

The LNT Hypothesis May Have Outlived Its Usefulness for Low-LET Radiation

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Hormesis

- **Low-dose stimulation, high-dose inhibition.**
- **Term usually applied to beneficial effects.**
- **Dose-response curve can be U-shaped, J-shaped, etc.**

International Hormesis Society recently formed: <http://www.hormesissociety.org/>

BELLE: <http://www.belleonline.com/>

BEIR VII vs. French Academies

- **BEIR VII:** data consistent with LNT; even background low-LET radiation harms; **hormesis dismissed**.
- **French Academies:** LNT may not apply to low-LET doses < 100 mGy; back-ground radiation may be beneficial (**hormetic effect**).

What We Have Learned from DOE-Sponsored Basic Research

- For low-LET radiation, **nonlinearity in dose-response** may be more the rule than the exception for stochastic effects.
- **Hormetic-type, dose-response curves** can arise for low-LET irradiation (via adaptive response).

DOE Low Dose Radiation Research

Program: <http://lowdose.tricity.wsu.edu/>

Low-Dose, Low-LET Radiation Protects!

- 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**)!
- Suppresses occurrence of diseases other than cancer (**Kazuo Sakai's group**)!

Protective Biological Processes Induced By Low-LET Radiation

- **DNA repair/apoptosis competition**, which depends on the p53 gene.
- **Apoptosis alone** (p53-gene independent).
- Immune system stimulation (*in vivo*).

Apoptosis: cell commits suicide; cell next to it may be OK. Selective cell killing.

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
(**self destruction**).

NEOTRANS₃ 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 (2005a in press; 2005b, accepted)

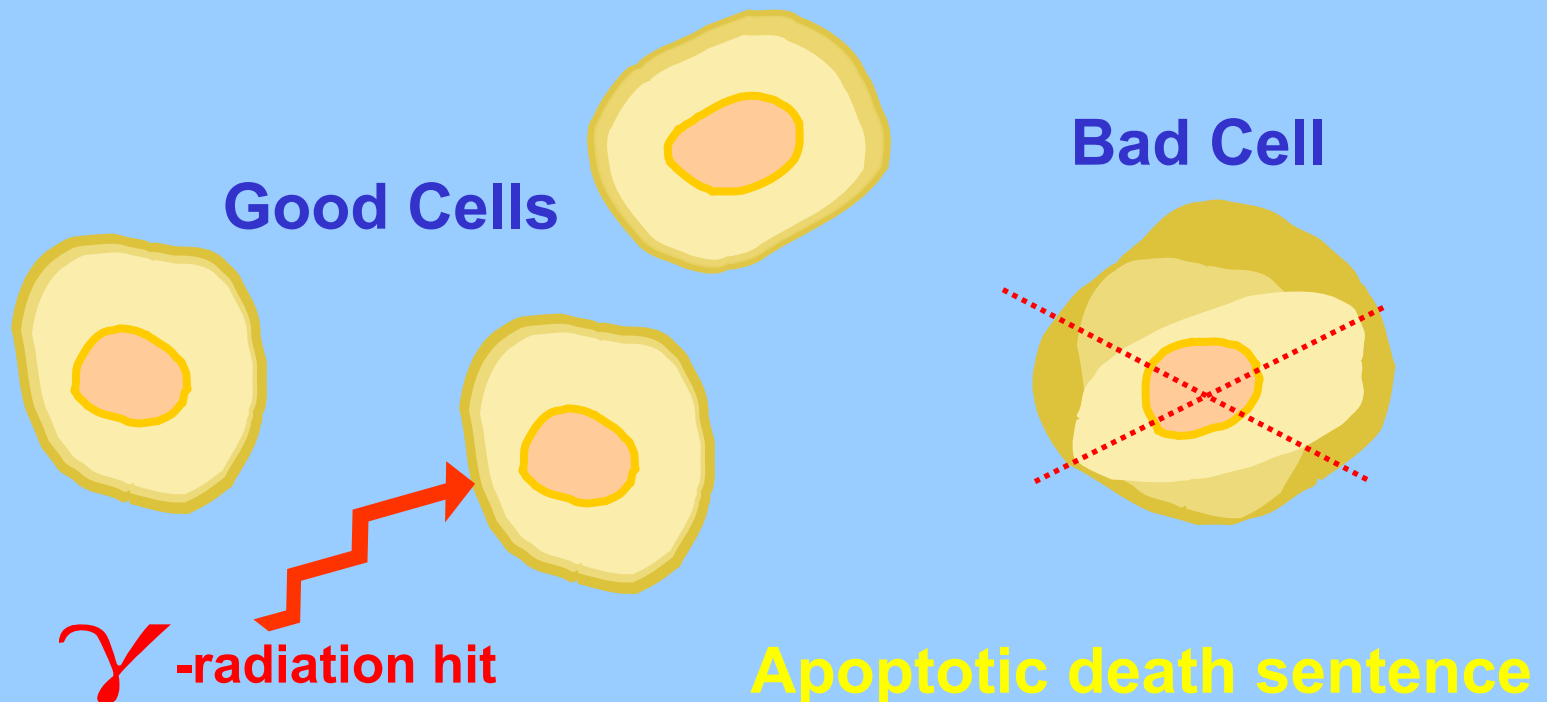
Protective Processes Associated with NEOTRANS₃ Model

