It's Time for a New Low-Dose Radiation Risk Assessment Paradigm – One That Acknowledges Hormesis

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Contents

- Evidence for low-LET radiation-induced adapted protection (hormesis)
- Epidemiological tricks that hide hormetic effects and promote LNT
- Novel hormetic relative risk model
- Hormesis implications for low-dose-radiation risk assessment
- A way to account for hormesis in regulating radiation exposure

Different Classifications of Radiation-Related Hormesis (Calabrese *et al.* 2007)

- **Radiation conditioning hormesis**
- **Radiation hormesis**
- **Radiation post-exposure conditioning hormesis**

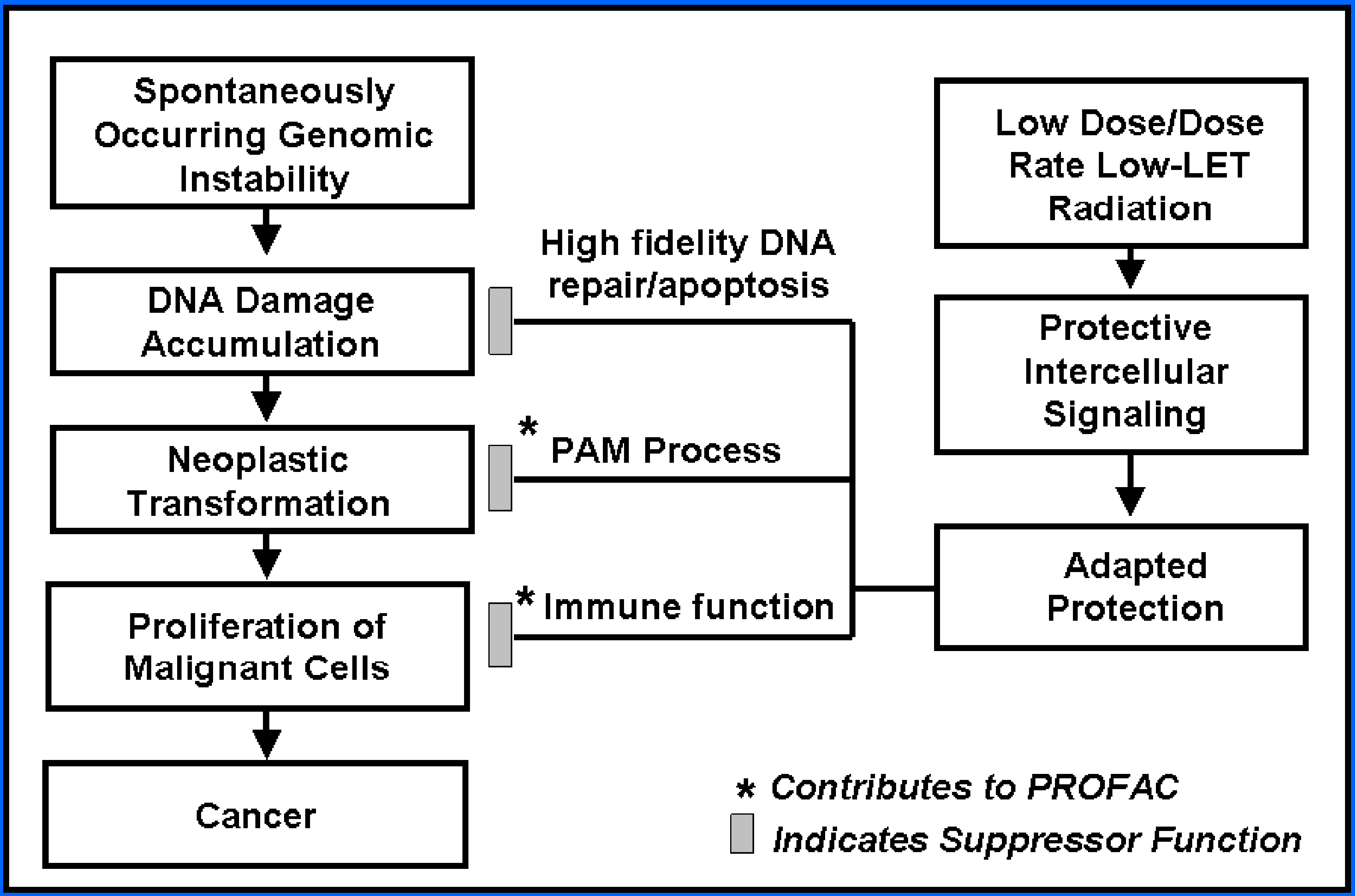
Low Doses/Rates of Low-LET Radiation Protect Us From Harm: Hormesis

- Activate protective genes (Brenda Rogers's group)
- Protect against chromosomal damage (Ed Azzam's and Noy Rithidech's groups).
- Protect against mutation induction (Pam Sykes's group), even when the low dose follows a large dose (Tanya Day's work).
- Protect against neoplastic transformation (Les Redpath's and Ed Azzam's groups).
- Protect against high dose chemical- and radiation-induced cancer (Kazou Sakai's group).

