The Role of Low-Dose Radiation in the Maintenance of Life

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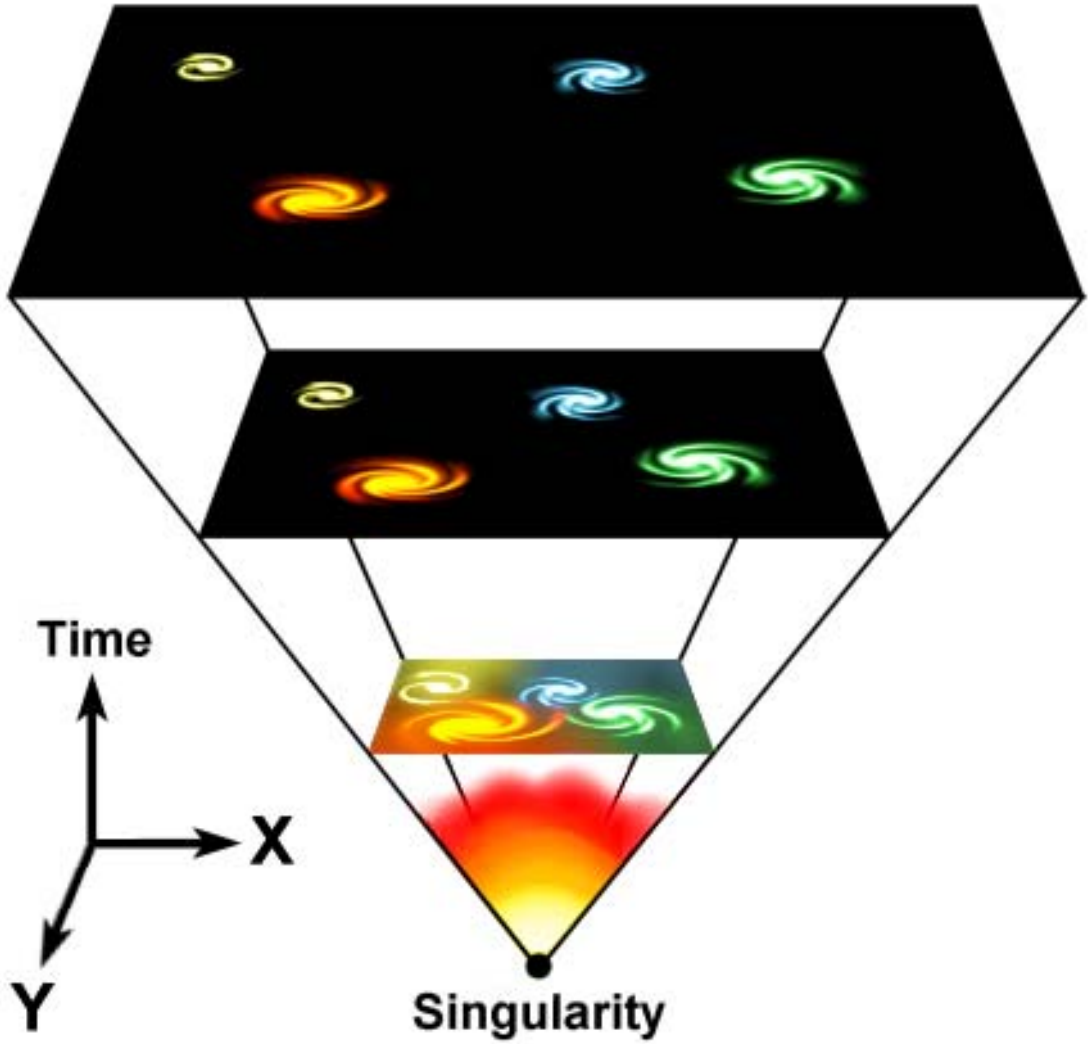
http://www.radiation-scott.org

Contents

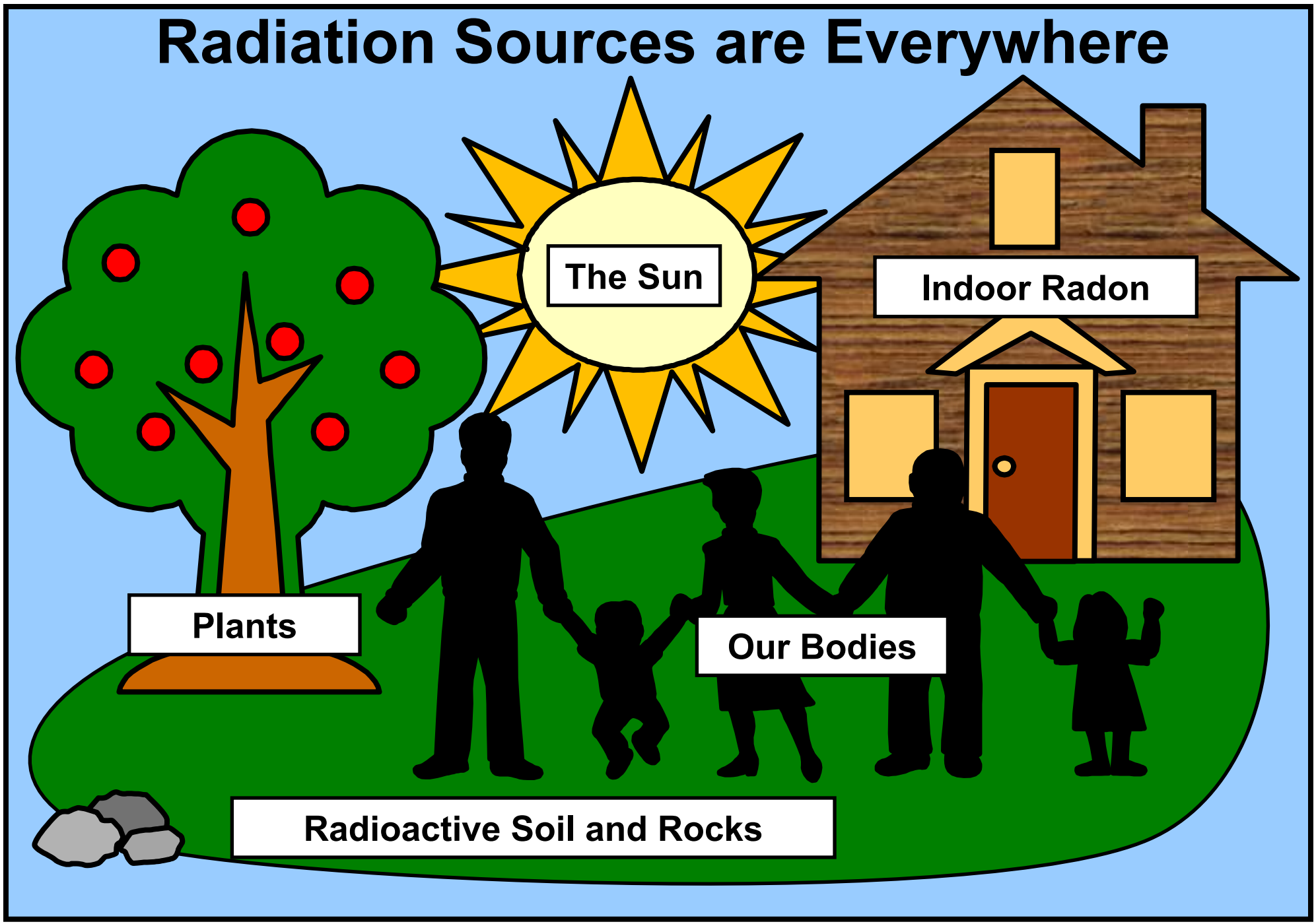
- Ionizing radiation and its sources
- Spontaneous and radiation-induced damage
- Radiation adaptive response (hormesis)
- Biological basis for radiation hormesis
- Radiation risk-assessment paradigms (LNT vs. hormetic) for cancer
- LRRI hormetic cancer relative risk model
- Evidence that low doses of radiation are facilitating the maintenance of life
- Conclusions

Radiation Has Existed Since the Beginning of the Universe

Universe created 10 - 20 billion years ago from a cosmic explosion



Radiation Sources are Everywhere



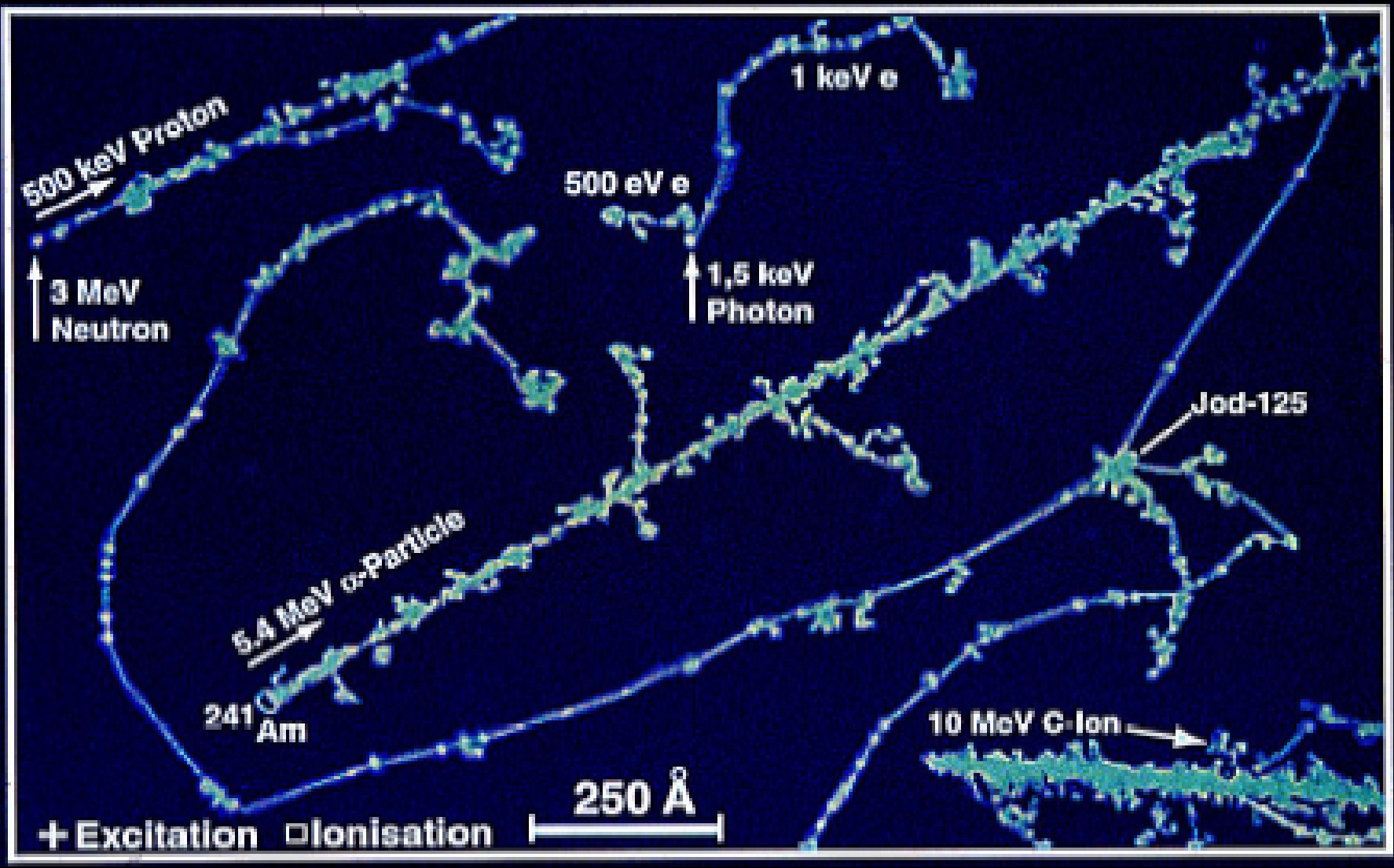
Forms of Radiation

- Non-ionizing and Ionizing.
- An example of non-ionizing radiation is UV rays.
- Ionizing radiation is either particulate or electromagnetic.
- Gamma and X-ray photons are electromagnetic forms.
- Protons, beta particles, neutrons and heavy ions are examples of particulate ionizing radiation.