- **p53-gene-dependent**, high-efficiency DNA repair/apoptosis.
- **p53-gene-independent**, protective apoptosis mediated (**PAM**) process.
- **Stochastic thresholds** (**StoThresh**) jointly activate these protective processes.
- Higher StoThresh also inhibits PAM process.

PAM Process

Target Cell Population

Cells talk to each other



Chemical and biological signaling (Scott 2005a,b).

StoThresh Associated with NEOTRANS₃ Model

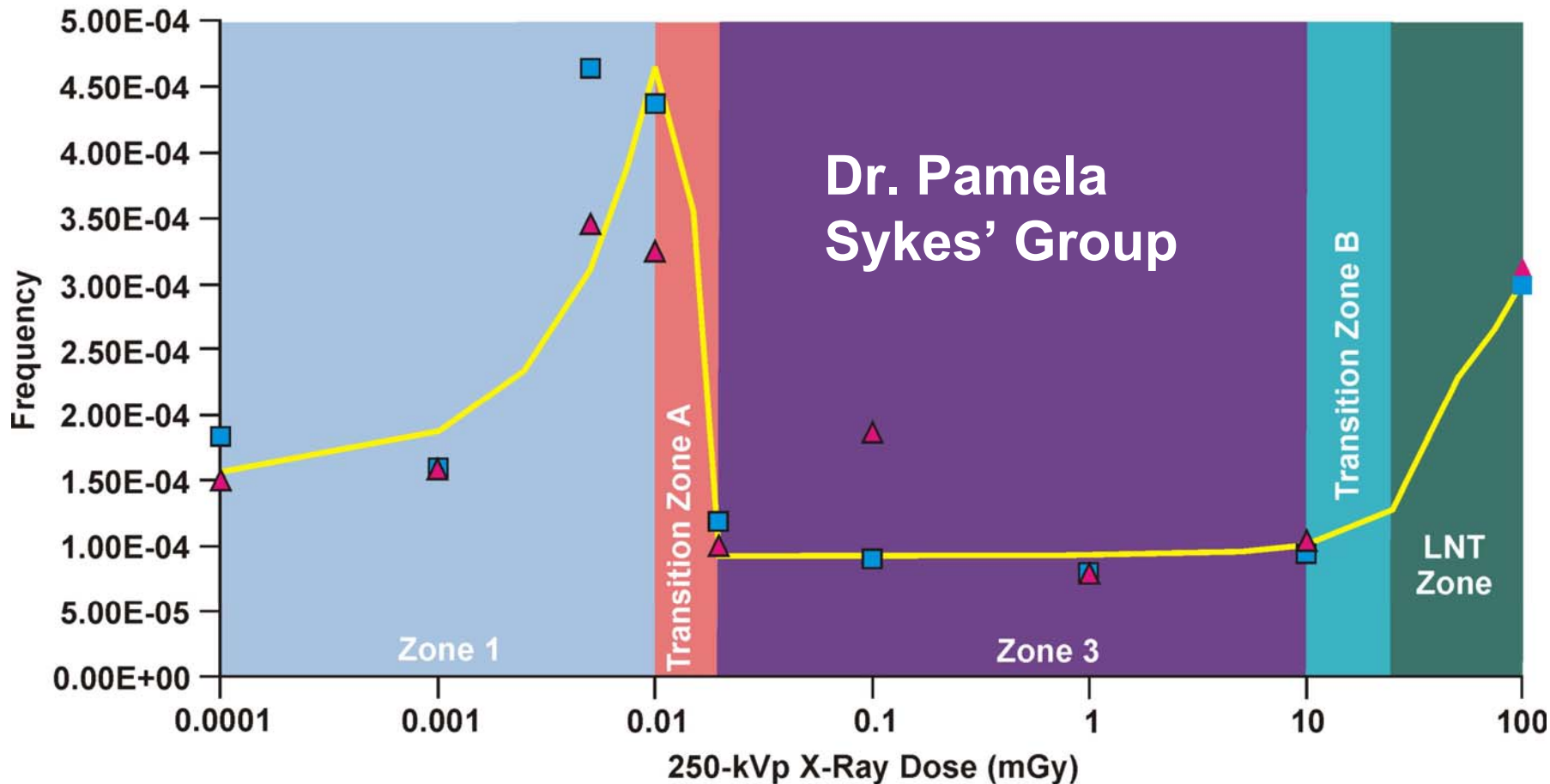
- D_{PAM} , activates PAM as well as high-efficiency DNA repair/apoptosis.
- D_{off} , inactivates PAM but not high-efficiency DNA repair/apoptosis.