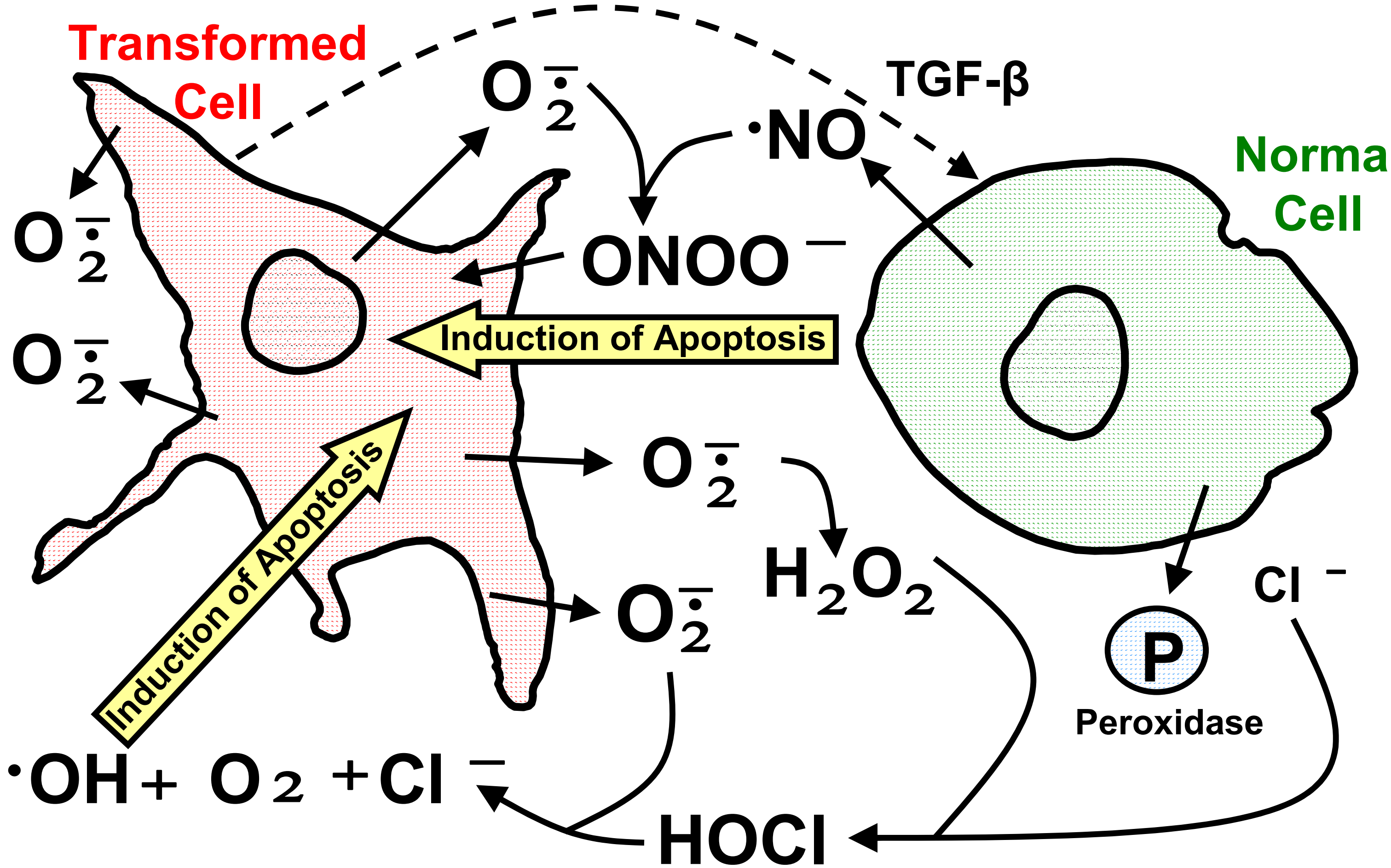
Low Doses/Rates Protect (continued)

- Stimulate increased immune system defense (Shu-Zheng Liu's and Brenda Laster's groups).
- Suppress cancer induction by alpha radiation (Chuck Sanders's 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).