Low- and High-LET Forms

- **LET (linear energy transfer) is the average energy lost by radiation when traversing a small thickness of material.**
- **Two types (low-LET and high-LET) are considered.**
- **Examples of low-LET radiation are X-ray photons, gamma-ray photons, beta particles (energetic electrons), and protons.**
- **Examples of high-LET radiation are alpha particles, neutrons, and heavy ions (e.g., 10-MeV carbon ions from an accelerator).**

Individual Particle Tracks in Water



On average, ~ 30 reactive oxygen species (ROS) are produced per absorbed keV

Feinendegen L, IHS 2006

Some Typical Radiation Doses

- **Typical chest X-ray, 0.1 mGy (low-LET radiation).**
- **Average annual low-LET dose, worldwide, about 1 mGy.**
- **Annual DOE/NRC individual low-LET dose limit for public, 1 mGy (1 mSv for mixed low- and high-LET radiations).**
- **Annual EPA low-LET dose limit for releases to air, 0.1 mGy (0.1 mSv for mixed low- and high-LET radiations).**
- **Annual EPA low-LET dose limit for drinking water, 0.04 mGy (0.04 mSv for mixed low- and high-LET radiations)**

Unacknowledged problems with mSv dose concept discussed later.

Adverse Consequences of Exposure of Humans to Radiation

- **Low and high radiation doses can cause stochastic effects such as cancer and genetic effects.**
- **High doses and dose rates can cause life-threatening effects such as severe damage to organs as well as serious morbidity.**
- **Damage to DNA above the spontaneous level is largely responsible for most detrimental radiobiological effects.**

DNA Double Strand Breaks

- Considered most serious form of radiation-induced genomic damage.
- Are largely repaired via error-prone non-homologous end joining.
- May occasionally be repaired via less error-prone homologous recombination.
- Damage threshold appears to be required to activate double-strand-break repair pathways.
- Natural background radiation may be important for maintaining the damage threshold.
- Misrepair can lead to genomically unstable mutant and neoplastic transformed cells.

Does Low Dose Radiation Play and Important Role in Maintaining Life?

- **Natural background low-LET radiation probably does.**
- **How? Via activating adapted protection (hormesis)!**

Hormesis (Adapted Protection)

- **Survival of all organisms on Earth depends upon their ability to adapt to environmental and other stresses.**
- **Numerous genes evolved over time to mediate adaptive responses to both internal and external genotoxic stresses (e.g., genes involved in stabilization and in post-translational regulation of the p53 protein).**
- **Hormesis: low-dose-induced adapted protection; high-dose inhibition.**

Proteins Likely Involved in Radiation-Induced Adapted Protection

- **The tumor suppressor protein p53 and BAX.**
- **Stress-response proteins involved in transiently stabilizing p53.**
- **Proteins (e.g., ATM) involved in post-translational modifications of p53.**

Appella E and Anderson CW. Eur. J. Biochem. 268:2764-2772, FEBS 2001

Radiation Adaptive Response is and Evolutionary Conserved Response

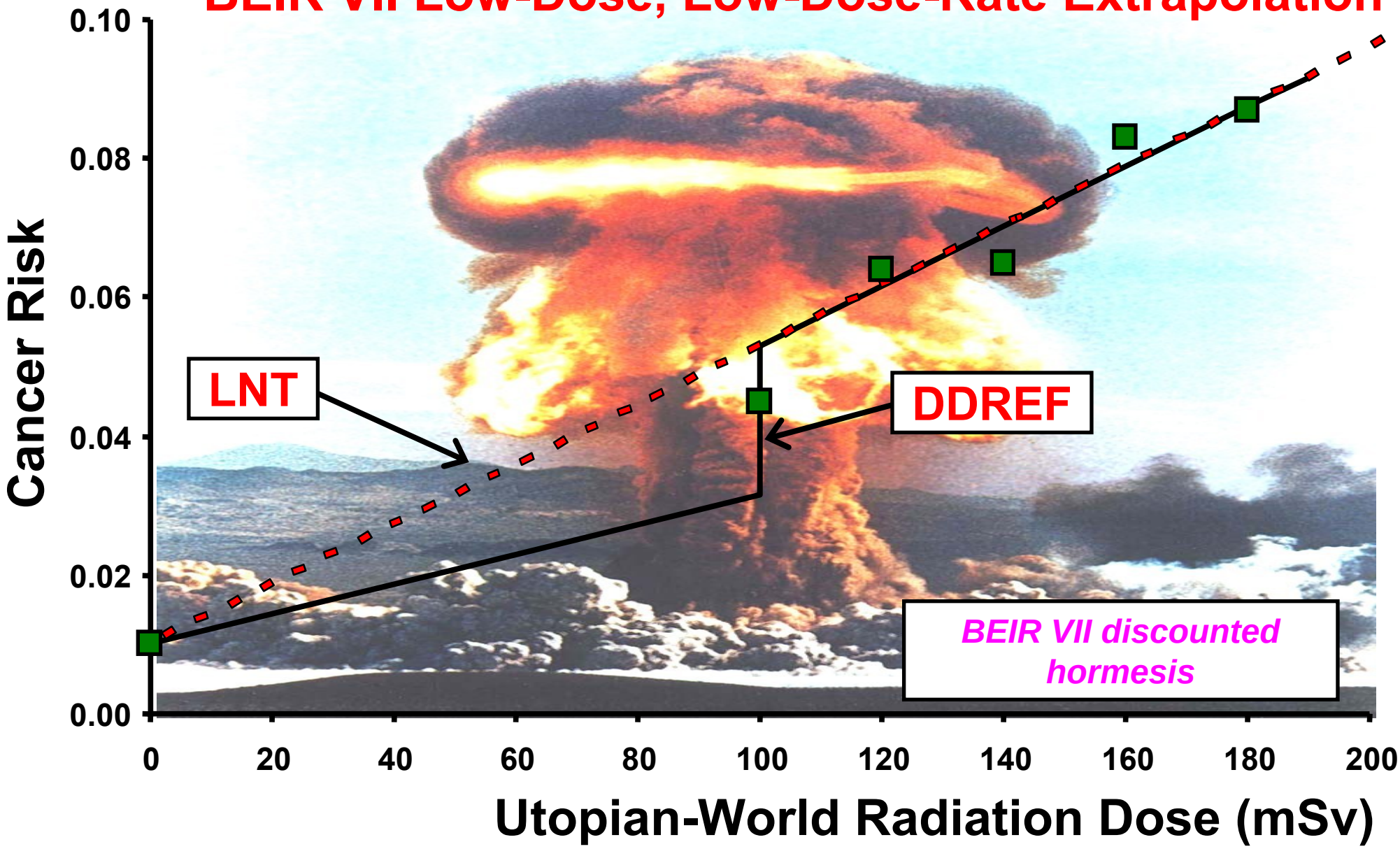
Occurs in:

- **Single cell organisms**
- **Insects**
- **Plants**
- **Lower vertebrates**
- **Mammalian cells**
- **Mammals including humans**

Mitchel REJ (2006 IHS Meeting presentation)

Current Radiation Risk Assessment Paradigm: Utopian-World LNT

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

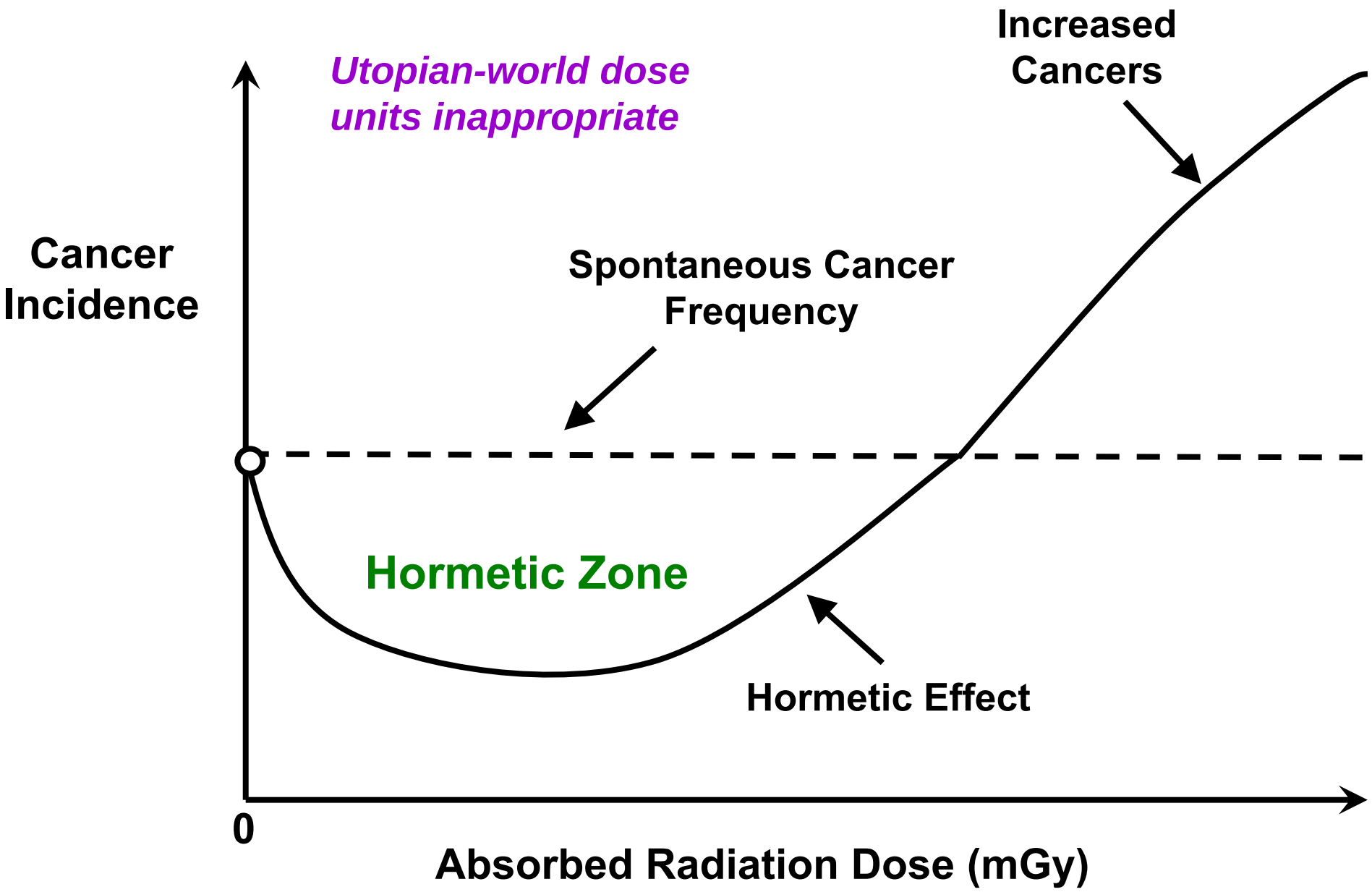


Utopian-World Dose Units

The following are fantasy-world dose units, based on hypothetical straight-line cancer risk vs. dose relationships, irrespective of the dose, type of radiation, or radiation combinations:

