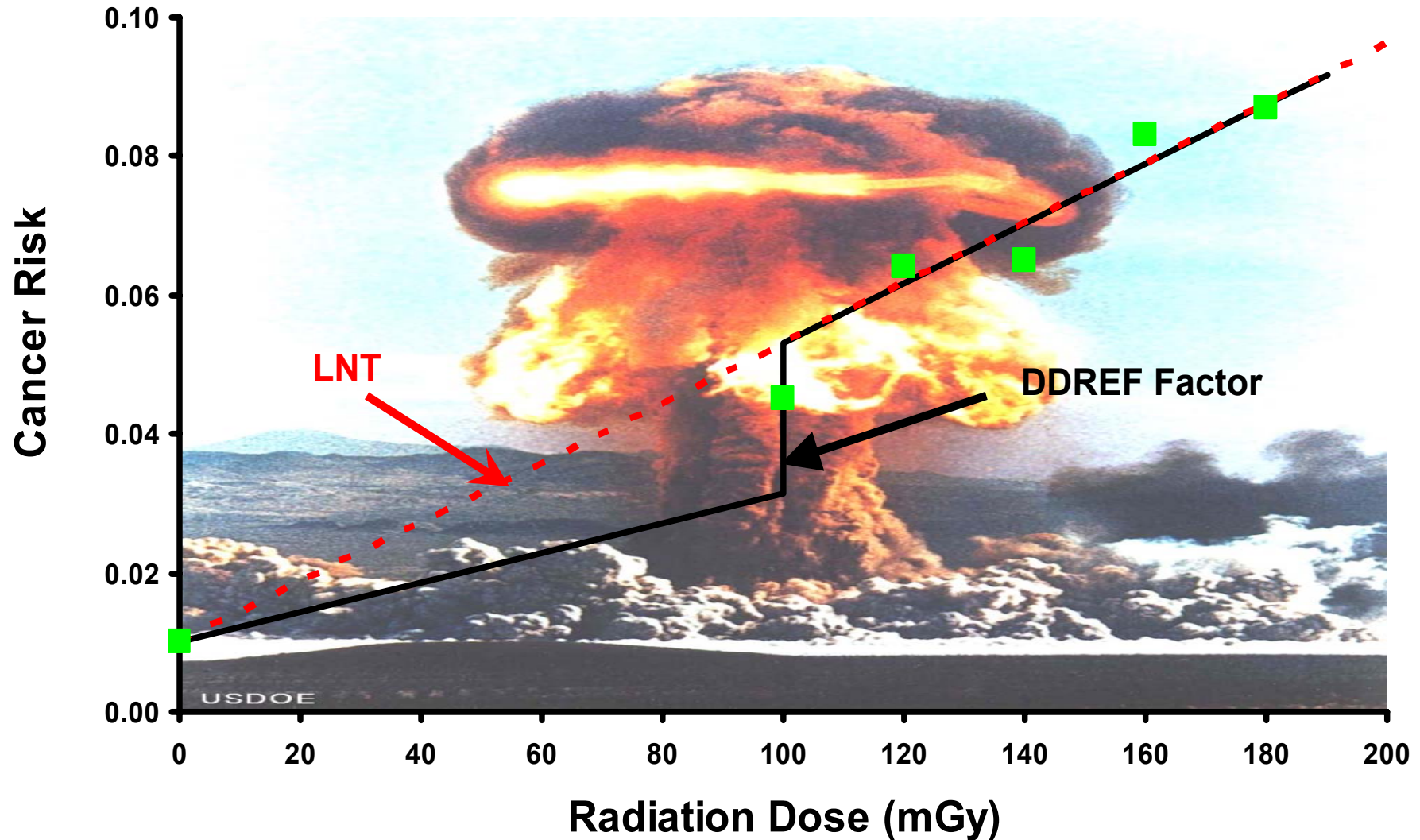
# Biological Effects from Residual Radiation Exposure

- After inhalation or ingestion of radionuclides, **serious biological effects occur only after a time delay** that depends on absorbed-dose-rate and absorbed-dose histories.
- **Many opportunities should exist for implementing radiation countermeasures.**
- Low doses and dose rates can cause **stochastic effects** such as cancer.
- High doses and dose rates can cause **deterministic** and stochastic effects.
- **This presentation focuses on stochastic effects.**

# LNT Approach to Low Dose Cancer Risk Assessment

- **LNT hypothesis**: cancer risk increases as a linear, no-threshold (LNT) function of dose.
- Applies to both single and combined radiation exposures (via use of dose weighting factors).
- Hypothesis has remained **controversial for years**.

# BEIR VII Low-Dose, Low-Dose-Rate Extrapolation



# Radiation Hormesis

- **Hormesis**: low dose stimulation and high dose inhibition (**Calabrese, 2003**).
- **Radiation hormesis**: low doses of radiation protect, high doses harm.

*Calabrese EJ. Annu. Rev. Pharmacol. Toxicol 43:175-197, 2003.*

# BEIR VII vs. French Academies on LNT and Radiation Hormesis

## BEIR VII

## French Academies

<b>Selectively-chosen A-bomb survivor cancer data was consistent with LNT</b>	<b>LNT may not apply to low-LET doses &lt; 100 mGy</b>
<b>Even natural background low-LET radiation harms</b>	<b>No evidence of harm from natural background radiation; may be beneficial</b>
<b>Radiation hormesis dismissed</b>	<b>Radiation hormesis not dismissed</b>
<b>Looked at basic research results and ignored</b>	<b>Considered implications of basic research results</b>



# **Incorrect Implications of BEIR VII**

## **Use of LNT**

- **Any amount of radiation (e.g., from a single CT scan or chest X-ray) is harmful.**
- **Natural and man-made background radiation increases cancer risk.**
- **A gamma-ray dose  $< 1$  mGy to first responders after a radiological terrorism event increases cancer risk.**
- **A protracted gamma-ray dose  $< 100$  mGy to the public over a lifetime after a radiological terrorism event increases cancer risk.**
- **Any residual radiation exposure in a government building after a terrorism event will increase cancer risk to inhabitants.**

# Low-Dose and Low-Dose Rate, Low-LET Radiation Protect Us (Hormesis):

- **Suppresses occurrence of allergic, endocrine, metabolic disorders and pneumonia (data presented later).**
- **Protects against mutation induction (Pam Sykes' group).**
- **Protects against neoplastic transformation (Les Redpath's group).**
- **Protects against cancer occurrence (epidemiological and animal data).**
- **Extends tumor latent period (Ron Mitchel's group).**

# Protective Biological Processes Are Induced By Radiation

- **Normal DNA repair/apoptosis competition** (presumed *p53*-dependent).
- **Auxiliary apoptosis** (presumed *p53*-independent).
- **Immune system stimulation.**

*Activation thresholds for such processes vary for different individuals and are therefore stochastic.*

# Bystander Effects: Deleterious and Protective

- **Deleterious bystander effect:** bystander un-hit cell damaged.
- **Protective bystander effect:** bystander un-hit aberrant cell selectively removed via apoptosis.

# NEOTRANS<sub>3</sub> Model for Low-Dose Radiation-Induced Stochastic Effects

- Includes protective bystander effects.
- Applies to low doses and dose rates.
- Models mutation or neoplastic transformation frequency.
- Relative risk equations for transformation adapted for cancer induction (allows for immune-system stimulation).

*Scott BR. Mut. Res. 568:129-143, 2004.*

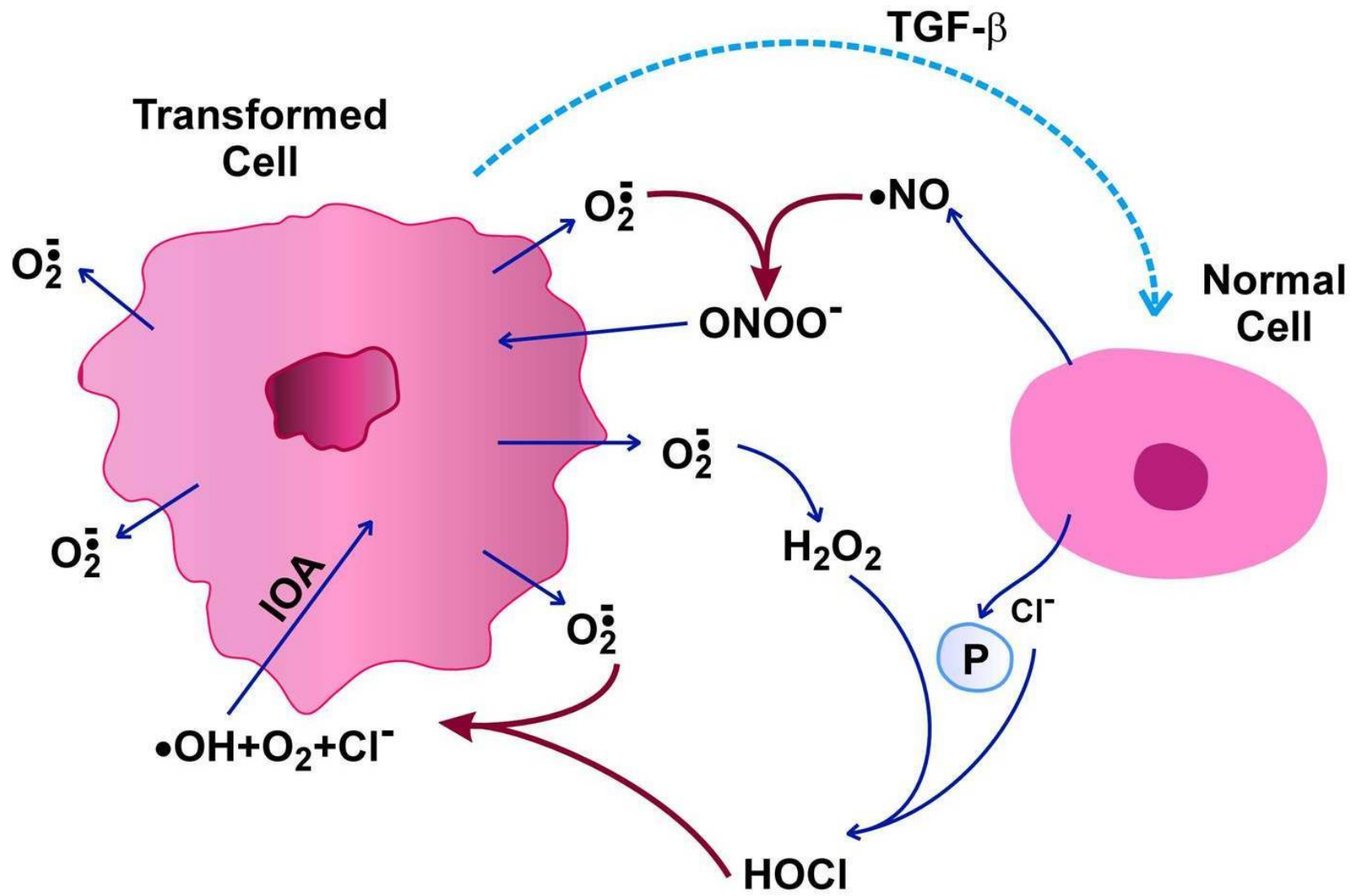
*Scott BR. Nonlinearity (in press), 2006a,b.*