Radiation-Hormesis-Associated Protection

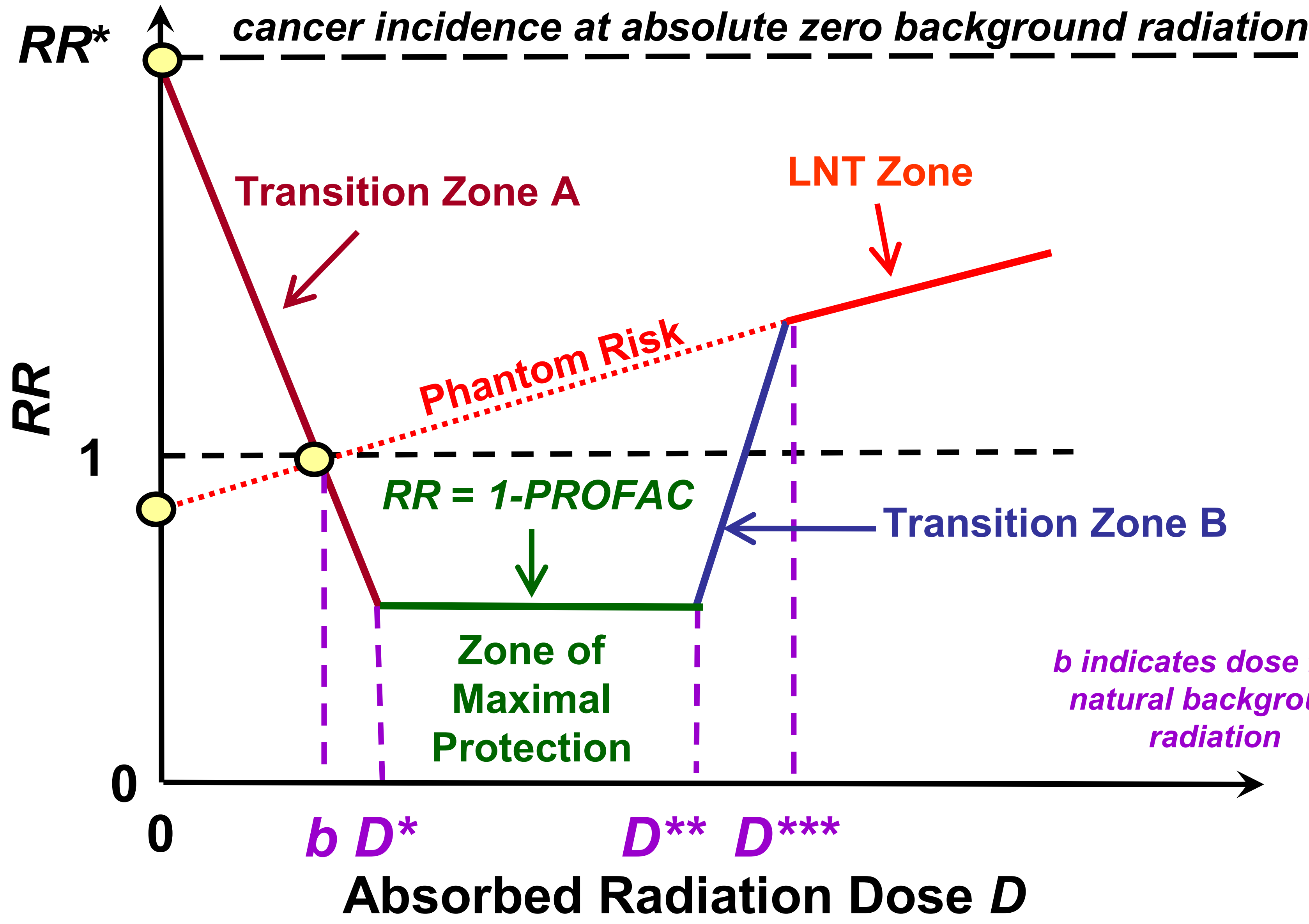


Protective Apoptosis-Medicated (PAM) Process in Fibroblast: Protective Intercellular Signaling