- **Sievert (Sv)**
- **mSv**
- **μSv**

Hormetic Risk (J-Shaped) Curve



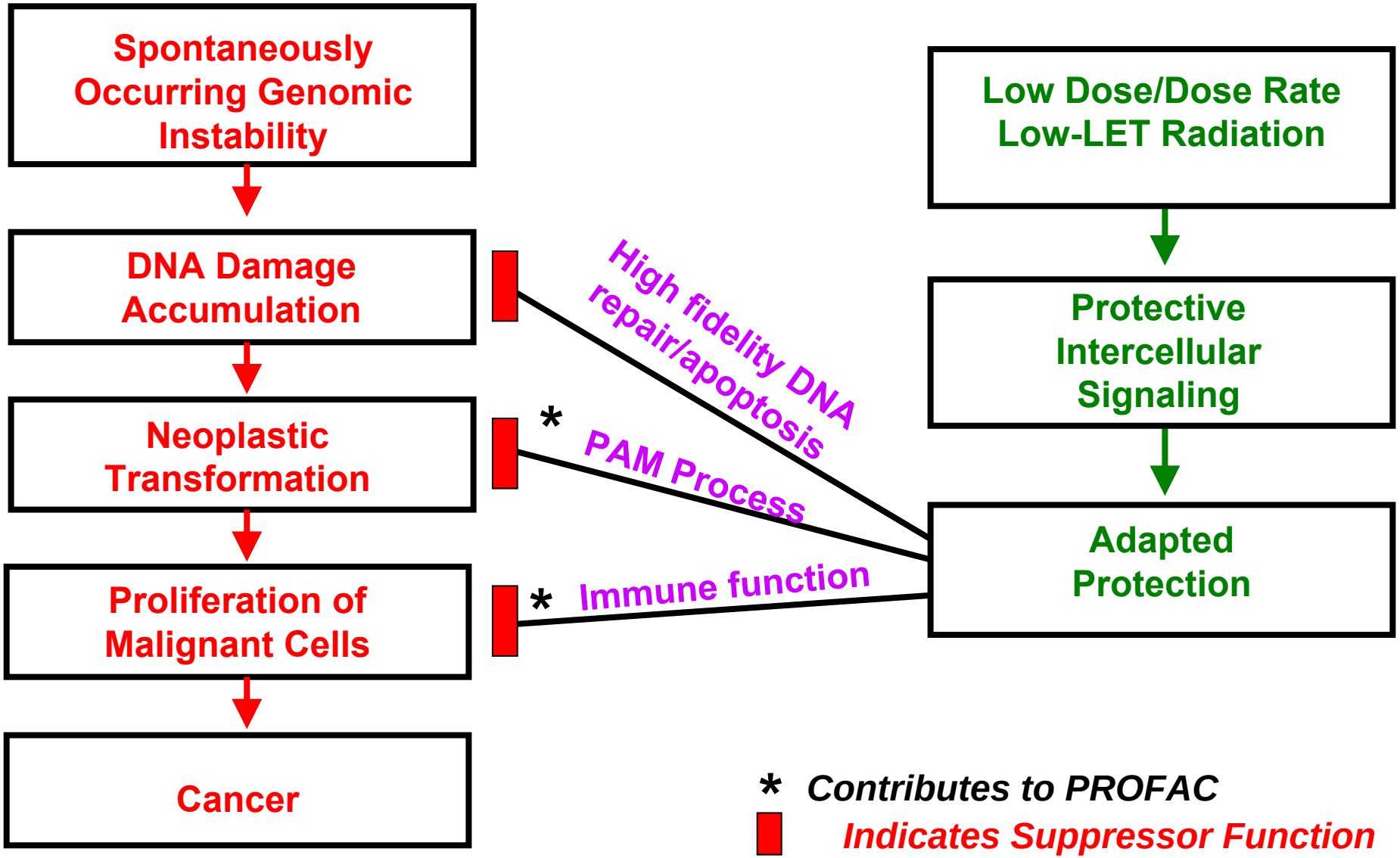
BEIR VII vs. French Academies on LNT and Radiation Hormesis

BEIR VII	French Academies
Selectively-chosen A-bomb cancer data was consistent with LNT	LNT should not be applied to low-LET doses < 100 mGy
Even natural background low-LET radiation harms	No evidence of harm from natural background radiation; may be beneficial
Radiation hormesis dismissed	Radiation hormesis not dismissed
Looked at basic research results and ignored	Considered implications of basic research results

Low Doses and Dose-Rates of Low-LET Radiation Protect Us From Harm: Hormesis

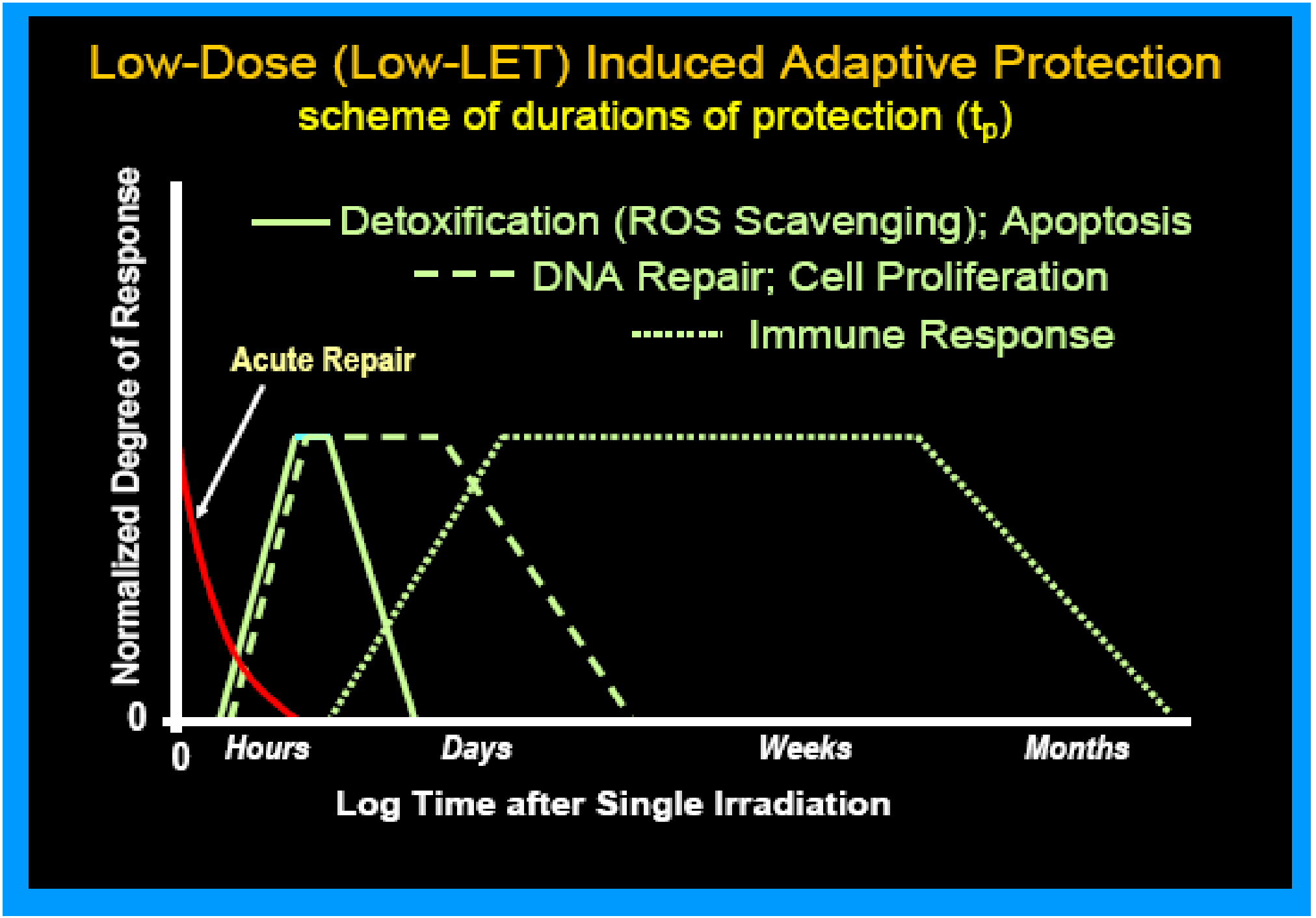
- Protect against chromosomal damage (Ed Azzam's group)!
- Protect against mutation induction (Pam Sykes' group), even when the low dose follows a large dose (Tanya Day's work)!
- Protect against neoplastic transformation (Les Redpath's group)!
- Protect against high dose chemical- and radiation-induced cancer (Kazou Sakai's group)!
- Stimulate increased immune system defense (Daila Gridley's group)!
- Suppress cancer induction by alpha radiation (Chuck Sanders group)!
- Suppress metastasis of existing cancer (Kiyohiko Sakamoto's group)!
- Extend tumor latent period (Ron Mitchel's group)!
- Protect against diseases other than cancer (Kazuo Sakai's group)!

Biological Basis for Hormetic Zone for Low-LET Radiation



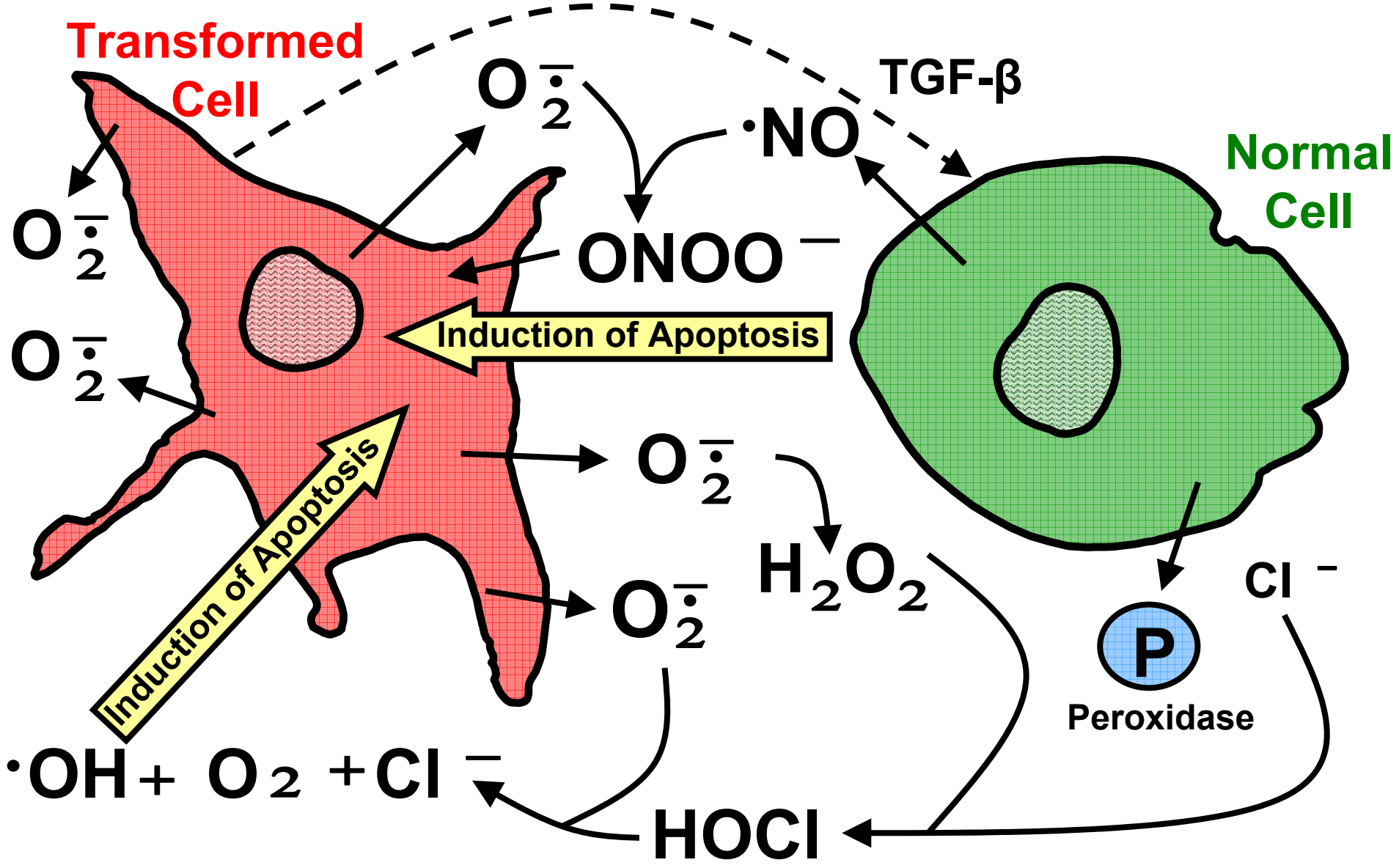
Scott 2006

ROS scavenging contributes to protection



Feinendegen L, IHS 2006

Protective Apoptosis Medicated (PAM) Process in Fibroblast: Protective Intercellular Signaling