$$D_{\text{off}} \gg D_{\text{PAM}}$$

$D_{\text{off}}\{\text{min}\}$, minimum for D_{off} .

Uniform prior distributions currently used in our Bayesian analyses.

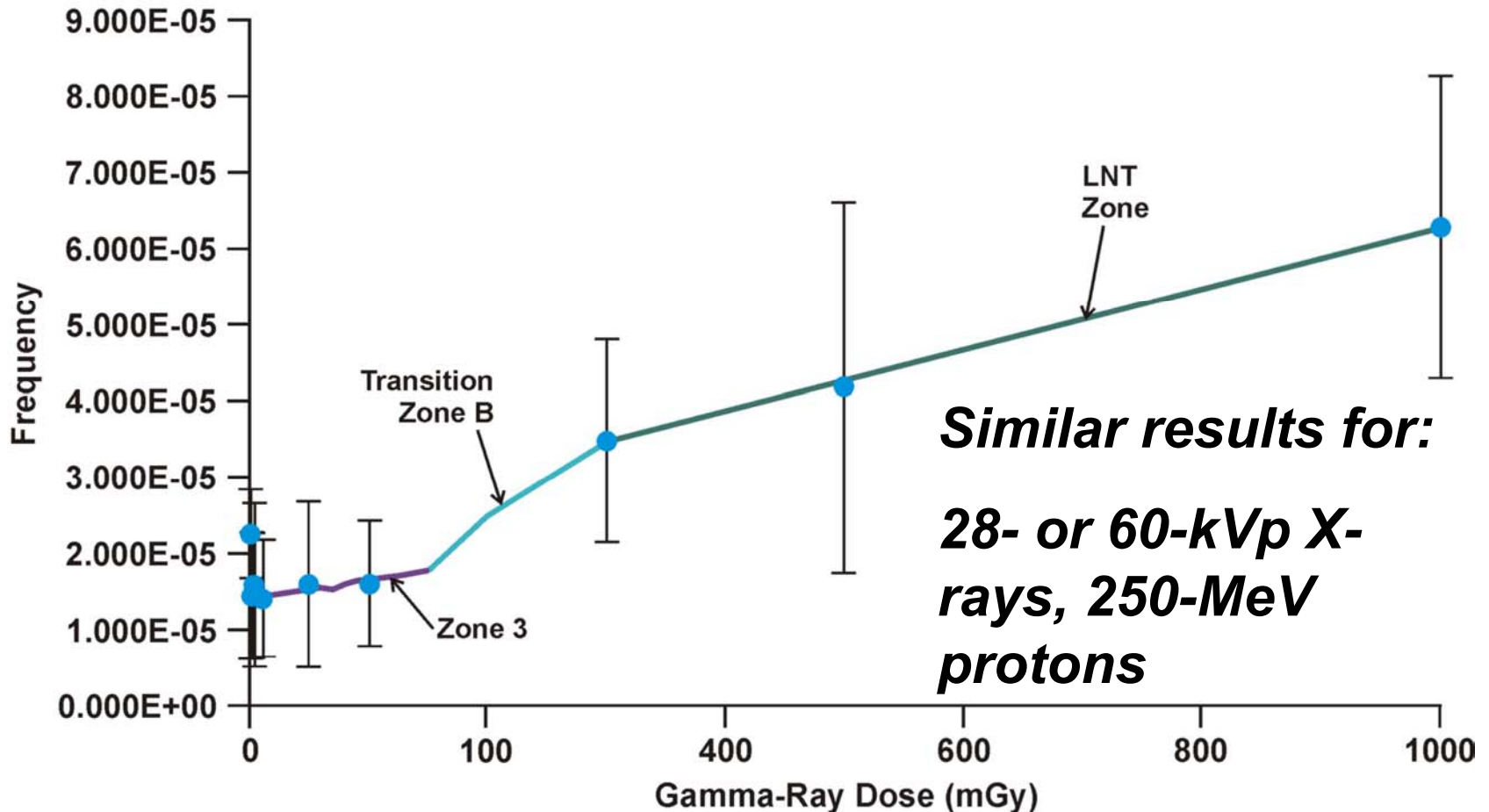
Inversion Mutation Frequency in pKZ1 Mice: Spleen data from Hooker et al. (2004)