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

Hormetic Relative Risk (HRR) Model

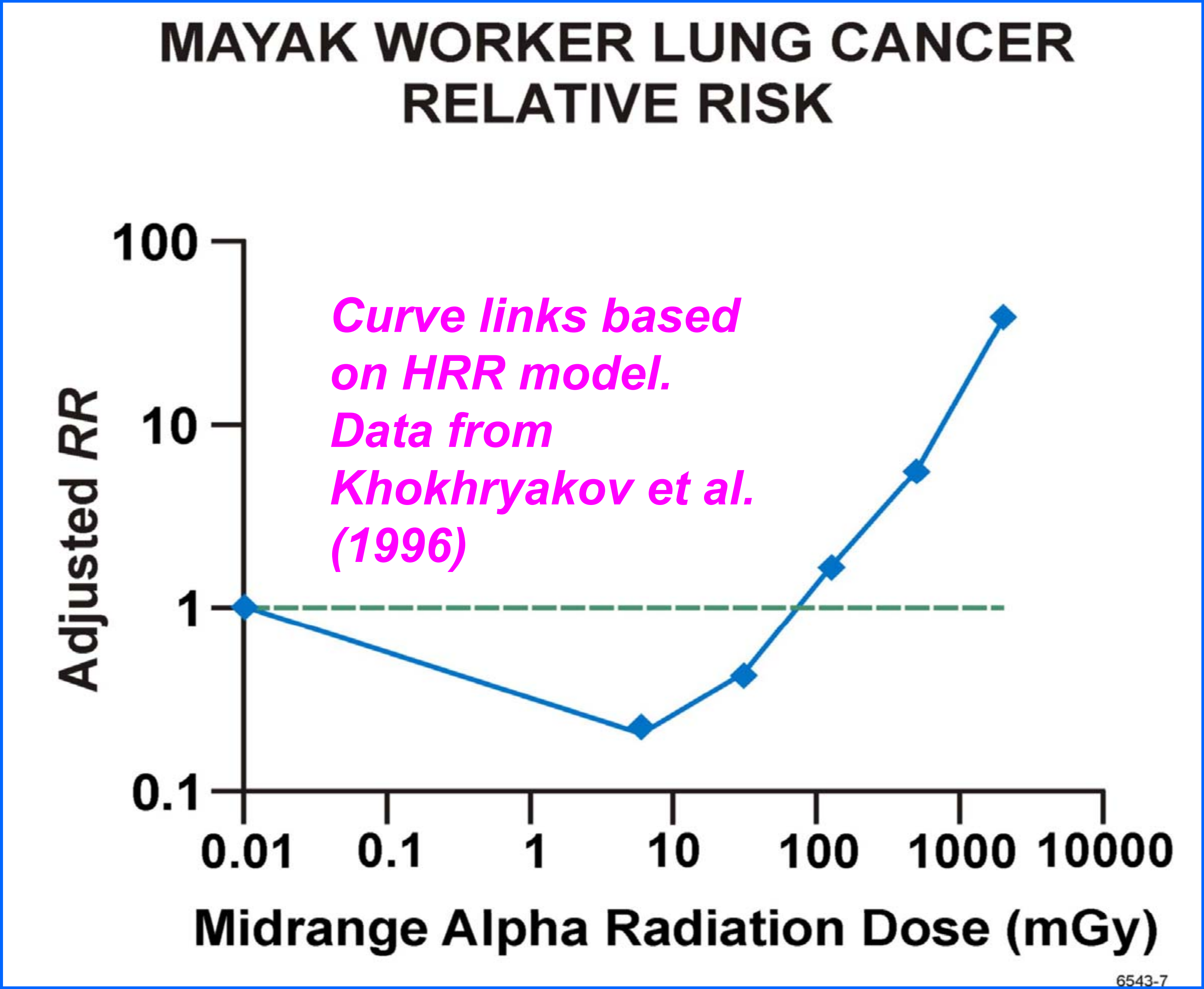


Protective and Deleterious Stochastic Thresholds

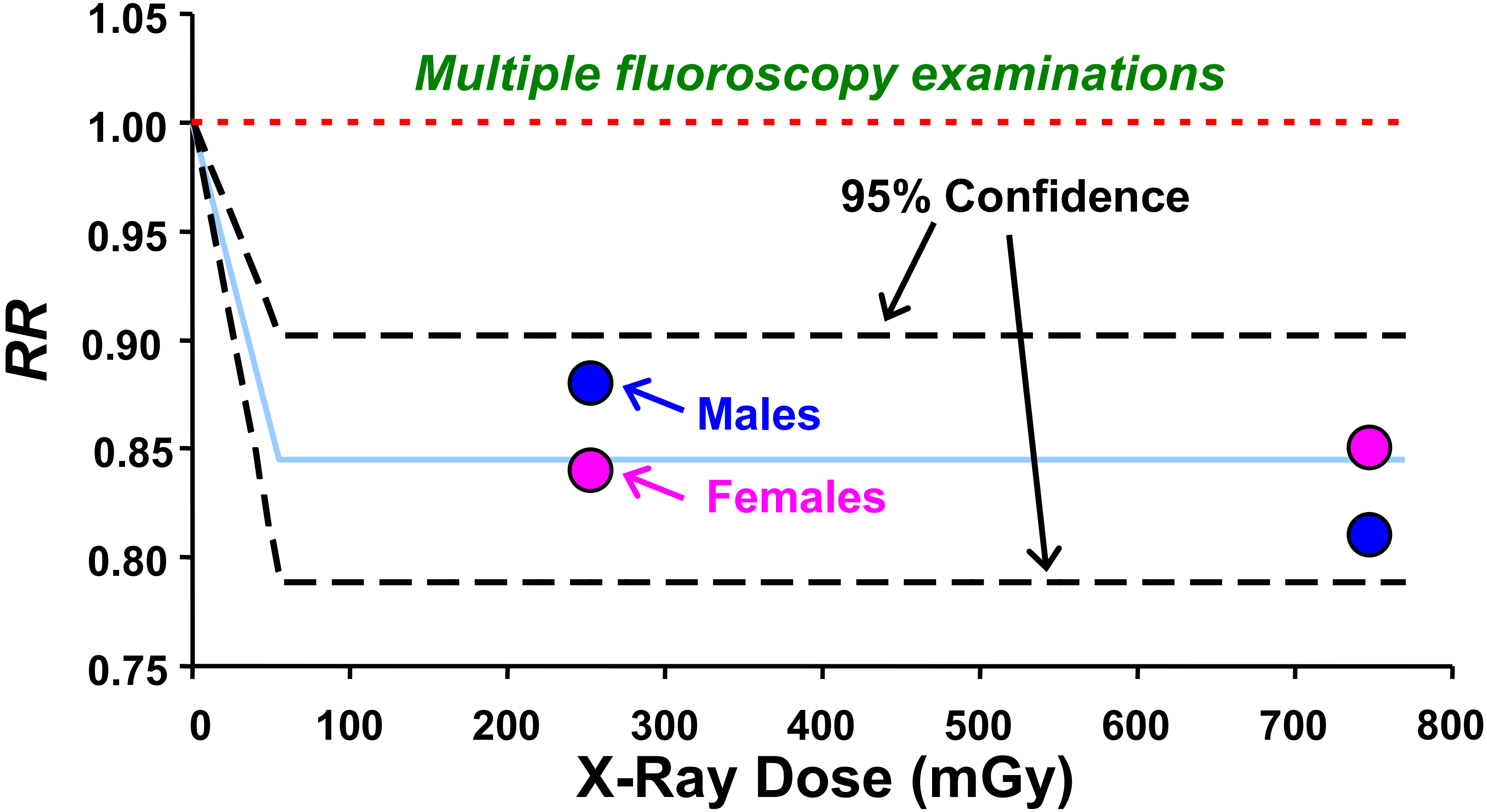
- **Protective stochastic thresholds occur in Transition Zone A.**
- **Deleterious stochastic thresholds occur in Transition Zone B.**
- **These thresholds are influences by dose rate, microdose distribution, genetic susceptibility/resistance.**

Genetic Influences on Radiation Sensitivity/Resistance

- Genetic polymorphisms in genes involved in DNA-repair pathways.
- Genetic polymorphisms in genes that regulate cell-cycle checkpoints.
- Genetic polymorphisms in apoptosis-related genes.
- Genetic polymorphisms in genes that are involved in regulating the immune system.