G. Bauer. Histol. Histopathol. 11:237-255, 1996

PAM Process Signaling

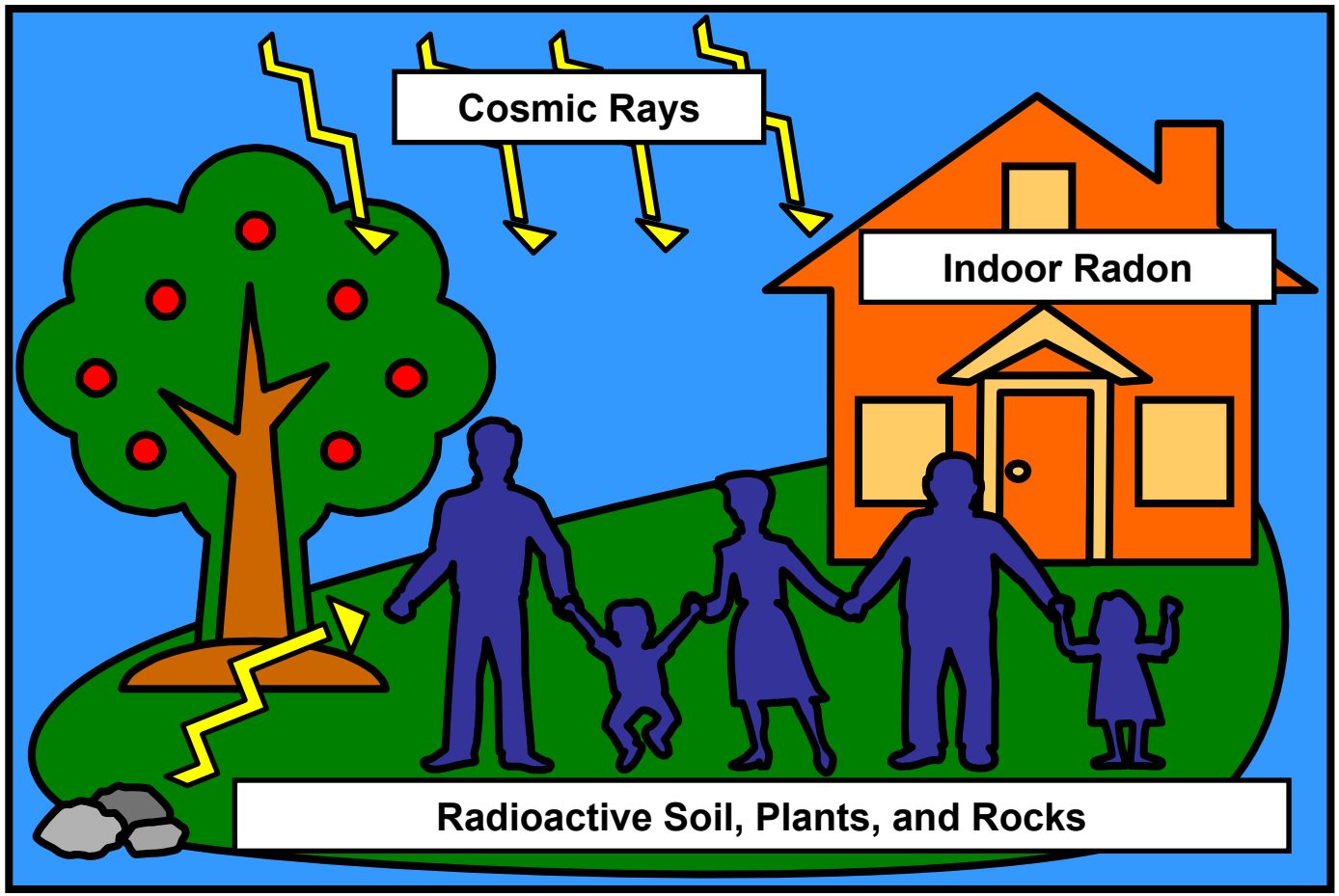
- Can eliminate genomically unstable cells caused by different agents.
- May vary for different stressing agent (e.g., ionizing radiation, UV radiation, chemical, etc.).
- May differ for different organs/tissue.
- Role of p53 protein (if any) not clear.
- TGF-β appears to play and important role.

Types of Radiation Hormesis

- Environmental radiation hormesis
- Medical radiation hormesis
- Therapeutic radiation hormesis
- Occupational-Exposure-Associated Radiation Hormesis

Environmental Radiation Hormesis

Natural and human-activity-related background radiation induced hormetic effects have been found to be associated with the suppression of spontaneous cancers and other diseases.



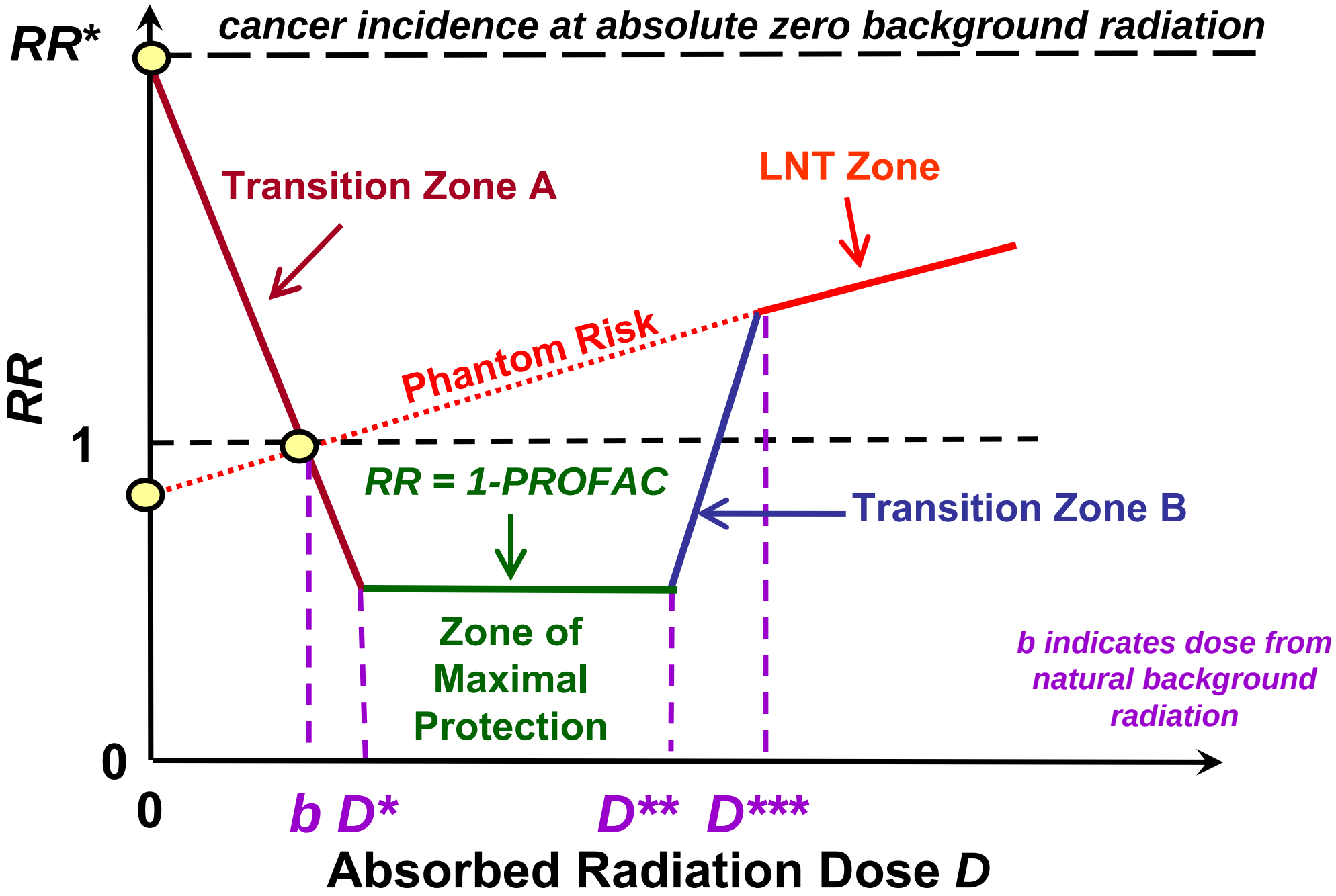
LRRI Cancer Hormetic Relative Risk (HRR) Model

- **Key Assumption:** cancer arises from cells with persistent genomic instability through a series of stochastic changes, independent of how the instability originate, but dependent on the number of cells with this instability in an organ.
- Cancer relative risk (*RR*) proportional to neoplastic transformation *RR*.
- Neoplastic transformation *RR* based on $NEOTRANS_3$ model developed at LRRI.
- Protective and deleterious stochastic dose thresholds cause hormetic dose-response curve shape.

Stochastic Thresholds

- Each of us has a different radiation threshold (organ specific) for activating protective processes.
- Each also has a different higher threshold for inhibiting some of the protection.
- Such thresholds are called stochastic thresholds (StoThresh) and are characterized by distributions rather than a fixed value for everyone.
- Uniform distributions are currently presumed for StoThresh.

LRRI Hormetic Relative Risk (HRR) Model



Some Expected Benefits of Radiation Doses in the Zone of Maximal Protection (Hormetic Zone)

- **Suppression of spontaneous and other cancers (i.e., *RR < 1*, *SMR < 1*).**
- **Suppression of cancer metastasis.**
- **Suppression of other genomic-instability associated diseases.**
- **Suppression of inflammation caused by other agents.**

PROFAC, A Measure of Hormetic Effects

- ***PROFAC*** **stands for protection factor.**
- **Mutation and neoplastic transformation *PROFAC*: fraction of mutant or transformed cells eliminated via hormesis (adapted protection).**
- **Cancer suppression *PROFAC*: fraction of cases that do not occur that would have occurred if it were not for induced hormesis.**

Protection Factors Against Cancer in Humans[1]