# Protective Processes Associated with NEOTRANS<sub>3</sub> Model

- **p53-dependent**, high-fidelity DNA repair/apoptosis competition.
- **p53-independent** (Hipp and Bauer, 1997), protective apoptosis mediated (PAM) process.
- **Stochastic thresholds (StoThresh)** activate these protective processes.
- Higher StoThresh also inhibits PAM process.

*Hipp ML and Bauer G. Oncogene 17(7):791-797, 1997.*

# Intercellular Communications During the PAM Process



**IOA: Induction of Apoptosis**

**P: Peroxidase**

## The PAM Process

- Eliminates cells transformed by radiation, chemicals, oncogenic retroviruses, herpes simplex virus, and viral oncogenes such as *ras* and *src* (Scott *et al.*, 2004).
- Recognizes a variety of DNA damage and may also remove mutant and other aberrant cells (e.g. cells with virally altered DNA).
- Does not require *p53* (Hipp and Bauer, 1997).
- Likely induced by different stressors that appears to include amifostine.

Scott BR *et al.*, *Nonlinearity* 2(3):185-211, 2004.

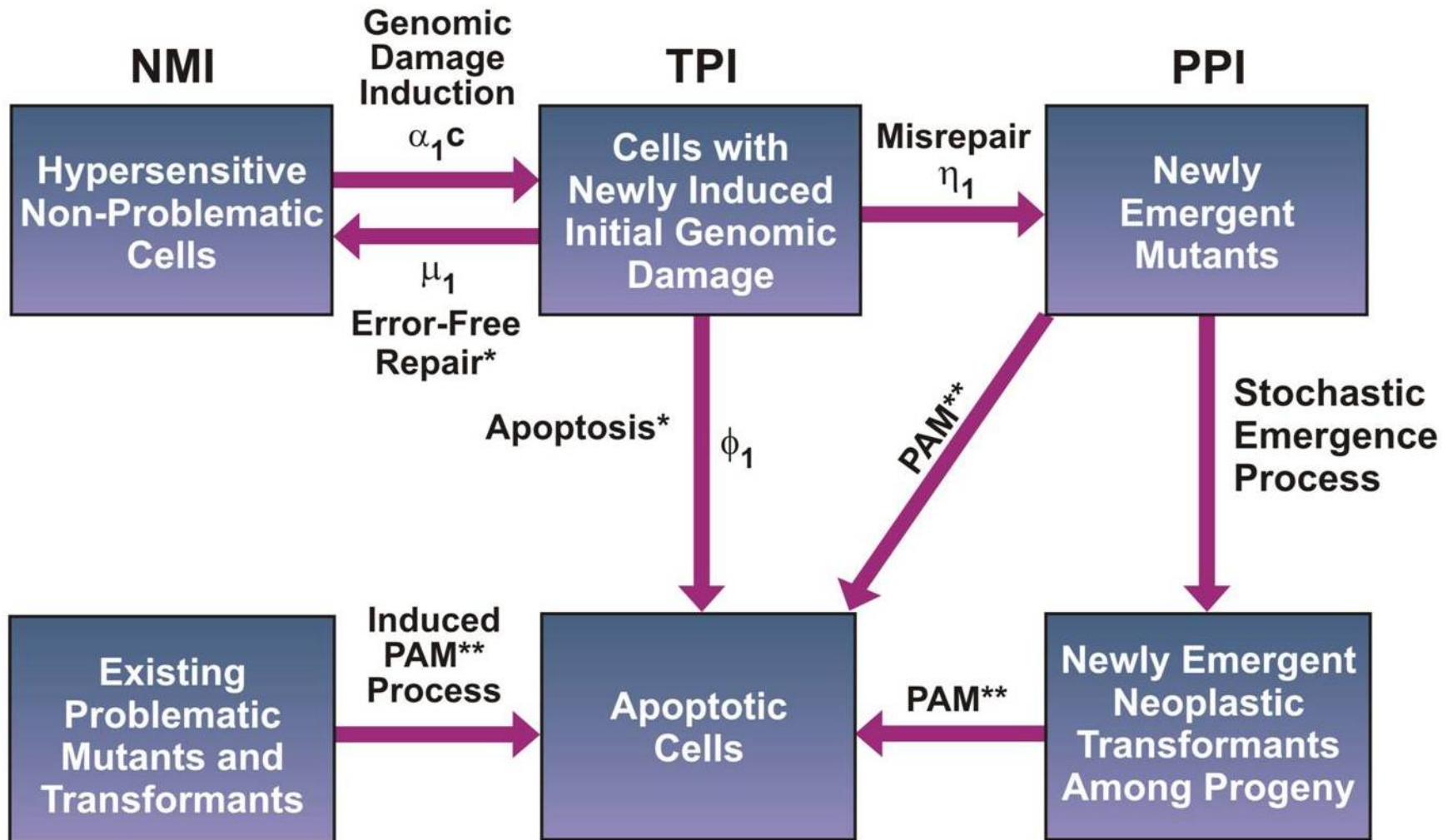
Hipp ML and Bauer G., *Oncogene* 17(7):791-797, 1997.



# Experimental Studies of Biological Basis for the PAM Process

- *Jürgensmeier JM et al. Cancer Res 54(2):393-398, 1994.*
- *Hipp ML and Bauer G. Oncogene 17(7):791-797, 1997.*
- *Bauer G. Anticancer Res. 20(6B):4115-4139, 2000.*
- *Engelmann I and Bauer G. Anticancer Res 20(4)2297-2306, 2000.*
- *Schwieger A et al. Carcinogenesis 22(9):1385-1392, 2001.*
- *Haberstroh K et al. Int. J. Oncol. 21:145-151, 2002.*

# NEOTRANS<sub>3</sub> Model



\*p53-Dependent  
 \*\*p53-Independent

# StoThresh Associated with NEOTRANS<sub>3</sub> Model

- $D_{\text{PAM}}$ , activates PAM as well as high-efficiency DNA repair/apoptosis.
- $D_{\text{off}}$ , inactivates PAM but not high-efficiency DNA repair/apoptosis.
- $D_{\text{off}} \gg D_{\text{PAM}}$ .
- Each of you has a different StoThresh.