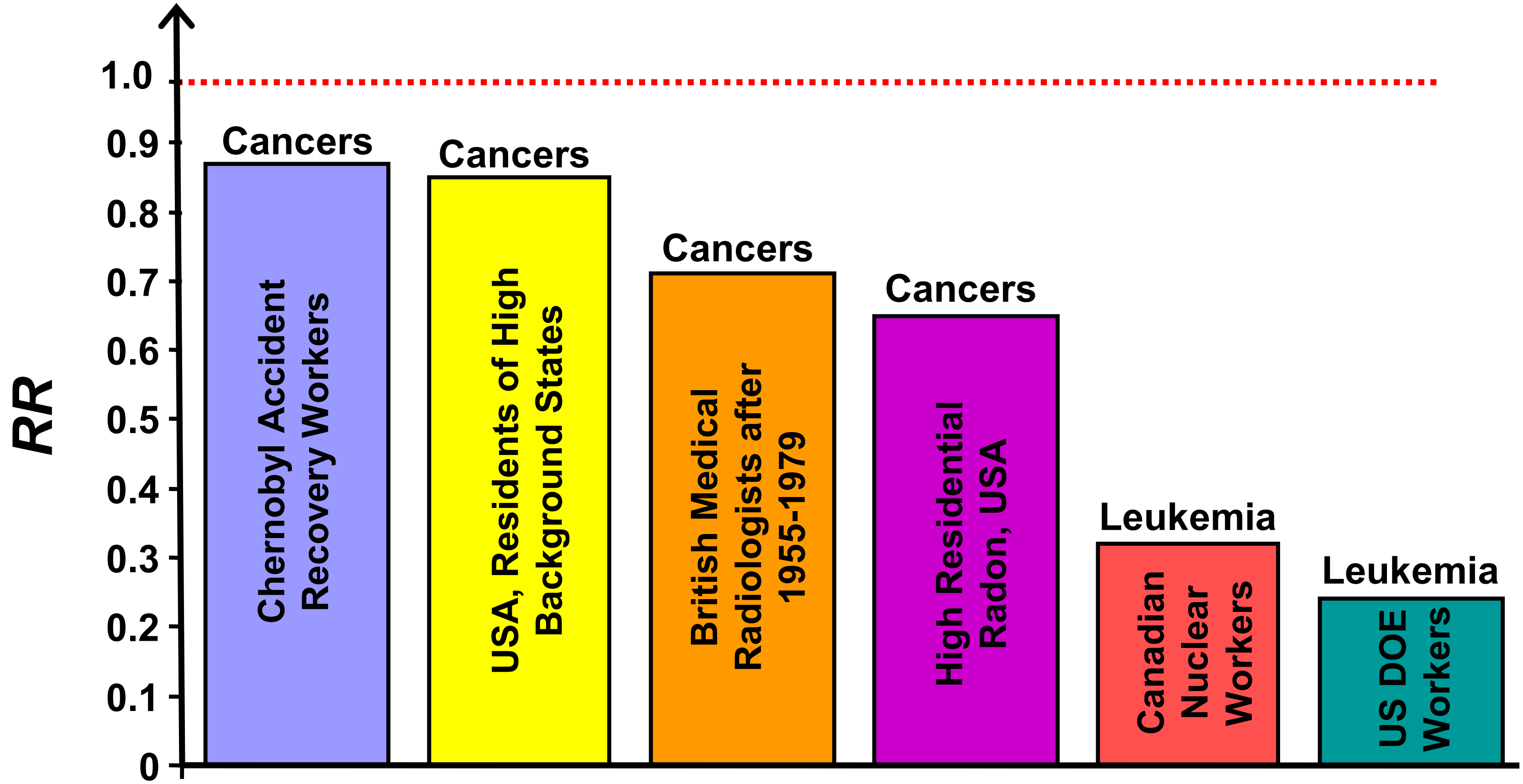

MAYAK WORKER LUNG CANCER
RELATIVE RISK
100
10
1
0.1
Adjusted RR
Curve links based
on HRR model.
Data from
Khokhryakov et al.
(1996)
0.01
0.1
1
10
100
1000
10000
Midrange Alpha Radiation Dose (mGy)
6543-7