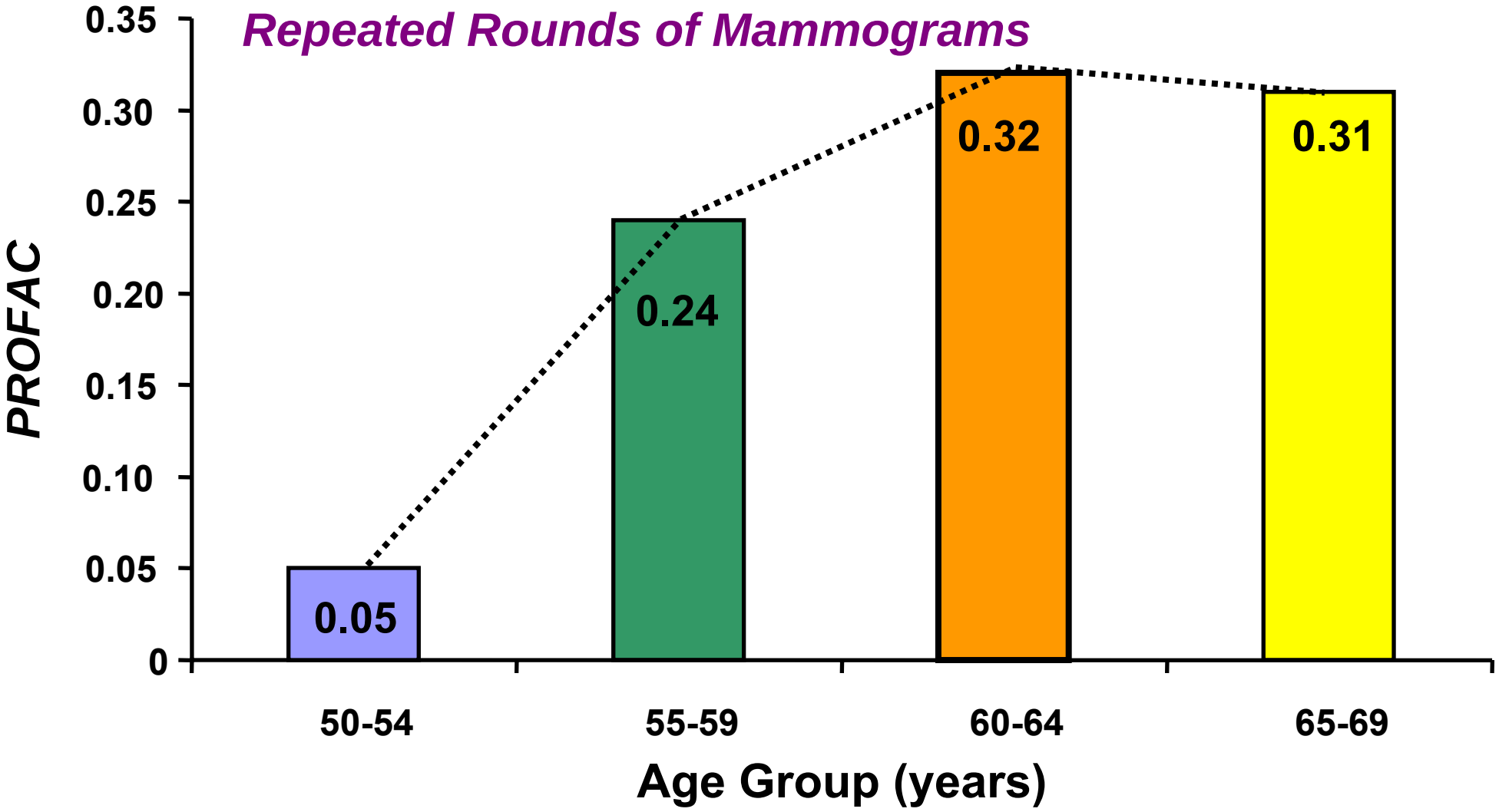
Region or Group	Effect	*PROFAC*
High residual radon, USA	all cancers	0.35
Canada, nuclear industry workers	Leukemia	0.68
US DOE labs workers	Leukemia	0.78
Mayak Plutonium facility workers	lung cancer	0.86[2]

Proportion of spontaneous and other cancers prevented!

[1] *Jaworowski Z. Symposium "Entwicklungen im Strahleschutz", Munich, 29 November 2001.*

[2] *Scott BR. Nonlinearity (in press), 2006a .*

Medical Radiation Hormesis: Breast Cancer Suppression by Diagnostic X-Rays



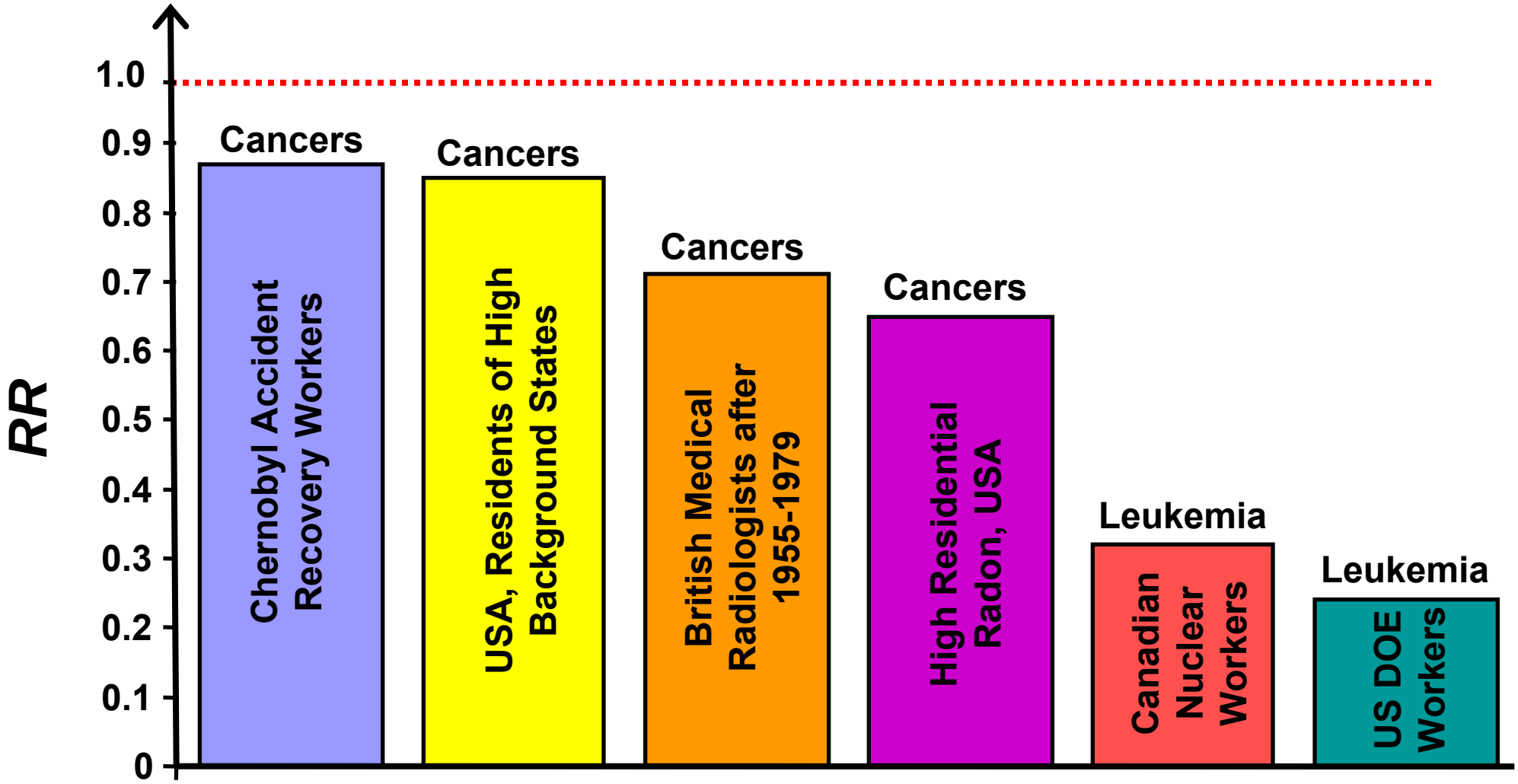
Based on data from Nyström et al. 2002

PROFACs for Nuclear Shipyard Workers Chronically Exposed to γ Rays

Cause of Death	SMR	*p* value	*PROFAC*
Allergic, endocrine, metabolic	0.69 ± 0.12	4.3×10^{-3}	0.31
All respiratory disease	0.62 ± 0.08	1.4×10^{-6}	0.38
Pneumonia	0.68 ± 0.04	2.4×10^{-14}	0.32
Emphysema	0.63 ± 0.26	7.2×10^{-2}	0.38
Asthma	0.30 ± 0.43	5.1×10^{-2}	0.70
All infectious & parasitic	0.86 ± 0.72	4.2×10^{-1}	0.14
Total mortality	0.78 ± 0.04	0.00	0.22

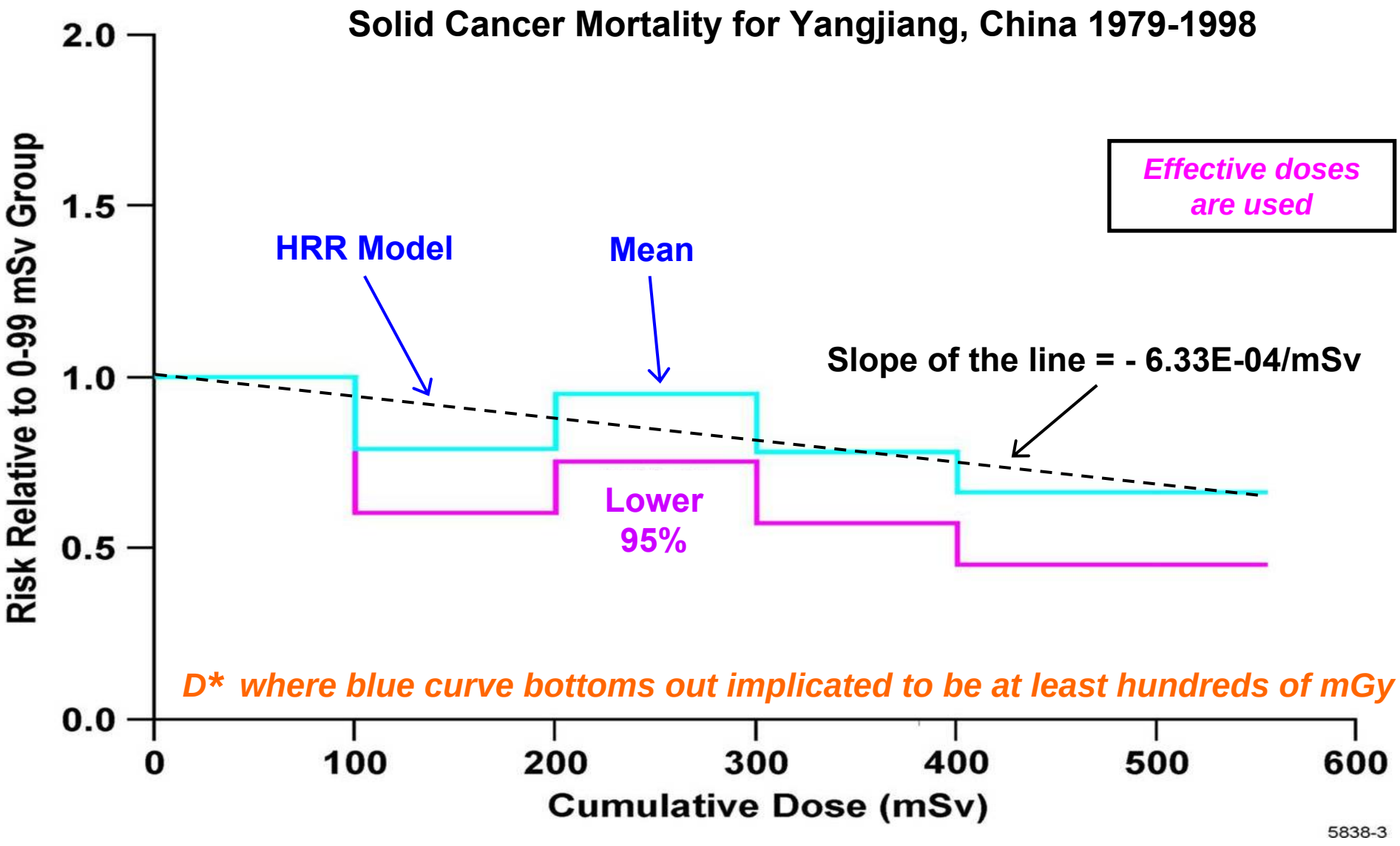
Sponsler R and Cameron JR. Int. J. Low Radiat. 1(4):463-478, 2005.