*Scott BR. Nonlinearity (in press), 2006b.*

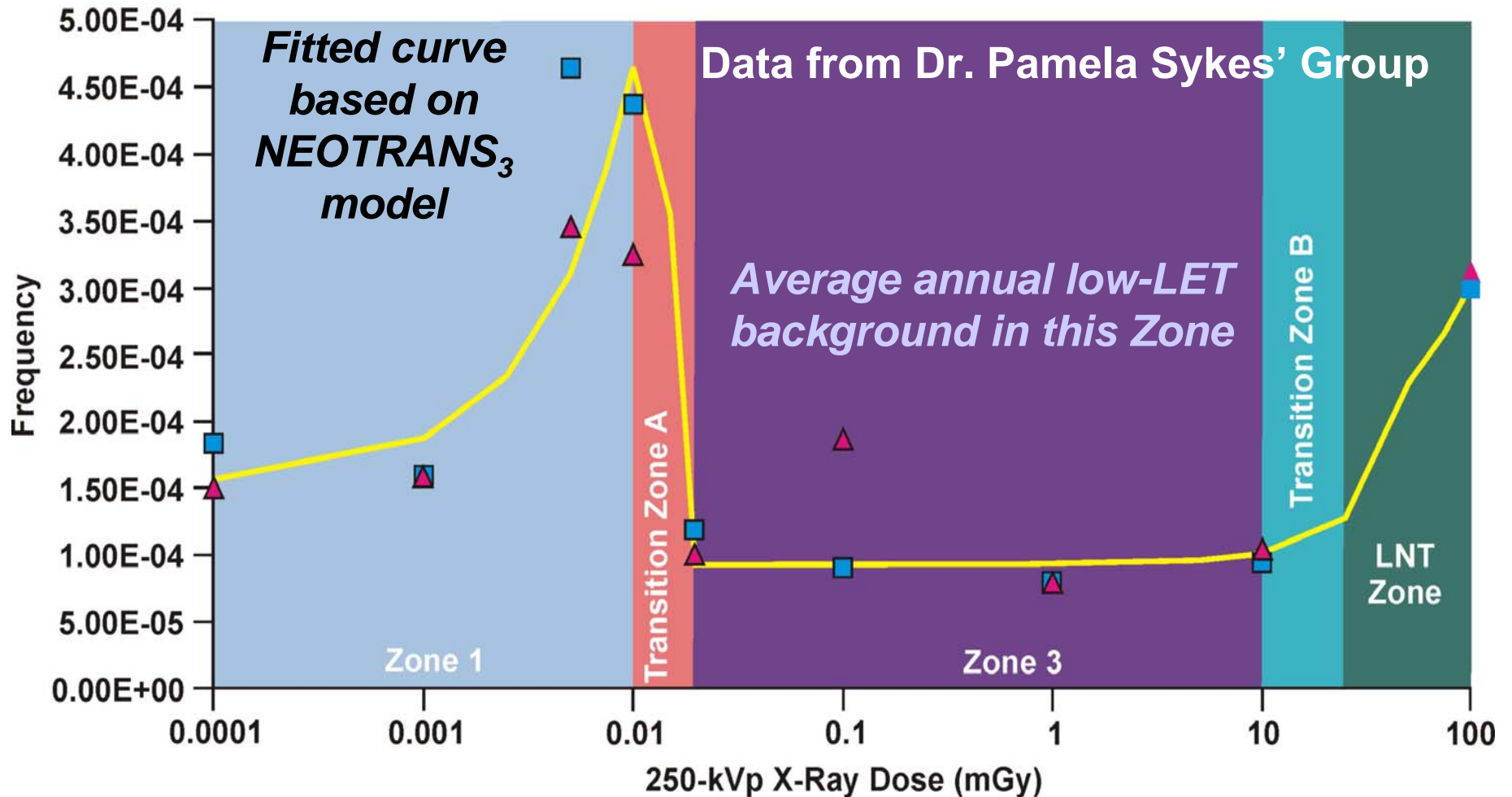
# Markov Chain Monte Carlo Implementation of NEOTRANS<sub>3</sub>

- Number of chains = 2.
- **WinBUGS software used.**
- **Uniform prior distributions assigned for model parameters.**
- **Relative statistical weights applied, based on reciprocal standard deviations for response frequency (mutations, transformation).**

# Dose Zones Considered

- **Zone 1 (ultra low doses):** Below minimal threshold for activating protective processes.
- **Zone 2 (very low doses):** “**Transition Zone A**” containing  $D_{PAM}$ .
- **Zone 3 (low doses):** Zone of maximal protection.
- **Zone 4 (moderate doses):** “**Transition Zone B**” containing  $D_{off}$ .
- **Zone 5 (higher doses):** “**LNT Zone**”, PAM process inhibited, immune system may be suppressed.

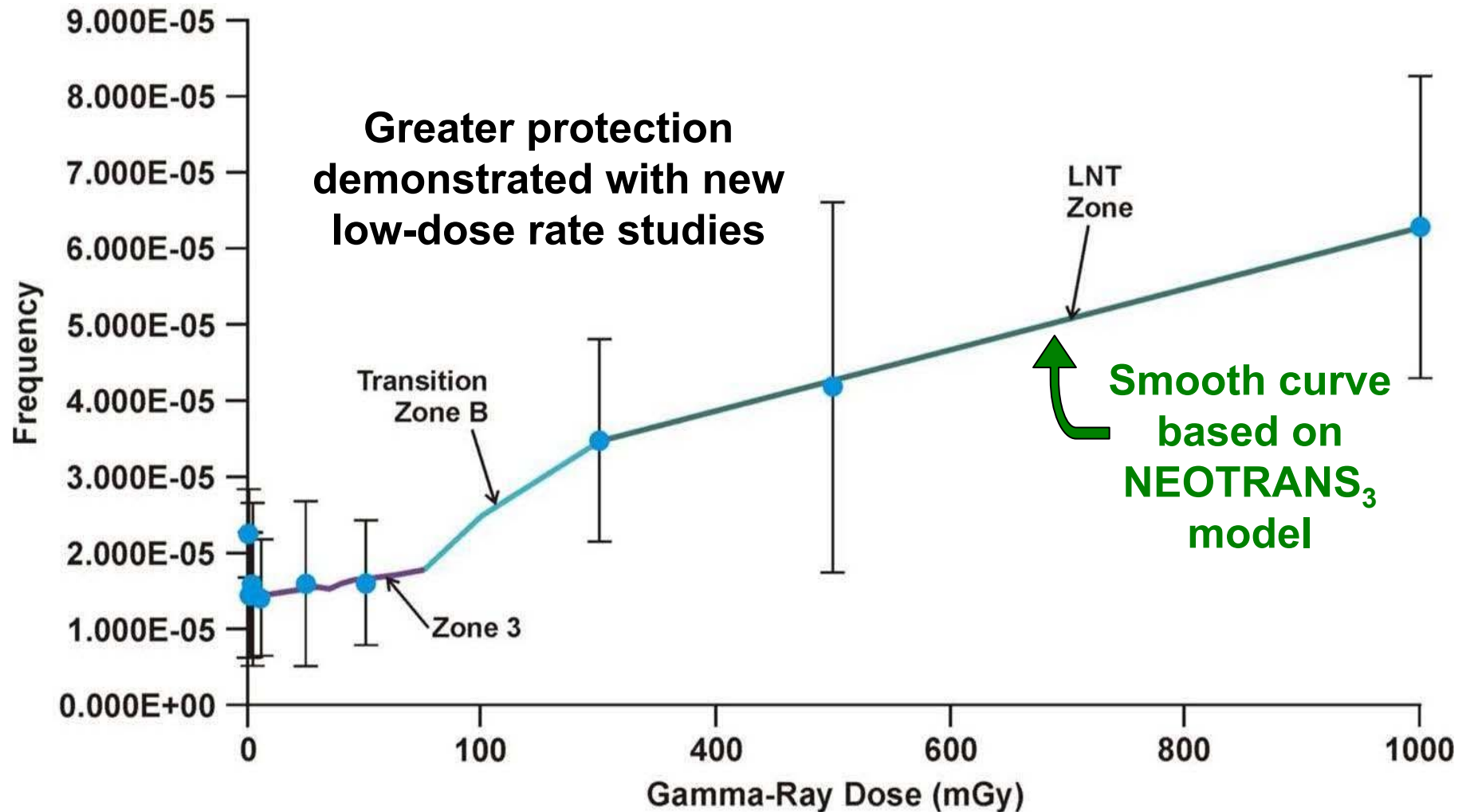
# Inversion Mutation Frequency in pKZ1 Mice: Spleen data from Hooker *et al.* (2004)



5785-2a

*Hooker AM. et al. Radiat. Res. 162(4):447-452, 2004.*  
*Scott BR. et al. Int. J. Low Radiat. (accepted), 2006.*

# Transformation Frequency *in vitro*: HeLa x Skin Fibroblast Human Hybrid Cells



*Redpath L. et al. Radiat. Res. 156:700-707, 2001.*

# **Relative Risk Modeling to Account for Hormetic Effects**



***Les Redpath's Observation***  
***RR(Transformation)  $\cong$  RR(Cancer)***

**Relative risk (RR) equations for neoplastic transformation adapted to cancer induction.**

***Redpath LJ. et al. Radiat. Res. 156:700-707, 2001.***

***Scott BR. Nonlinearity (in press), 2006a,b.***

# Hormetic Relative Risk (HRR) Model for Cancer Induction

Low-LET irradiation:

$$RR_{HRR} = 1, \text{ Dose} = 0$$

$$RR_{HRR} = (1 - PROFAC)RR_{LNT}, \text{ otherwise}$$

$RR_{HRR} \cong (1 - PROFAC)$ , at low doses and  
dose rates (*dose independent zone*)

$RR_{LNT}$  is relative risk based on LNT.

*Dose-independent zone increases importance  
of highly-criticized ecological studies!*

# **PROFAC**

- For cancer induction, the **PROFAC** gives the proportion of cancers prevented due to radiation hormesis that would otherwise have occurred.
- Ranges from 0 to 1.
- The product **100\*PROFAC** gives the expected percentage of lives saved (cancer deaths avoided) due to radiation hormesis among the irradiated population.

*Scott BR, Nonlinearity (in press), 2006a,b.*

# HRR Model: $\alpha + \gamma$ Irradiation, Low Doses

$$RR_{HRR} = 1, D = 0,$$

$$RR_{HRR} \cong (1-PROFAC)[1 + F(B)KD], D > 0$$

$F(B) = (1-B)/B$ , for baseline incidence  $B$ .

$PROFAC = 0$ , for alpha radiation alone.