5785-2a

Average annual low-LET background in Zone 3. Fitted curve based on NEOTRANS₃ model implemented with Markov chain Monte Carlo.

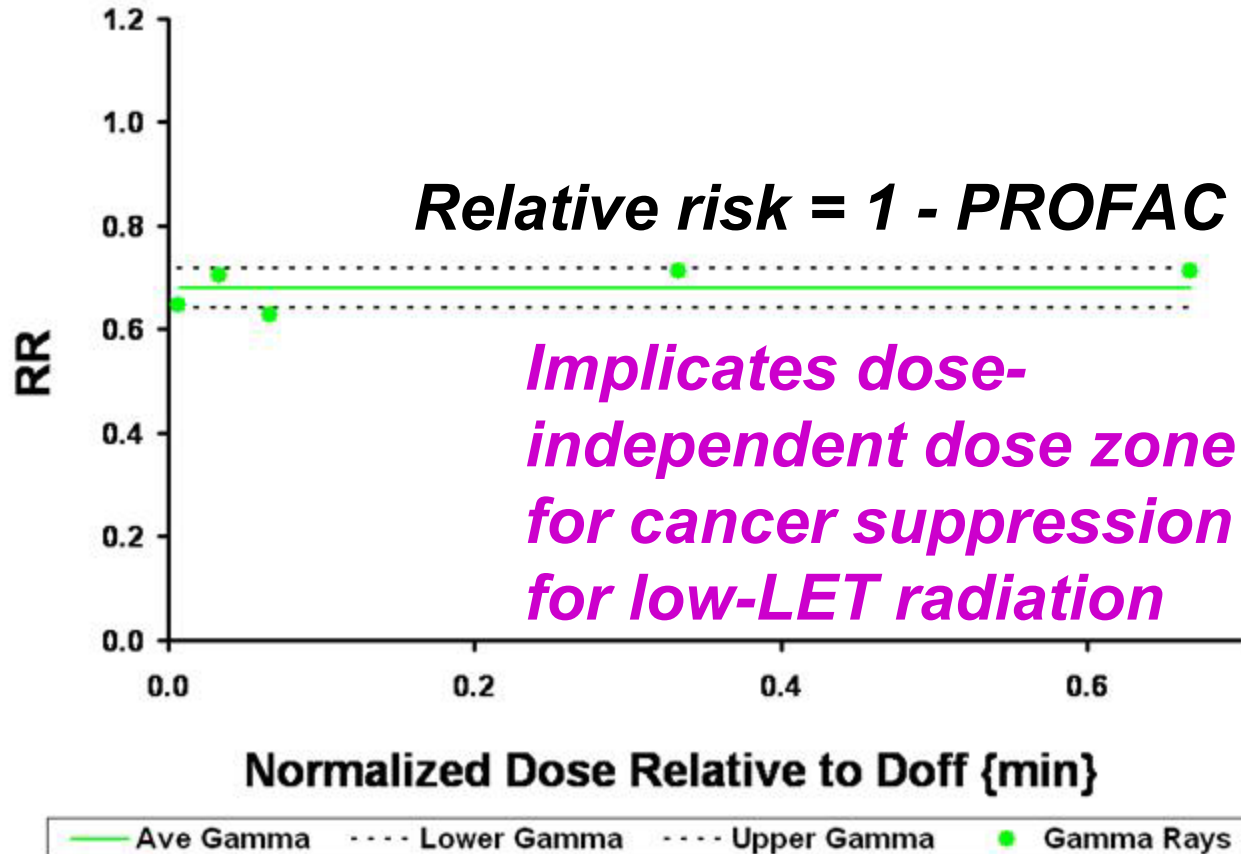
Transformation Frequency: Cells Irradiated in Culture (Redpath et al. 2001)