Cancer Relative Risk In Hormetic Zone: Irradiated Human Populations



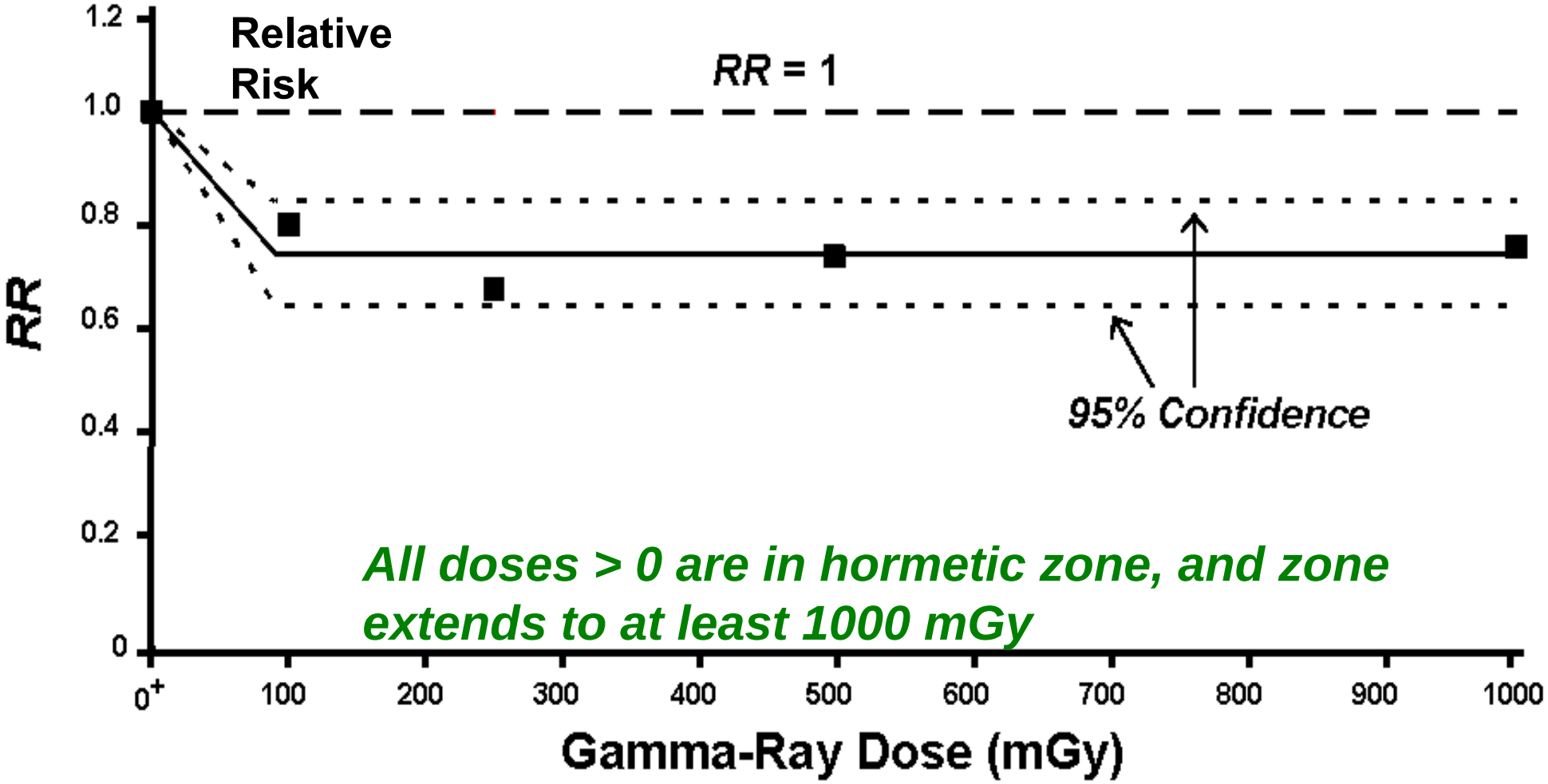
RR< 0.85 cannot be due to healthy worker effect (Sponsler and Cameron, 2005)

Environmental Radiation Hormesis



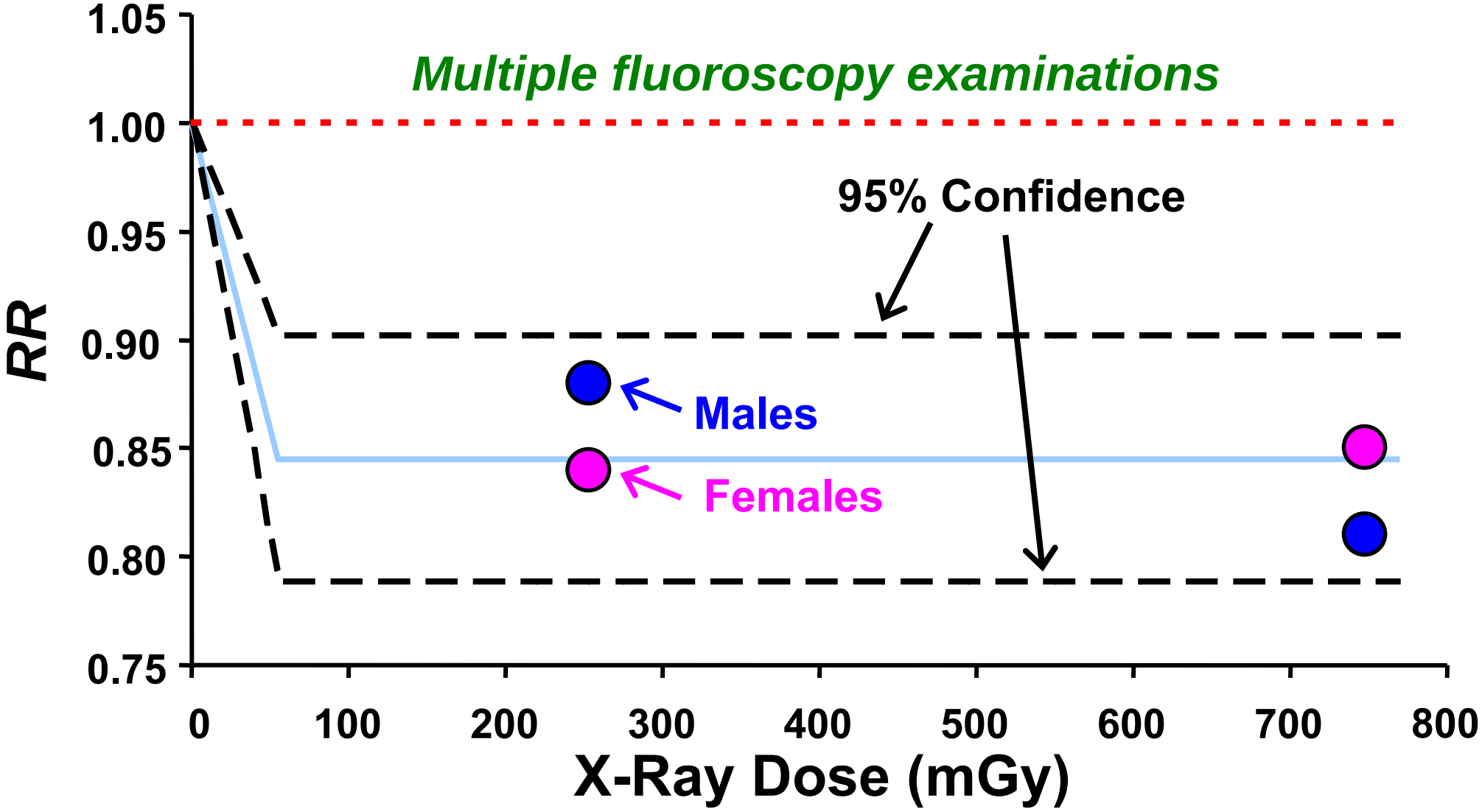
Wei and Sugahara. Int. Congress Series 1236:91-99 (2002)

Lung Cancer in Mice with High Spontaneous Frequency



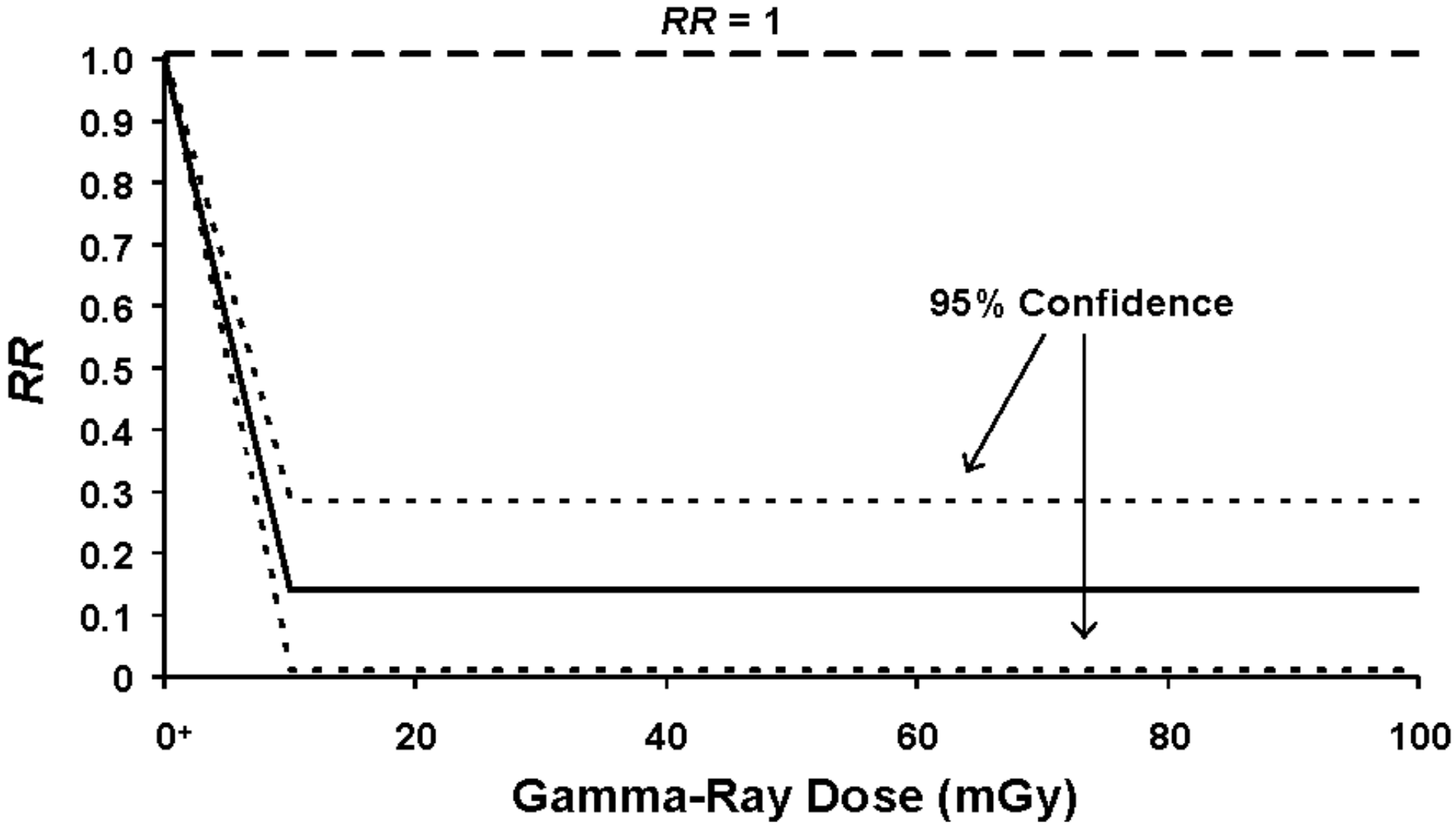
Study involved more than 15,000 mice (R. Ulrich et al., 1976). Curve shape currently thought to be representative of adult humans with significant spontaneous genomic instability burdens.