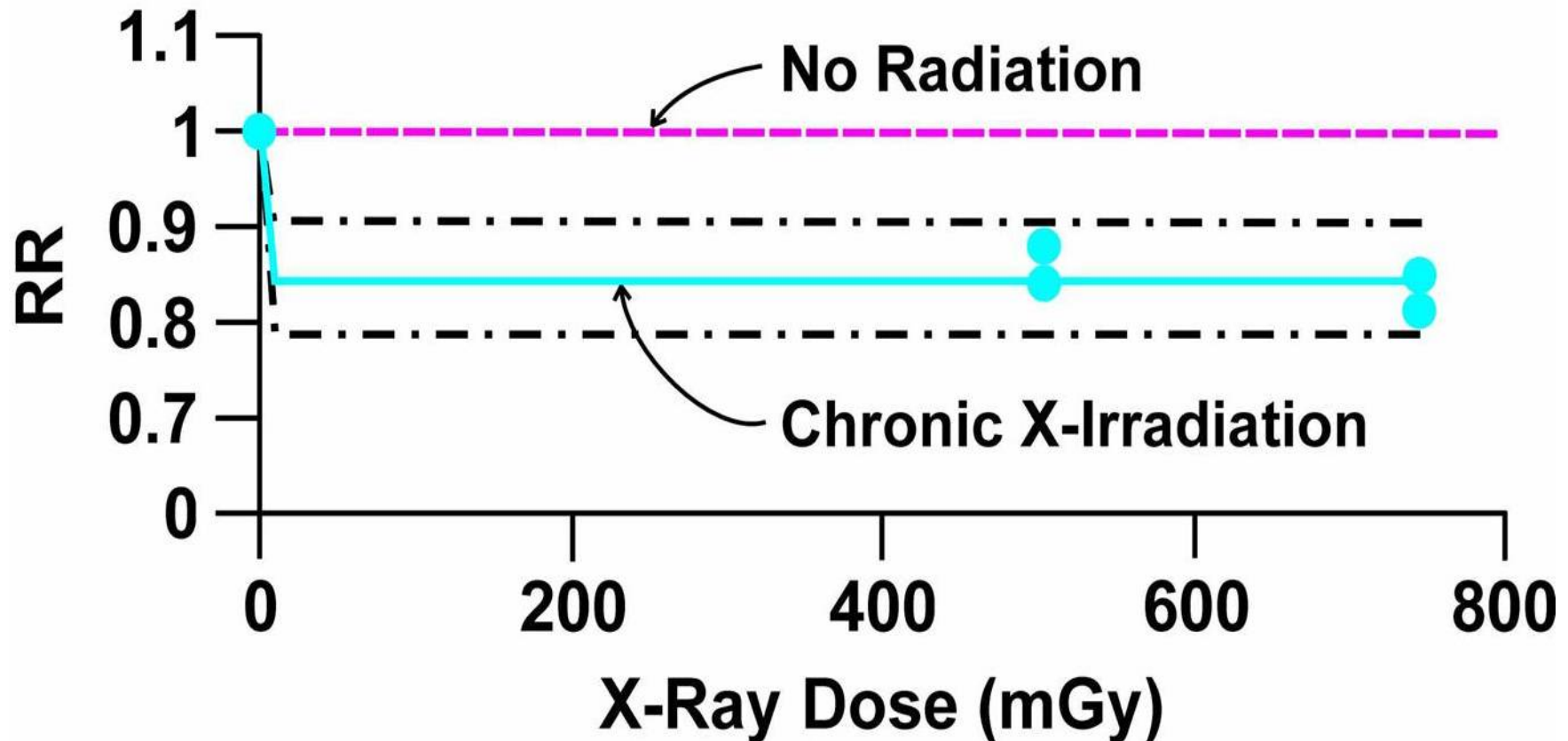
$D$  is the alpha radiation dose.

Scott BR. Nonlinearity (in press), 2006a,b.

# LNT-Related Low-Dose Epidemiological Study Design Issues

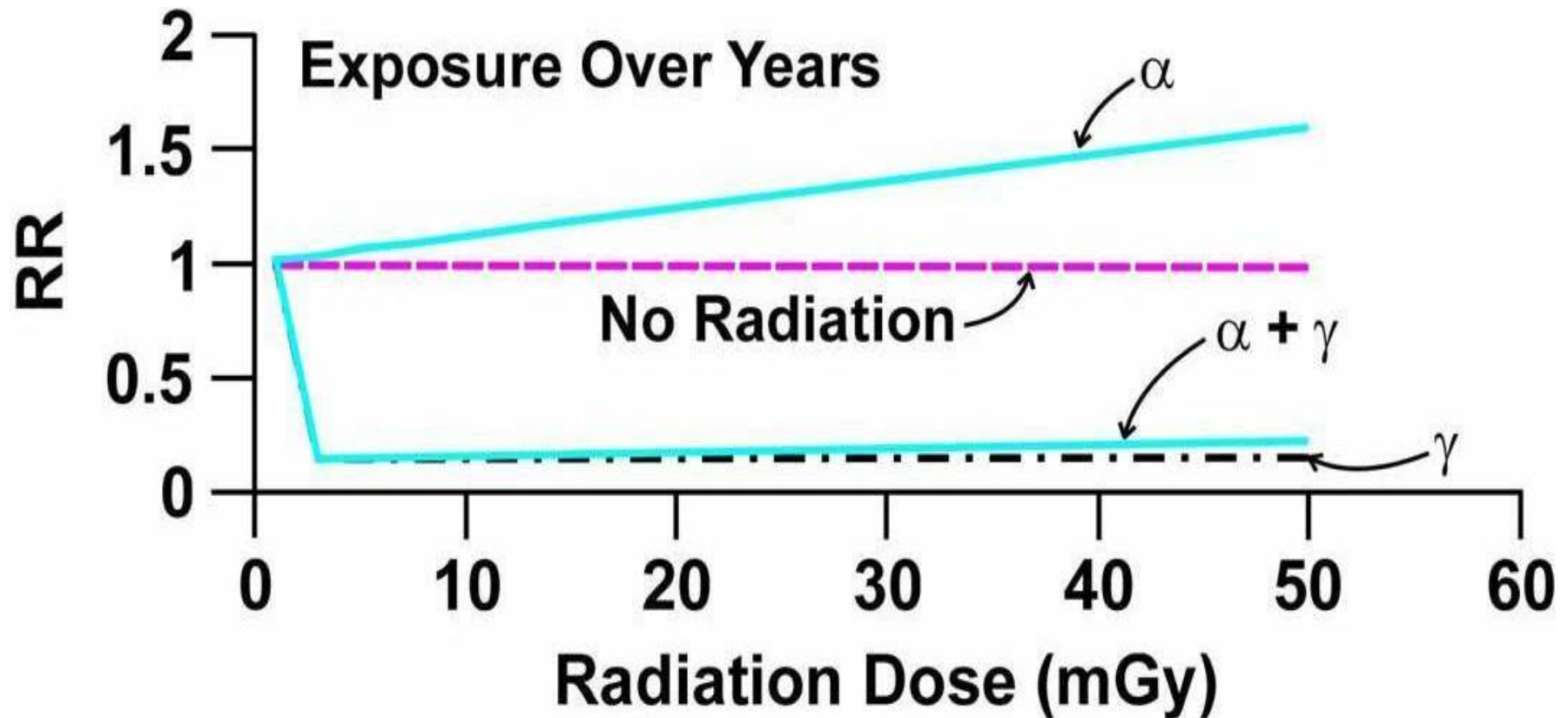
Design Feature	Issue
<b>Case-control study</b>	<b>Low power for distinguishing between LNT and HRR</b>
<b>Dose grouping with low-dose individuals in control group</b>	<b>Favors LNT over HRR; large systematic error possible when evaluating curve shape</b>
<b>Dose lagging (throwing away dose)</b>	<b>Could change HRR into LNT; contradicts LNT hypothesis; large systematic error likely</b>
<b>Including high-dose data</b>	<b>Assigns much more weight to high-dose groups than to low-dose groups</b>
<b>Encourages radiation phobia</b>	<b>Complicates managing radiological terrorism events</b>

# Lung Cancer Mortality Relative Risk: Canadian TB Patients



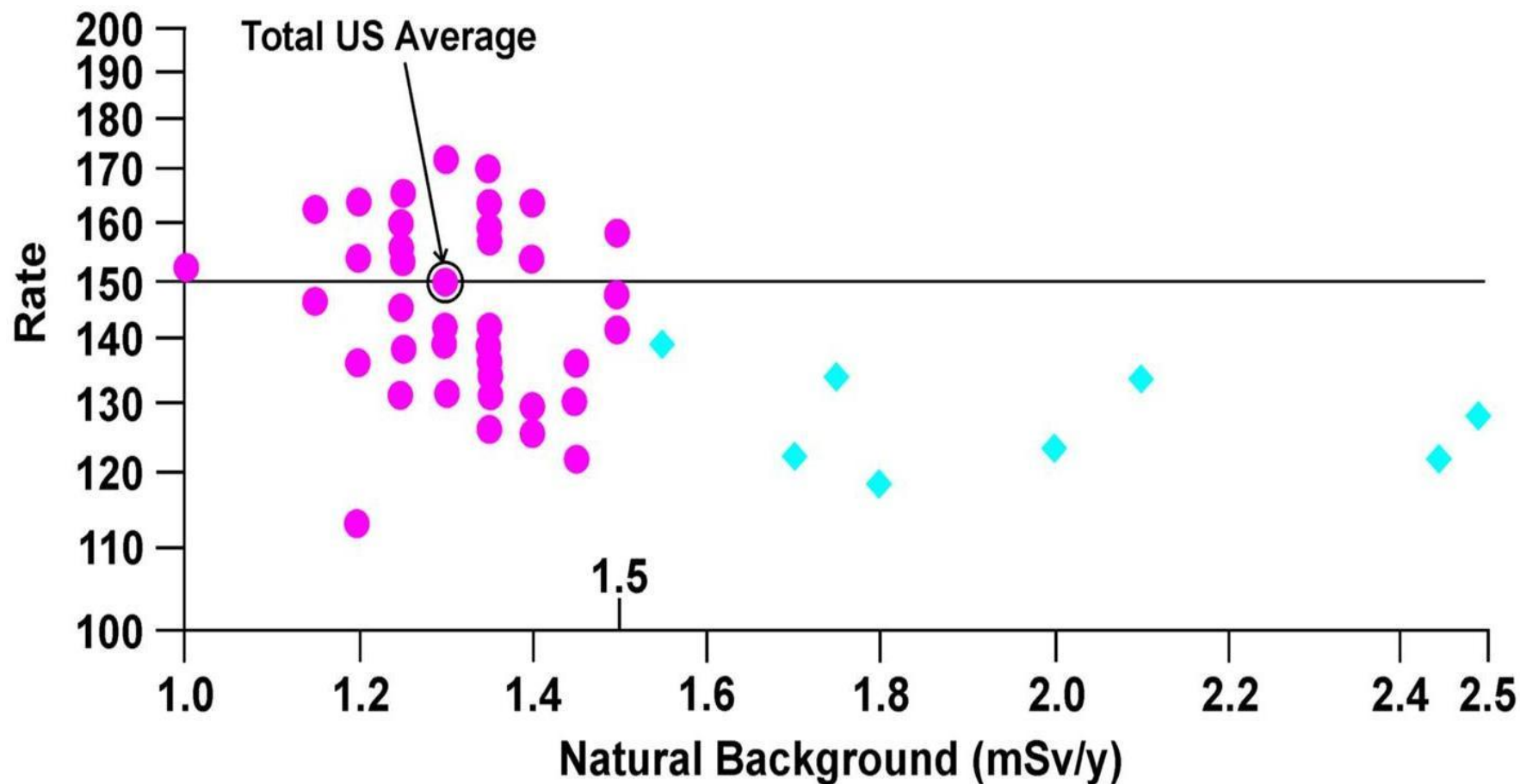
*Data from: Howe J. Radiat. Res. 142:295-304, 1995.  
PROFAC = 0.15, similar to the protection associated  
with high background radiation (ecological studies).*