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



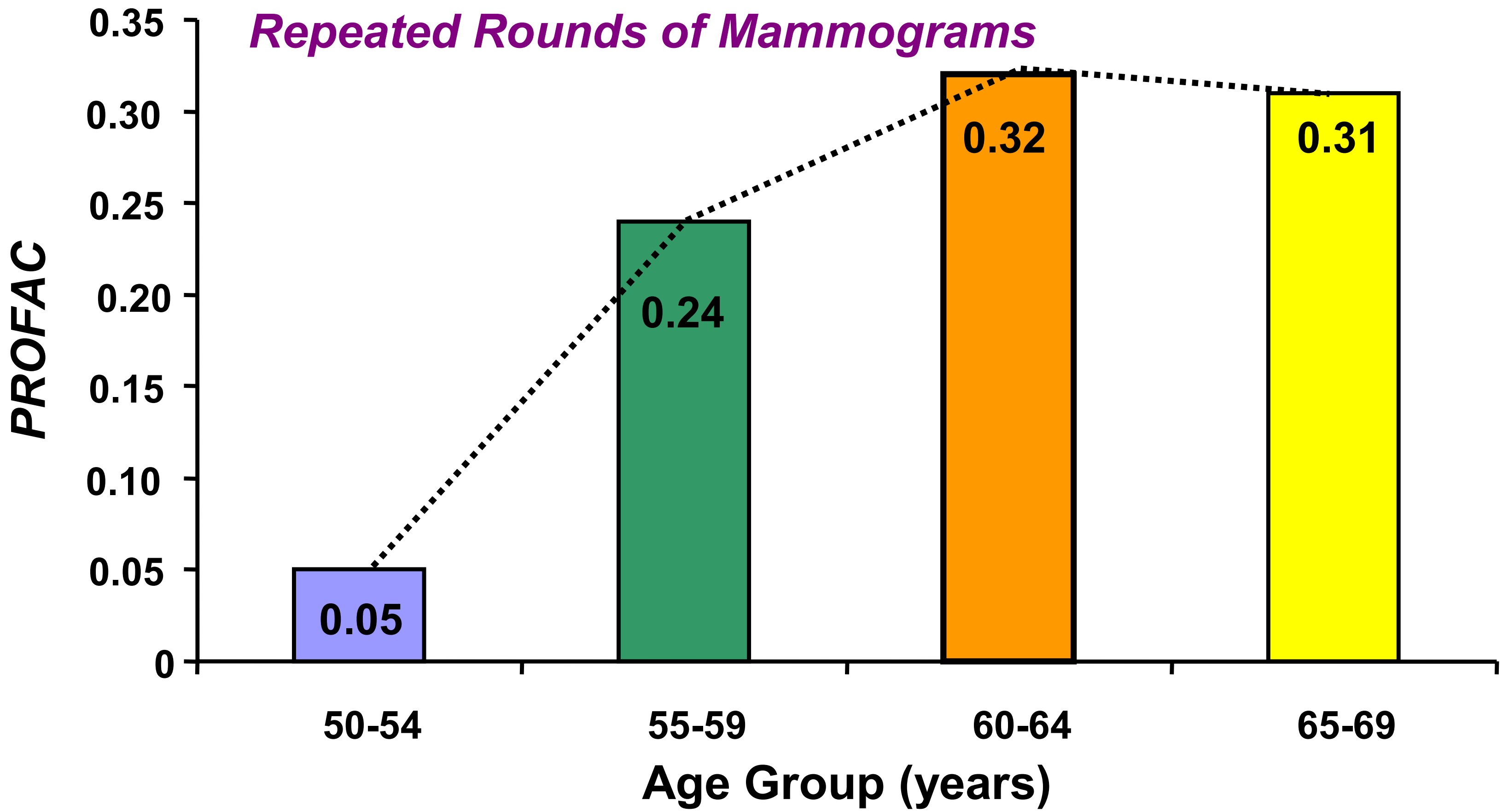
Data from GR Howe. Radiat. Res. 142:295-304,1995. Similar findings have been reported for breast cancer (Miller. N. Engl. J. Med. 321:1285-1289, 1989)

Cancer Relative Risk In Hormetic Zone: Irradiated Human Populations



Scott and Di Palma. Dose-Response (2007, in press).