**Similar results for:
28- or 60-kVp X-rays, 250-MeV
protons**

**Smooth curve based on NEOTRANS₃ model
implemented with MCMC.**

95% Confidence Region: Gamma Rays RR for Transformation



Width (absorbed dose) and depth of protective zone expected to increase as dose rate decreases.

RR(Transformation) \cong RR(Cancer)

Redpath et al. (2001)

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

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

Scott BR, Nonlinearity (2005a,in press).

Novel Low-Dose, Low-Dose Rate, Cancer Relative Risk Equations

Low-LET irradiation (dose-independent zone):

$$RR = 1, \text{ Dose} = 0$$

$$RR = 1 - \text{PROFAC}, \text{ otherwise}$$

PROFAC depends on dose rate pattern and exposure time; accounts for PAM and immune system stimulation. Dose-independent zone increases importance of highly-criticized ecological studies!

Combined Low-Dose, Low- and High-LET ($\alpha + \gamma$) Irradiation

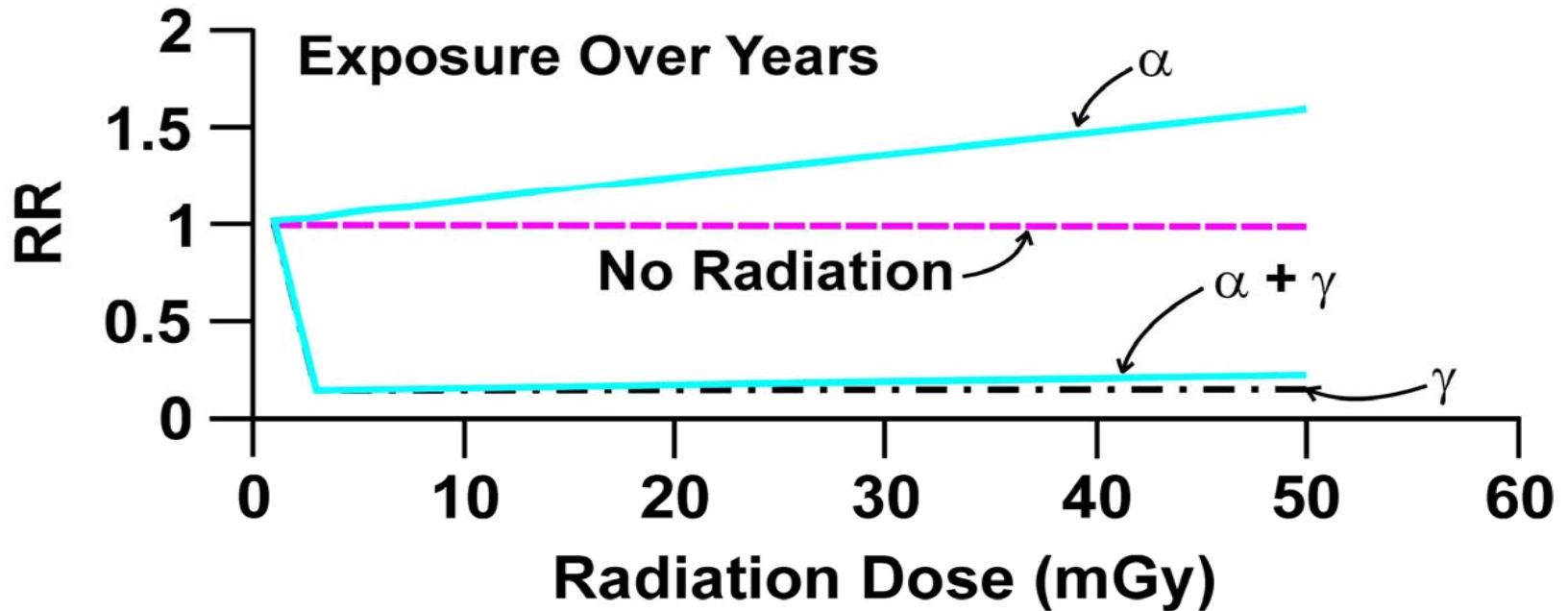
$$RR = (1-PROFAC)[1 + F(B)KD], D > 0$$

Low-LET radiation suppresses cancer via **protection factor (PROFAC)** (Scott 2005a,b).

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

PROFAC=0, for alpha radiation.

LUNG CANCER RELATIVE RISK: MAYAK WORKERS



5354-8

PROFAC = 0.86 (86% cancers prevented).

Simulated and Observed RR for Lung Cancer Among Mayak Workers¹

Alpha radiation dose (mGy)	Observed RR²	Simulated RR
0	1	1
0.1 to 12	0.39	0.36
12.1 to 50	0.53	0.56
50.1 to 200	1.58	1.59

¹Workers (2,346) chronically exposed to alpha and gamma radiations.

²Kokhryakov et al. 1996.; baseline from Russian national statistics.

Protection Factors Against Cancer in Humans (Jaworowski, 2001)

Region or Group	Effect	PROFAC
US or China, high background area	cancers	0.15 (relative to average)
Canada, nuclear industry workers	leukemia	0.68
US DOE labs workers	leukemia	0.78
Mayak Plutonium facility workers	lung cancer	0.86*
Taiwan, Cobalt-60 contaminated apartments	cancers	> 0.95*

Proportion of spontaneous cancers prevented!

****Scott BR (in press; Nonlinearity, 2005a)***

TD Luckey Appears to Be Right!