# Lung Cancer Relative Risk: Mayak Workers



**Hormetic dose-response curves** were obtained for chronic  $\gamma$  and  $\alpha + \gamma$  irradiation but not for chronic  $\alpha$  irradiation only; **PROFAC = 0.86** (Scott 2006a).

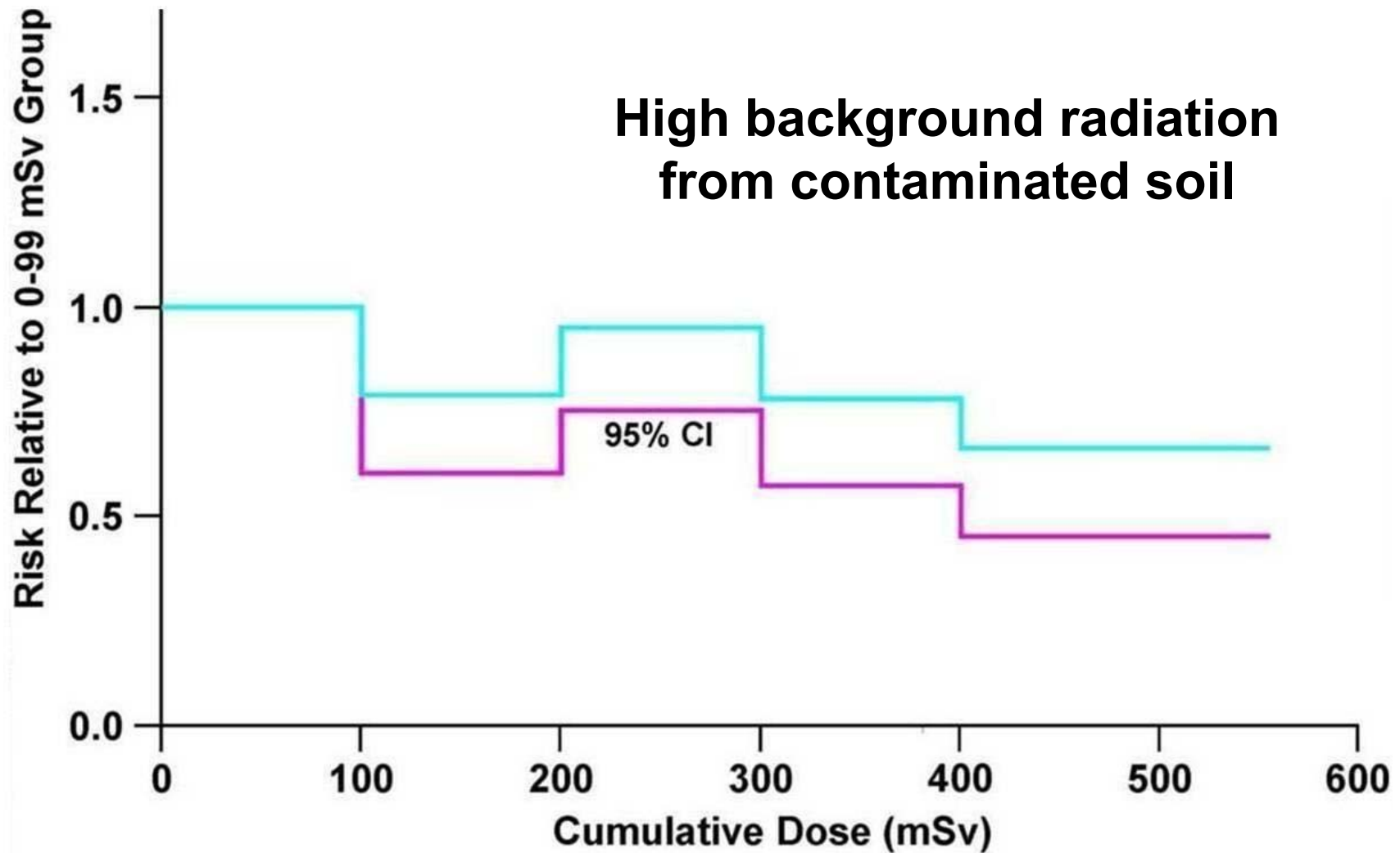
# Annual Cancer Mortality/100,000 For US States (1950-1967)



*Frigerio and Stowe, IAEA Publication, 1976.*



# Solid Cancer Mortality for Yangjiang, China (1979-1998)



*Wei and Sugahara. Int. Congress Series 1236:91-99, 2002.*

# Protection Factors Against Cancer in Humans<sup>1</sup>

Region or Group	Effect	PROFAC
High residual radon, USA	all cancers	0.35
Canada, nuclear industry workers	Leukemia	0.68
US DOE labs workers	Leukemia	0.78
Mayak Plutonium facility workers	lung cancer	0.86 <sup>2</sup>

**Proportion of spontaneous and other cancers prevented!**

<sup>1</sup>Jaworowski Z. Symposium “Entwicklungen im Strahleschutz”,  
Munich, 29 November 2001.

<sup>2</sup>Scott BR. Nonlinearity (in press), 2006a .

## Adjusted Standardized Mortality Ratios for Nuclear Shipyard Workers Chronically Exposed to $\gamma$ Rays

Cause of Death	SMR	<i>p</i> value	PROFAC
Allergic, endocrine, metabolic	<b>0.69 ± 0.12</b>	$4.3 \times 10^{-3}$	<b>0.31</b>
All respiratory disease	<b>0.62 ± 0.08</b>	$1.4 \times 10^{-6}$	<b>0.38</b>
Pneumonia	<b>0.68 ± 0.04</b>	$2.4 \times 10^{-14}$	<b>0.32</b>
Emphysema	<b>0.63 ± 0.26</b>	$7.2 \times 10^{-2}$	<b>0.38</b>
Asthma	<b>0.30 ± 0.43</b>	$5.1 \times 10^{-2}$	<b>0.70</b>
All infectious & parasitic	<b>0.86 ± 0.72</b>	$4.2 \times 10^{-1}$	<b>0.14</b>
Total mortality	<b>0.78 ± 0.04</b>	$2.2 \times 10^{-1}$	<b>0.22</b>

*Sponsler R and Cameron JR. Int. J. Low Radiat. 1(4):463-478, 2005.*

# Chernobyl Accident Associated Cancer Deaths: LNT Hypothesis vs. HRR Model

## LNT

Tens to hundreds of thousands of cancer deaths were initially projected by experts; approximately 4,000 cancer deaths now projected (IAEA, 2005)

## HRR

Spontaneous cancer incidence among 5 million persons in Belarus, Russia, and the Ukraine currently receiving annual doses  $< 1$  mSv, would be expected to decrease by more  $> 10\%$  (*PROFAC* expected to be  $> 0.10$ )

## Evidence for PROFAC >0.10

- Ivanov *et al.* (2001) found a **hormetic dose-response curve for cancer mortality** among Chernobyl emergency workers. **PROFAC = 0.13.**
- Ivanov *et al.* (2004) found a **hormetic dose-response curve for the solid cancer incidence among Chernobyl nuclear workers (liquidators).** **PROFAC = 0.17.**

*Ivanov VK et al. Health Phys. 81(5):514, 2001.*

*Ivanov VK et al. J. Radiat. Res. 45(1):41-44, 2004.*

# Low Dose Rates More Protective than High Dose Rates

- Low dose rates stimulate over and over again the transient PAM process.
- May also over and over stimulate the immune system which is suppressed at high doses and dose rates.
- *PROFAC* much larger for chronic exposure at a low rate than for brief exposure at a high rate.