Proportion of Breast Cancer Cases Avoided Due to Radiation Hormesis



Based on data from Nyström et al. 2002

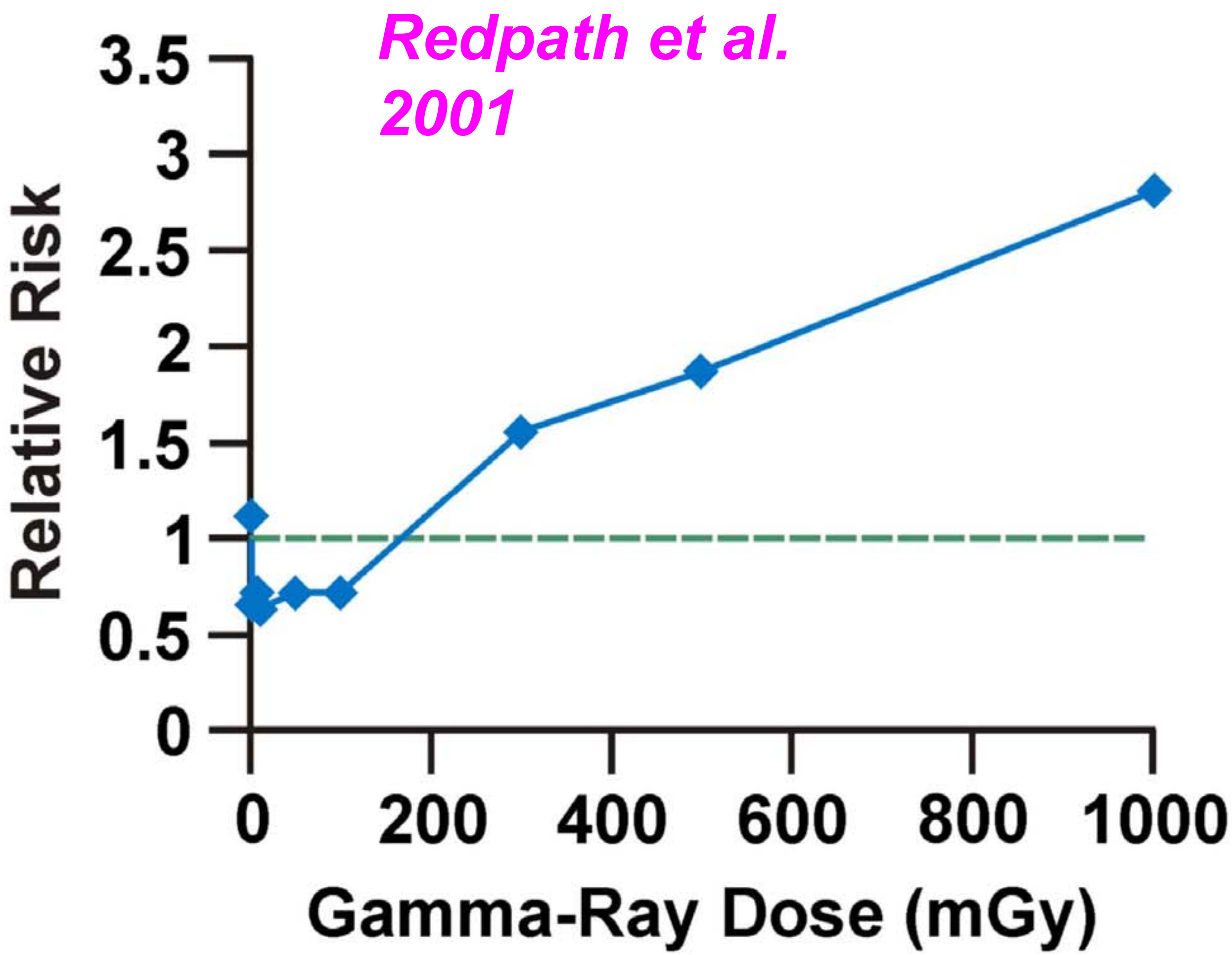
Epidemiological Tricks That Favor The LNT Pattern

- **Throwing away dose (dose lagging), effectively removing thresholds (e.g., in cohort and case-control studies).**
- **Averaging of odds over wide dose intervals (e.g., in case-control studies) when evaluating odds ratio (*OR*).**
- **Forcing the dose-response curve to have a positive slope.**

Examples of the Indicated Tricks

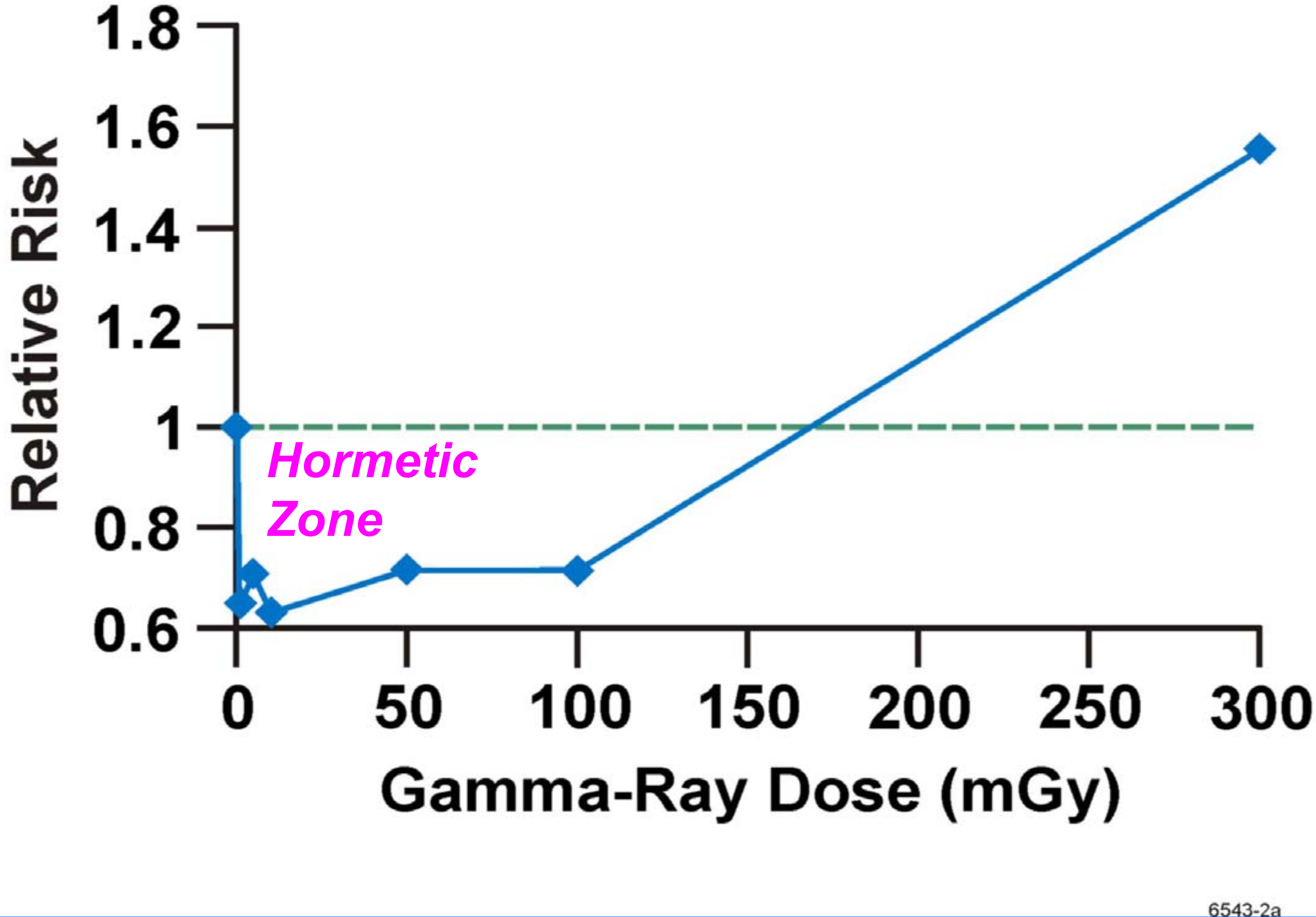
- **Will use data for *in vitro* neoplastic transformation.**
- **Neoplastic transformation dose-response curves have similar shapes as do cancer induction dose-response curves (Redpath *et al.* 2001).**