- According to TD Luckey, **1/3 of all cancer deaths are premature and preventable** by low-level ionizing radiation (e.g., elevated background).
- **Reducing background could harm us!**

Protective effect considered to be associated with low-LET radiation component of background radiation.

Implications of Dismissing Hormesis

“By dismissing hormesis, regulatory agencies such as EPA deny the public the opportunity for optimal health and avoidance of disease.”

Edward J. Calabrese, Human & Experimental Toxicology (2005) 24:265-270.

LNT-Caused Harm

“The **psychosomatic disorders** observed in the 15 million people in Belarus, Ukraine, and Russia¹ who were affected by the April 1986 Chernobyl accident are probably the accident’s most important effect on public health.² These disorders could not be attributed to the ionizing radiation but were assumed to be linked to the popular belief that any amount of man-made radiation ... can cause harm.”

Zbigniew Jaworowski, Physics Today, September 1999, pp. 24-29.

Hormesis Implications for Regulatory Low-LET Thresholds

- Thresholds for excess cancers likely exist for population exposures (hormetic dose response)!
- Very large thresholds ($\gg 100$ mGy) appear to be associated with chronic low-dose-rate exposure!
- 0.1 - 10 mGy annually likely protect from rather than cause excess cancer among a population of humans!
- Could be basis for setting annual regulatory thresholds (e.g. 1 mGy brief high-rate exposure, 10 mGy protracted low-rate exposure) for populations that include all ages.
- Special considerations could be given to sensitive subgroups (e.g. young and unborn).

Acknowledgement

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Additional Information on References

- **Hooker AM et al. Radiat. Res. 162:447-454, 2004.**
- **Jaworowski Z. Ionizing radiation in the 20th century and beyond. Symposium “Entwicklungen im Strahleschutz”, Munic, 29 November 2001.**
- **Khokhryakov VF et al. Radiation Safety No 2:51-55 1996 (Translated by E. Farfan).**