*Scott BR. Nonlinearity (in press), 2006a,b.*

# **Amifostine and Diagnostic X-Ray Protection After Radiological Terrorism Events**

# Low-Dose Protection Against Harm From a Prior Mutagenic Dose

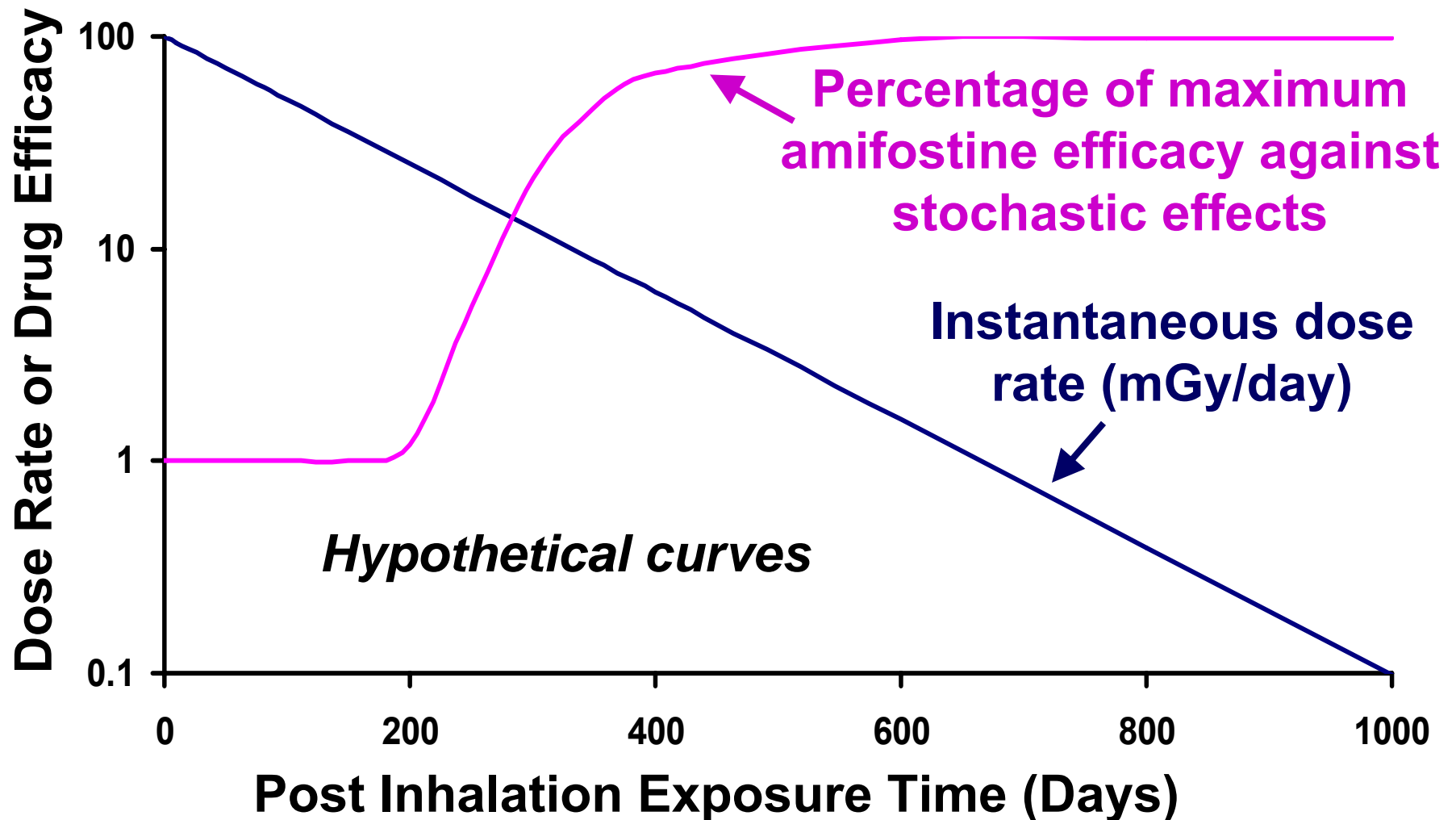
- **Low-dose X-rays suppress mutations in mice** when given after a mutagenic dose of X-rays (**Day et al., 2005**).
- **Low-doses of amifostine (WR-2721) suppress mutations in mice** after a mutagenic dose of neutrons (**Grdina et al., 1992**).
- **PAM process likely involved in both** suggesting residual radiation dose-rate dependence of amifostine.
- **Multiple applications of these agents could protect from cancer** after exposure to a carcinogenic radiation dose during a radiological terrorism event.

*Day T. et al., EMS 2005 Meeting presentation.*

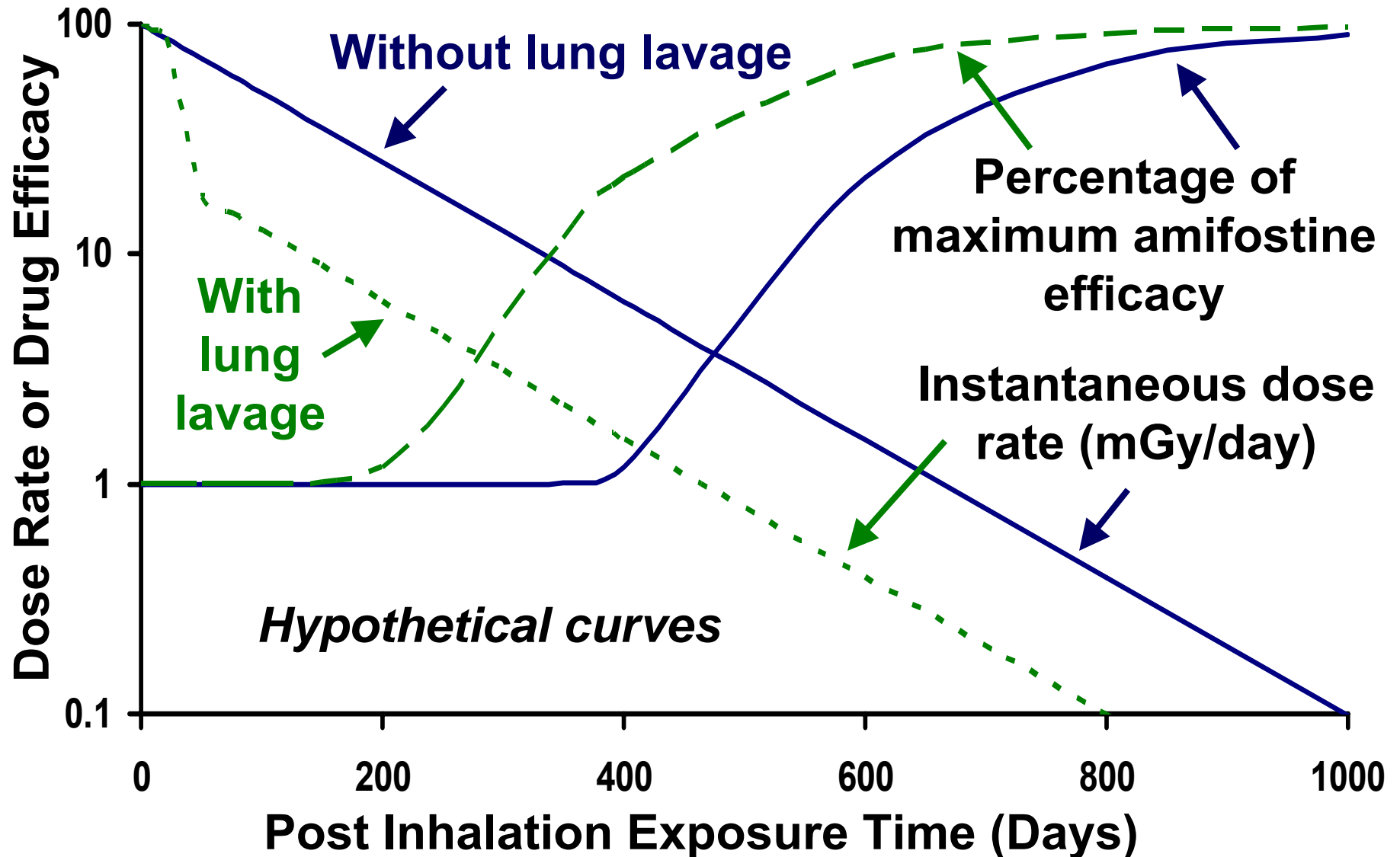
*Grdina D. et al. Carcinogenesis 13(5):811-814, 1992.*