Lung Cancer in Adult Humans Presumed to Have High Spontaneous Genomic Instability Burdens



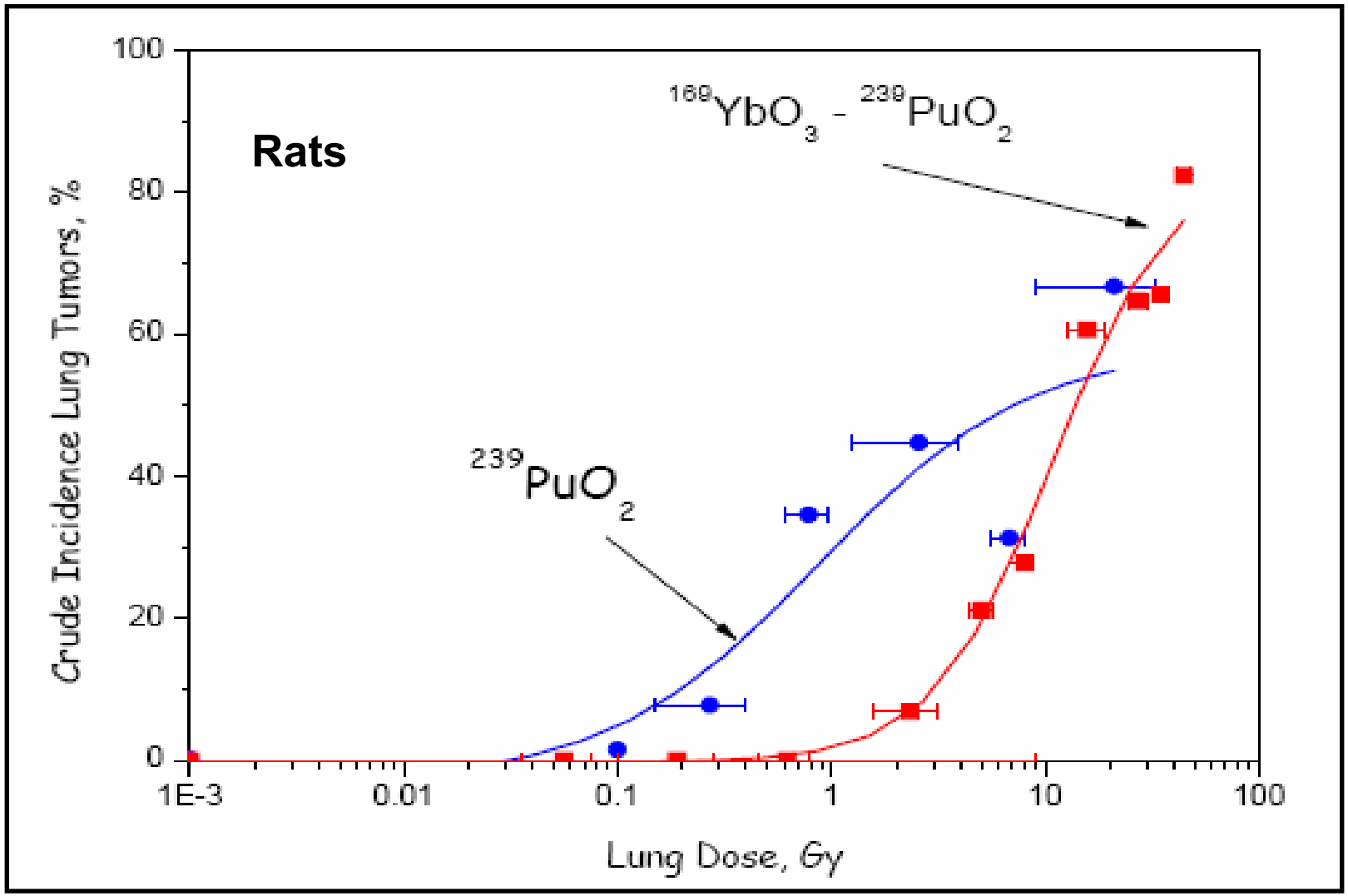
Data from GR Howe. Radiat. Res. 142:295-304,1995. ***Similar findings have been reported for breast cancer (Miller. N. Engl. J. Med. 321:1285-1289, 1989)***

Suppression of Spontaneous Lung Cancer in Mayak Plutonium Facility Workers



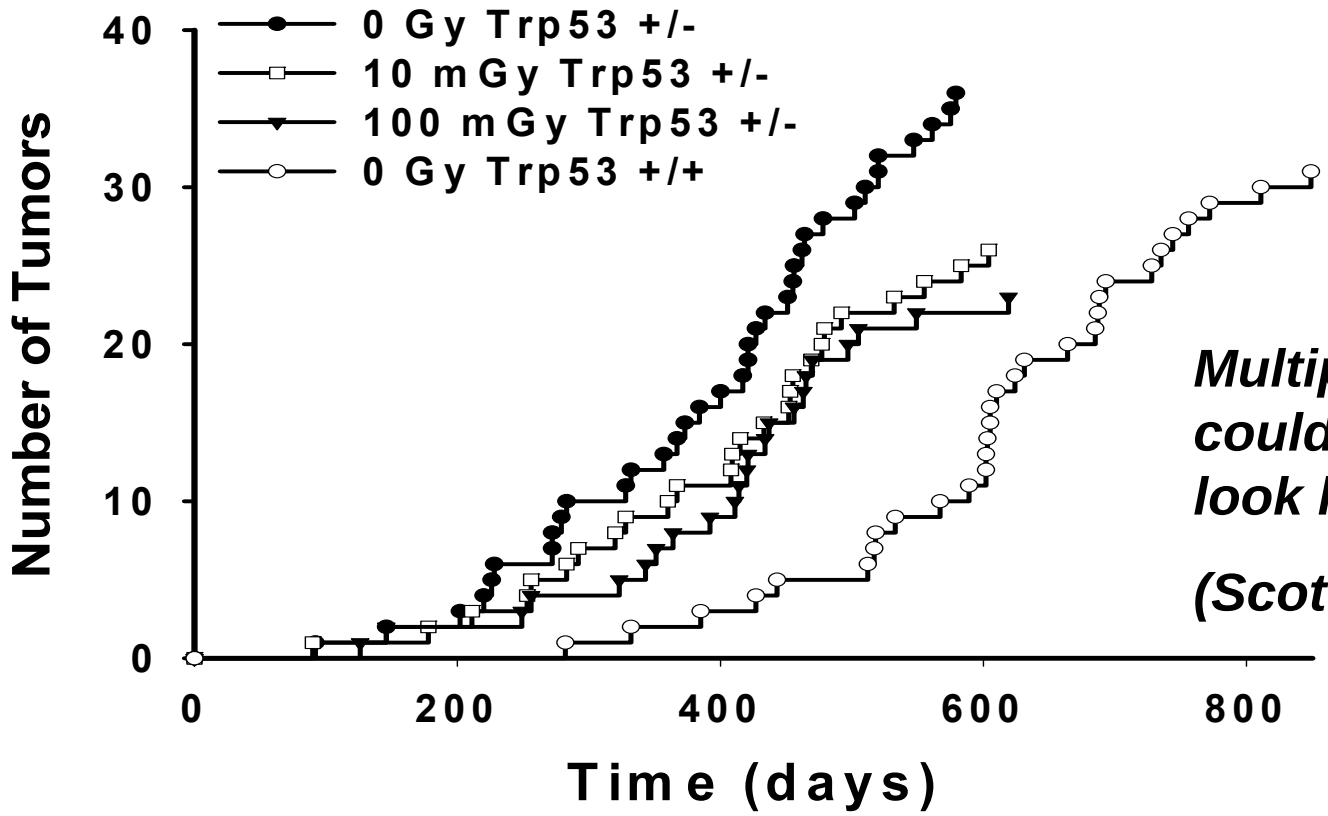
Data corrected for influence of alpha radiation (B. Scott, 2006).

Low-Dose-Rate Gamma Rays Protect from Alpha-Radiation-Induced Lung Cancer



C. L. Sanders, International Hormesis Conference, 2006

Low-Dose Gamma Rays Protected Trp53 Heterozygous Mice from Lymphomas

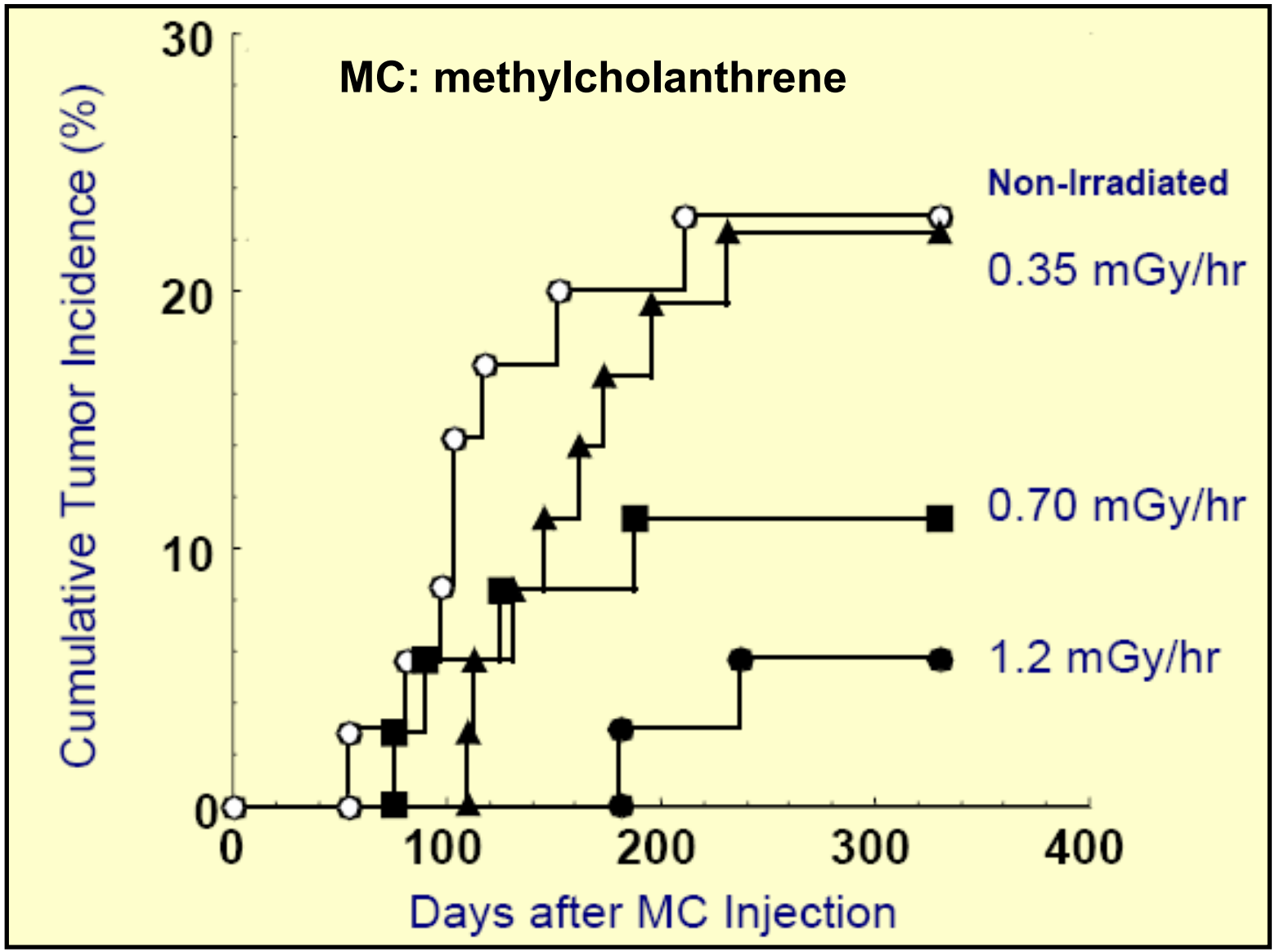


Multiple low doses could make Trp53 +/- look like Trp53 +/+

(Scott, 2006)