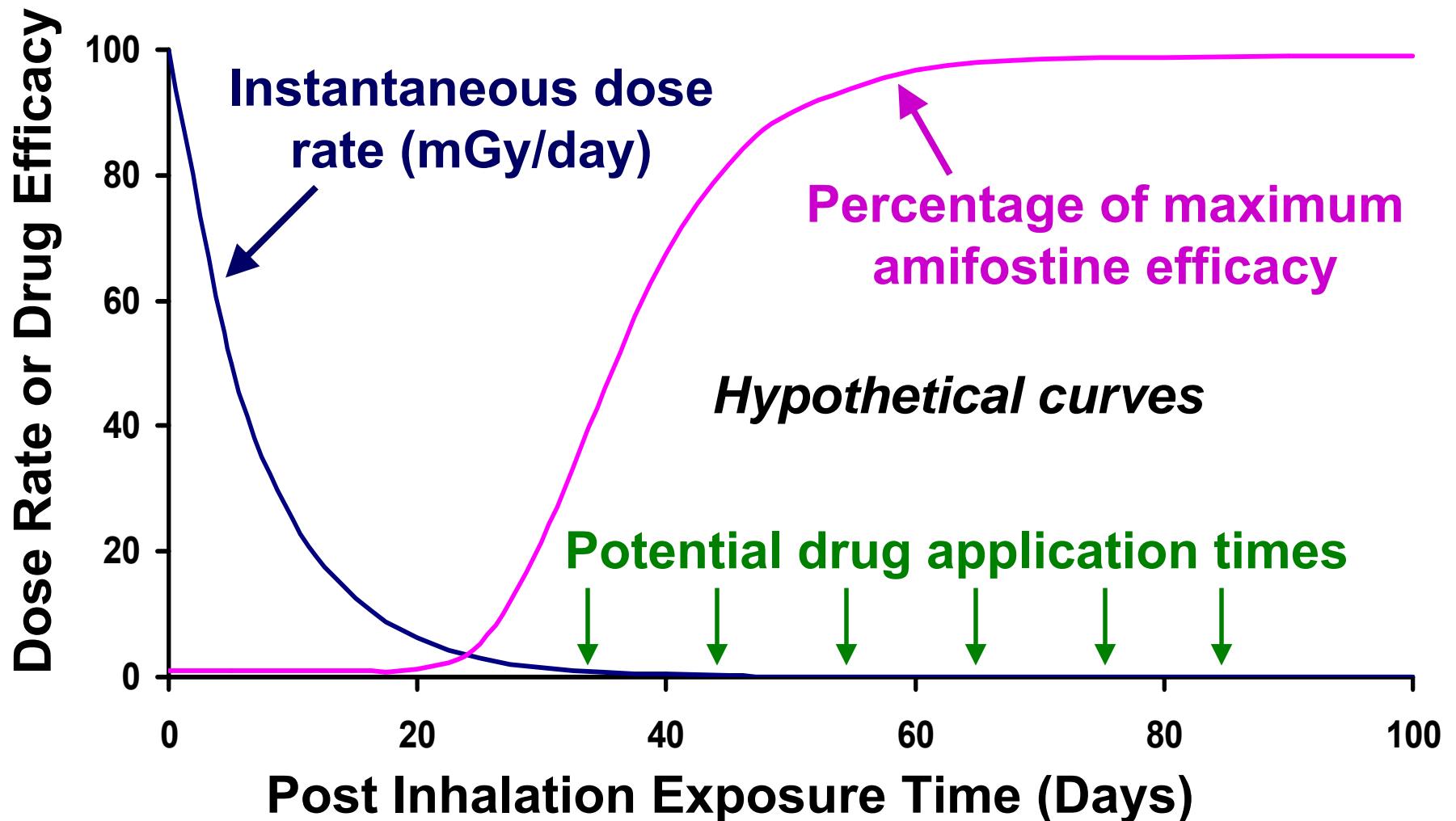
# Amifostine Efficacy Expected to Depend on Residual Radiation Dose Rate