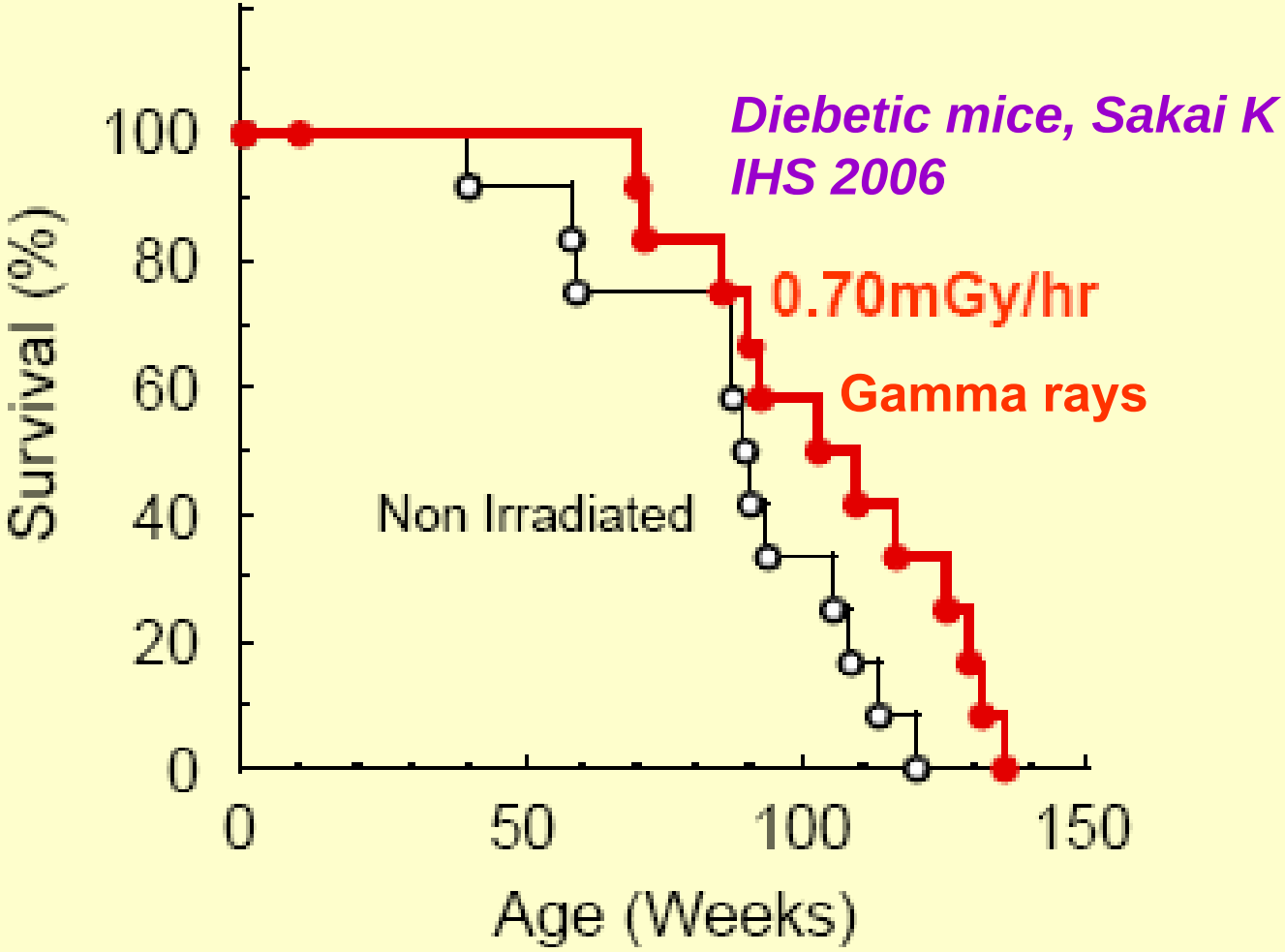
Mitchel et al. (2003); *low-dose gamma rays increased latency*

Low Rate Gamma Irradiation Suppressed MC-Induced Skin Tumors in Mice



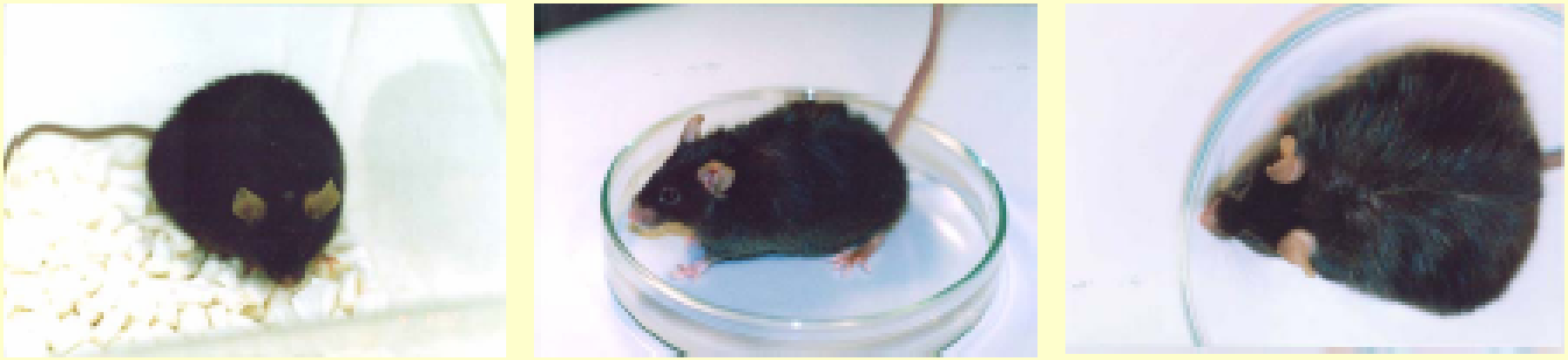
K. Sakai, International Hormesis Conference 2005

Prolongation of Life Span of db/db Mice by Low Dose Rate Irradiation

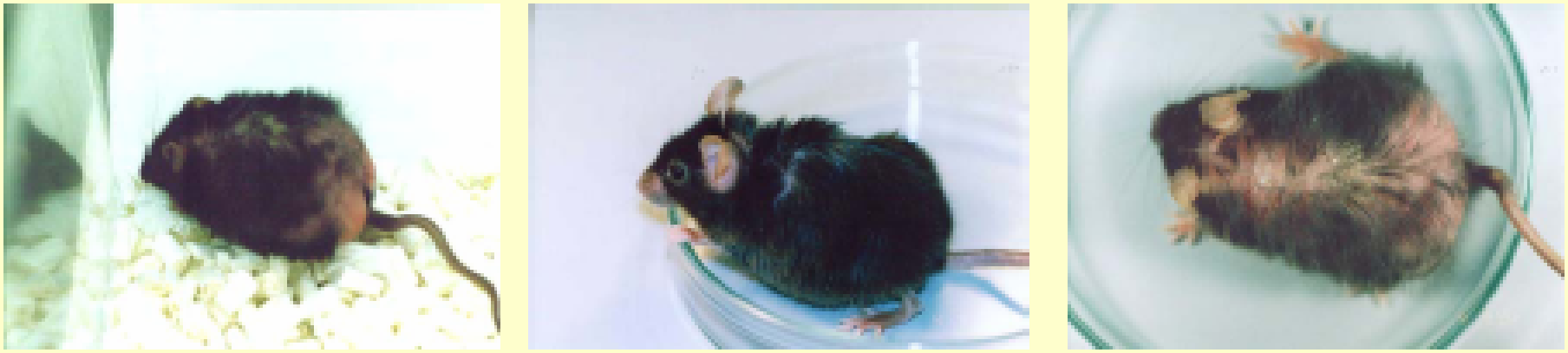


Appearance of *db/db* Mice at 90 Weeks of Age

Irradiated



Non-Irradiated



Sakai K, IHS 2006

Therapeutic Radiation Hormesis

- Cancer cells are resistant to undergoing apoptosis.
- New research is demonstrating ways of sensitizing cancer cells to undergo apoptosis (e.g., resveratrol).
- Applying low-dose, low-LET radiation (in the hormetic zone) alone or in combination with apoptosis sensitizing agents that target tumor cells can lead to curing cancer.
- Adding multiple small doses of antiangiogenic drugs may enhance efficacy of treatment.

Resveratrol

- **Trans-3,5,4'-trihydroxystilbene (resveratrol) is found in grapes, berries, peanuts, and other plants.**
- **Resvertrol sensitizes cancer cells to undergoing apoptosis and suppresses proliferation of a wide variety of tumor cells (e.g., lymphoid and myeloid cancers; multiple myeloma; cancers of the breast, prostate, stomach, colon, pancreas, and thyroid)**

Aggarwal BB et al. (Anticancer Res. 24, 2004)

Conclusions

- **The LNT risk assessment paradigm is appropriate (for accurate risk assessment) only for a utopian world!**
- **Dose units such as Sv, mSv, and μSv belong in the indicated utopian world, not in our world! Their useful life for our world has expired.**
- **Radiation hormesis (adapted protection) is real and has a biological basis for effects such cancer.**
- **Natural background low-LET radiation protects us from cancer and other diseases via induced adapted protection. Doses just above background provide added protection.**
- **The gamma-ray component of radon exposure in our homes is likely protecting us from cancer and other genomic-instability-associated diseases.**

Conclusions (continued)

- **Lung cancer in heavy smokers might be prevented via regular diagnostic chest X rays (low doses) to repeatedly activate transient adapted protection.**
- **The level of adapted protection is expected to increase as the number of genomically unstable cells in the body increase.**
- **The level of adapted protection appears to increase with age and children may not benefit from such protection except in circumstances where they possess significant numbers of genomically unstable cells.**
- **Combined low-dose radiation + drug (apoptosis sensitizing; antiangiogenic) therapy for cancer may save many lives while avoiding severe side effects. Multiple small doses would be applied at appropriate intervals.**

Future Research

- New AFOSR grant expected to be prepared: relates to protecting military personnel from cancer induction after exposure to high-dose radiation or genotoxic chemicals.
- Planned NCI follow-on grant: cancer prevention research in soon-to-come new program.
- Hope to venture into low-dose cancer therapy research in near future.

Recent LRRI Presentations on our Website (www.radiation-scott.org)

- ***Stochastic thresholds and nonlinearity*** **(IHS 2005 Plenary).**
- ***The LNT hypothesis may have outlived it usefulness for low-LET radiation*** **(PSA/ANS 05 Plenary; LANL 2005).**
- ***Hormesis implications for managing radiological terrorism events*** **(NIAID 2006; Rio Grande Chapter HPS 2006).**
- ***Medical and therapeutic radiation hormesis: Preventing and curing cancer*** **(IHS 2006).**
- ***Expected benefits from diagnostic imaging radiation: Suppression of cancer*** **(Diagnostic Imaging Conference, 2006)[*to be added*].**
- ***A cancer prevention perspective to radiation risk assessment*** **(NCI Radiation Carcinogenesis Workshop, 2006)[*to be added*].**
- ***Low-dose/dose rate low-LET radiation protects us from cancer*** **(DOE Low Dose Program Workshop, 2006).**

Upcoming Publications that May be of Interest to the General Public

- **Scott BR. Natural Background Radiation-Induced Apoptosis and the Maintenance of Mammalian Life on Earth. Chapter I in: *New Cell Apoptosis Research*, L. C. Vinter (Editor), Nova Science Publishers, Inc.**
- **Scott BR. Radiation Hormesis and the Control of Genomic Instability. Chapter VI in: *New Research on Genomic Instability*, Eleanor Glascow (Editor), Nova Science Publishers, Inc.**
- **Raloff J (Senior Editor). Science News articles on hormesis which will feature some our work.**

Collaborators and Student Participants

- **Scientists:** Pam Sykes, Tanya Day, Les Redpath, Chuck Sanders, Zoya Tokarskaya, Galina Zhuntova, Ed Calabrese, Others
- **Students:** Jenni Di Palma, Munima Haque

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