# Expected Impact of Lung Lavage on Amifostine Efficacy Against Stochastic Effects

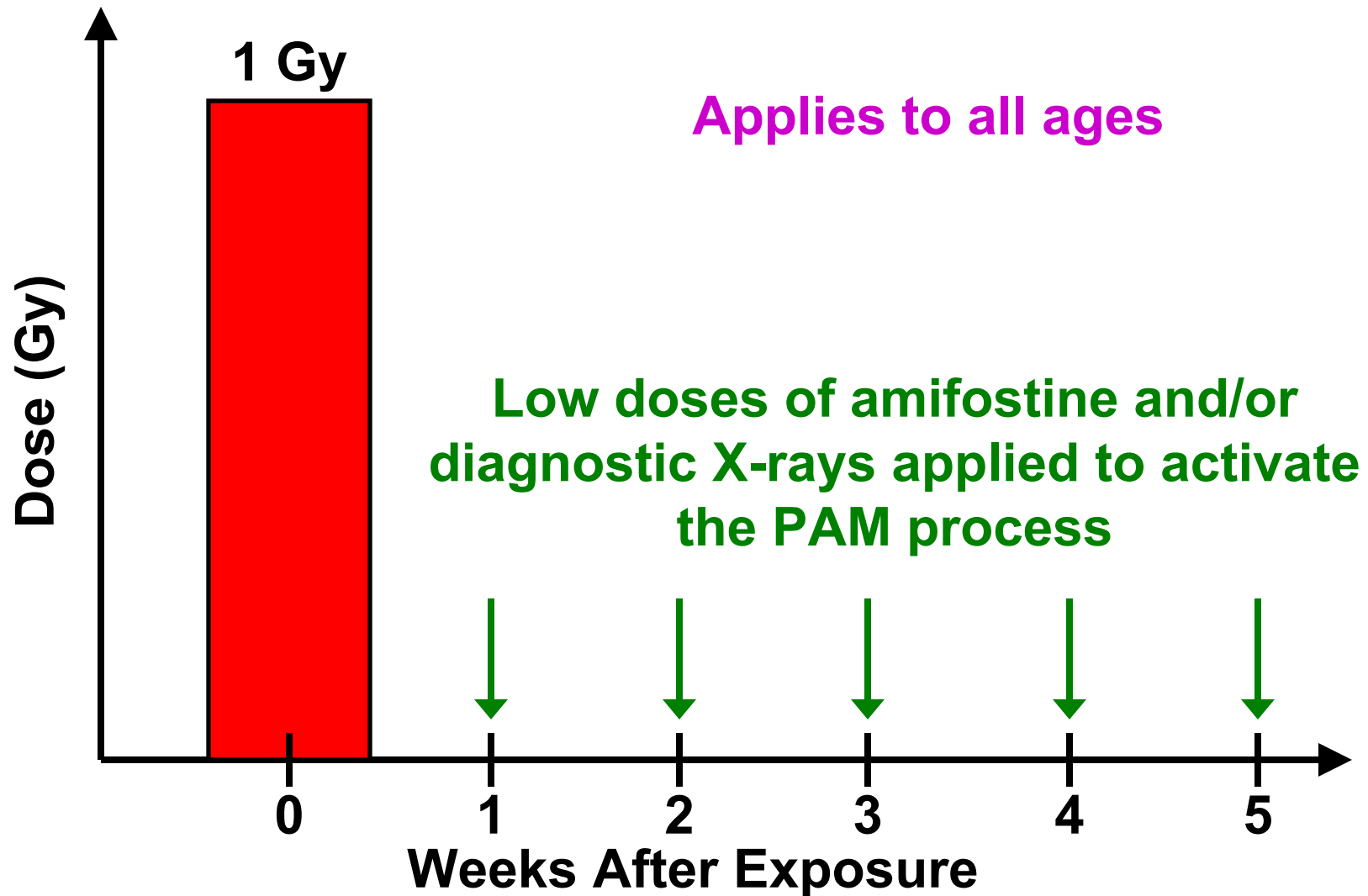


# Amifostine Expected to Protect Against Stochastic Effects Long After Irradiation Ceases

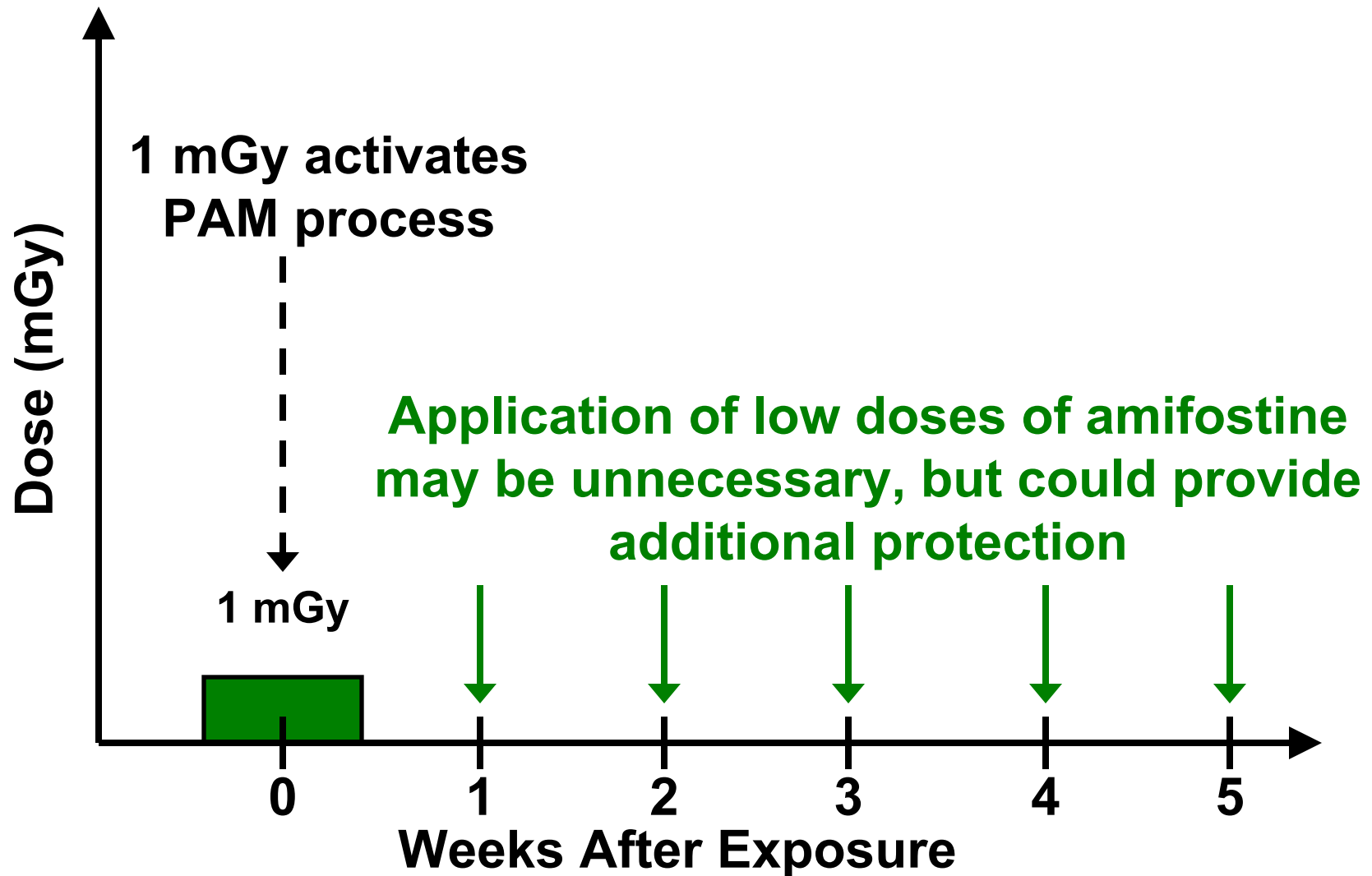


**Hidden Gamma-Ray Source  
Exposure Scenarios: Protecting  
from Stochastic Effects**

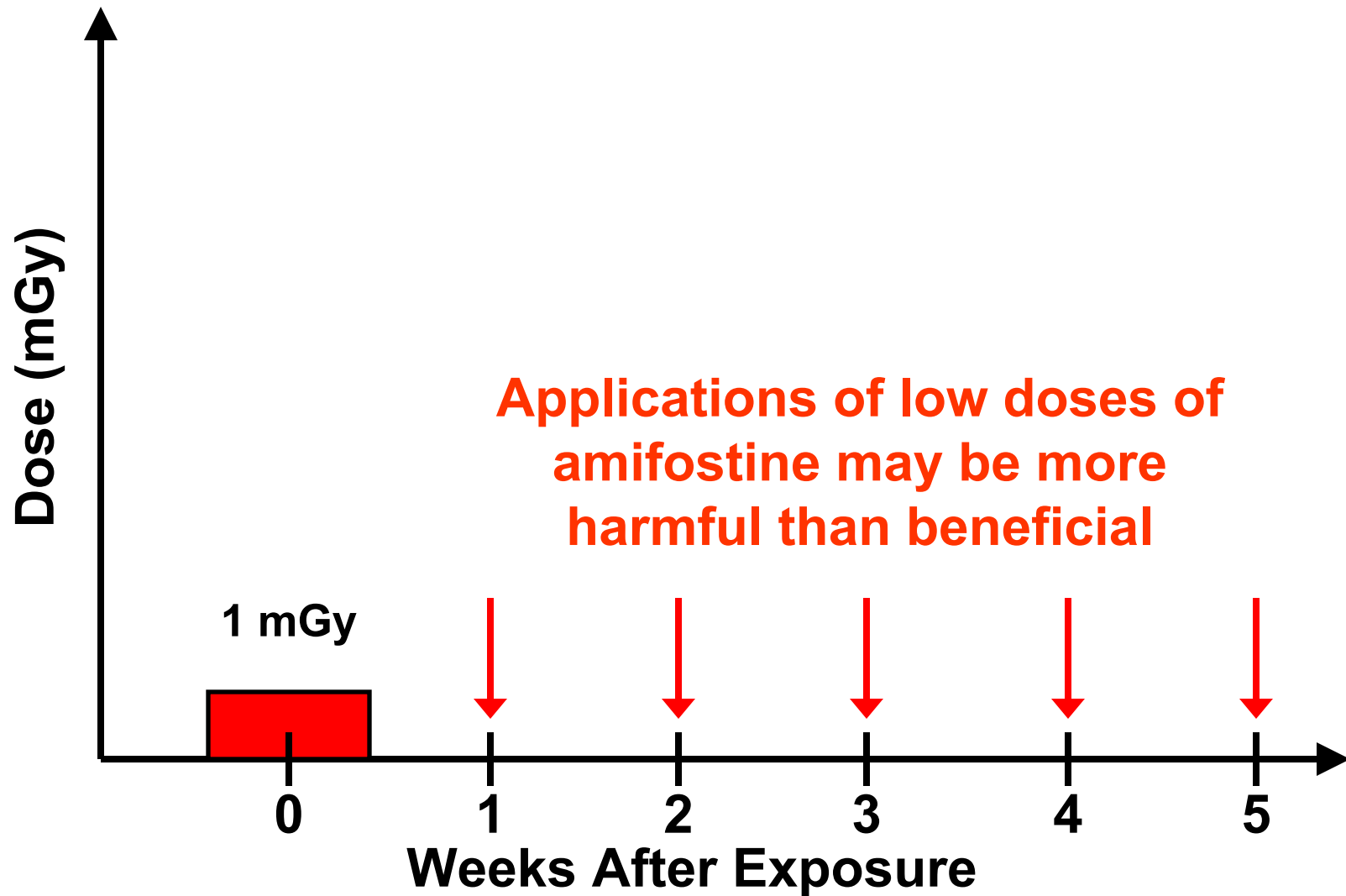
# Hidden Gamma-Ray Source Scenario 1: Post-Exposure Protection



# Hidden Gamma-Ray Source Scenario 2: Low Radiation Dose to an Adult



# Hidden Gamma-Ray Source Scenario 3: Low Radiation Dose to a Child



## **New Research Needs**

- **Examining radiation dose-rate-dependence of the efficacy of amifostine for inhaled radionuclide scenarios.**
- **Investigating combined protection from diagnostic X-rays and low doses of amifostine.**
- **Determining radioprotector drug efficacy as function of age.**
- **Developing optimal application schemes for radioprotector drugs and other forms of protection.**



# **Radiation Phobia and Managing Radiological Terrorism Events**

# LNT-Associated Radiation Phobia Following a Dirty Bomb Incident



## Radiation-Phobia-Associated Impacts:

- **Loss of lives** associated with frantic evacuations.
- **Severe injuries** during evacuations.
- **Increased suicides** and abortions.
- Increased **psychosomatic disorders**.
- Increased **drug/alcohol/cigarette abuse**.
- Permanent **abandonment of properties** with low-level contamination.

# Chernobyl-Associated Radiation Phobia

- “The **psychosomatic disorders** observed in the 15 million people in Belarus, Ukraine, and Russia... who were affected by the April 1986 Chernobyl accident are probably the accident’s most important effect on public health...<sup>1</sup>
- **Radiation phobia caused over 100,000 deaths by abortions in Western Europe, a tragic loss of life.**<sup>2</sup>

<sup>1</sup>*Zbigniew Jaworowski. Physics Today, September 1999, pp. 24-29.*

<sup>2</sup>*Ketchum LE. J. Nucl. Med. 28:413-422, 1987.*

# Implications for Managing Low-Dose\* Radiological Terrorism Events

## LNT Model

## HRR Model

<b>Harm to 1st responders</b>	<b>No harm to 1st responders</b>
<b>↑ cancers for public</b>	<b>↓ cancers for public</b>
<b>High remediation costs</b>	<b>Lower remediation costs</b>
<b>Abandoning of expensive facilities (e.g., government buildings)</b>	<b>Continued use of expensive facilities after cleanup</b>
<b>Many radiation-phobia-associated casualties</b>	<b>Fewer radiation-phobia-associated casualties</b>

\*Doses of low-LET radiation < 100 mGy.

# **A New Multi-Agency Hormesis Research Program Needed**

- **To facilitate improving homeland security practices regarding managing radiological, chemical, and biological terrorism events.**
- **To facilitate improving low-dose risk assessment and low-dose radiation therapy.**
- **Research should be included on hormetic effects for DNA damage repair, apoptosis, mutations, neoplastic transformation, cancer, and other diseases.**

# Conclusions

- Low doses and dose rates of low-LET radiation are **likely protecting us from cancer and other diseases.**
- Multiple, post-radiation exposure applications of low doses of amifostine and/or diagnostic X-rays **should protect persons of all ages** against cancer after exposure to moderate and large radiation doses from a radiological terrorism event.
- Post-radiation exposure application of low-doses of amifostine and/or diagnostic X-rays **may not provide any benefit to children** after low radiation doses received in a radiological terrorism event.

## Conclusions (continued)

- **Post-radiation exposure application of low doses of amifostine and/or diagnostic X-rays may not be needed for adults after low radiation doses that activate the PAM process.**
- **A new multi-agency radiation hormesis research program is needed with a focus on mitigating harm from radiological, chemical, and biological terrorism events and improving low-dose risk assessment.**

# Collaborators and Other Support

- **Dr. Galina Zhutova (SUBI, Ozersk)**
- **Dr. Zoya Tokarskaya (SUBI, Ozersk)**
- **Dr. Leslie Redpath (U. California, Irvine)**
- **Dr. Pamela Sykes (Flinders U., Adelaide)**
- **Ms. Tanya Day (Student, Flinders U.)**
- **Dr. Noelle Metting (DOE BER)**
- **Edward Calabrese (U. Mass.)**
- **Jennifer Di Palma (UNM student)**
- **Munima Haque (U. Illinois student)**
- **Others at LRRI**





**J. Di Palma**

**B. Scott**



**M. Haque**

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# **Residual Risks For Lethality After Application Of Medical Countermeasures Against Damage From Inhaled Gamma- emitting Radionuclides Released From A Radiological Weapon**

**Bobby R. Scott, Ph.D.**

**Seminar presented at the AFRRI on April 28, 2005**

**Available online at:**

**[http://www.radiation-scott.org/Residual\\_Risk\\_1B.pdf](http://www.radiation-scott.org/Residual_Risk_1B.pdf)**