HORMETIC DOSE-RESPONSE FOR NEOPLASTIC TRANSFORMATION OF HeLa x SKIN FIBROBLAST HYBRID CELLS

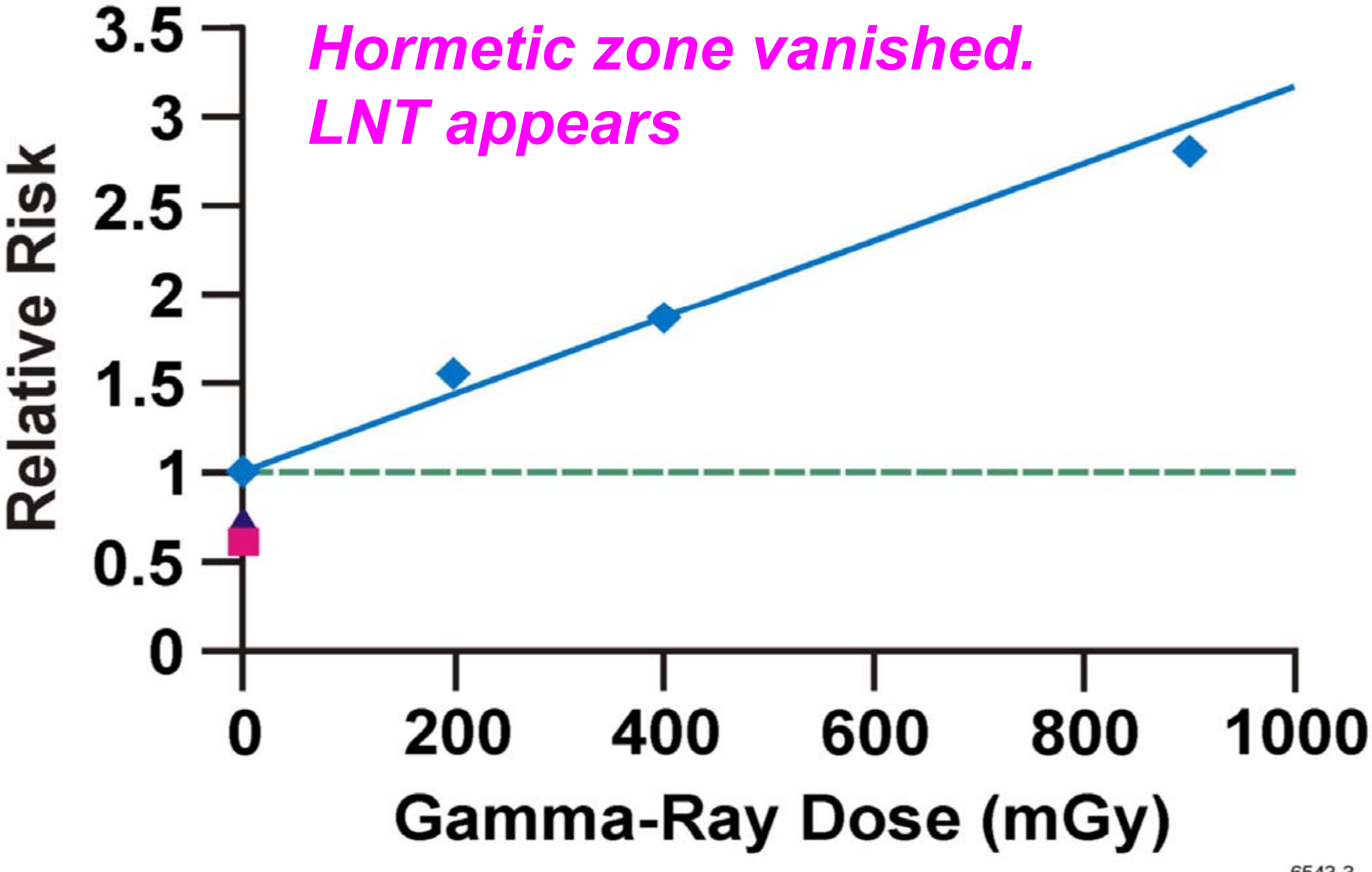


6543-1a

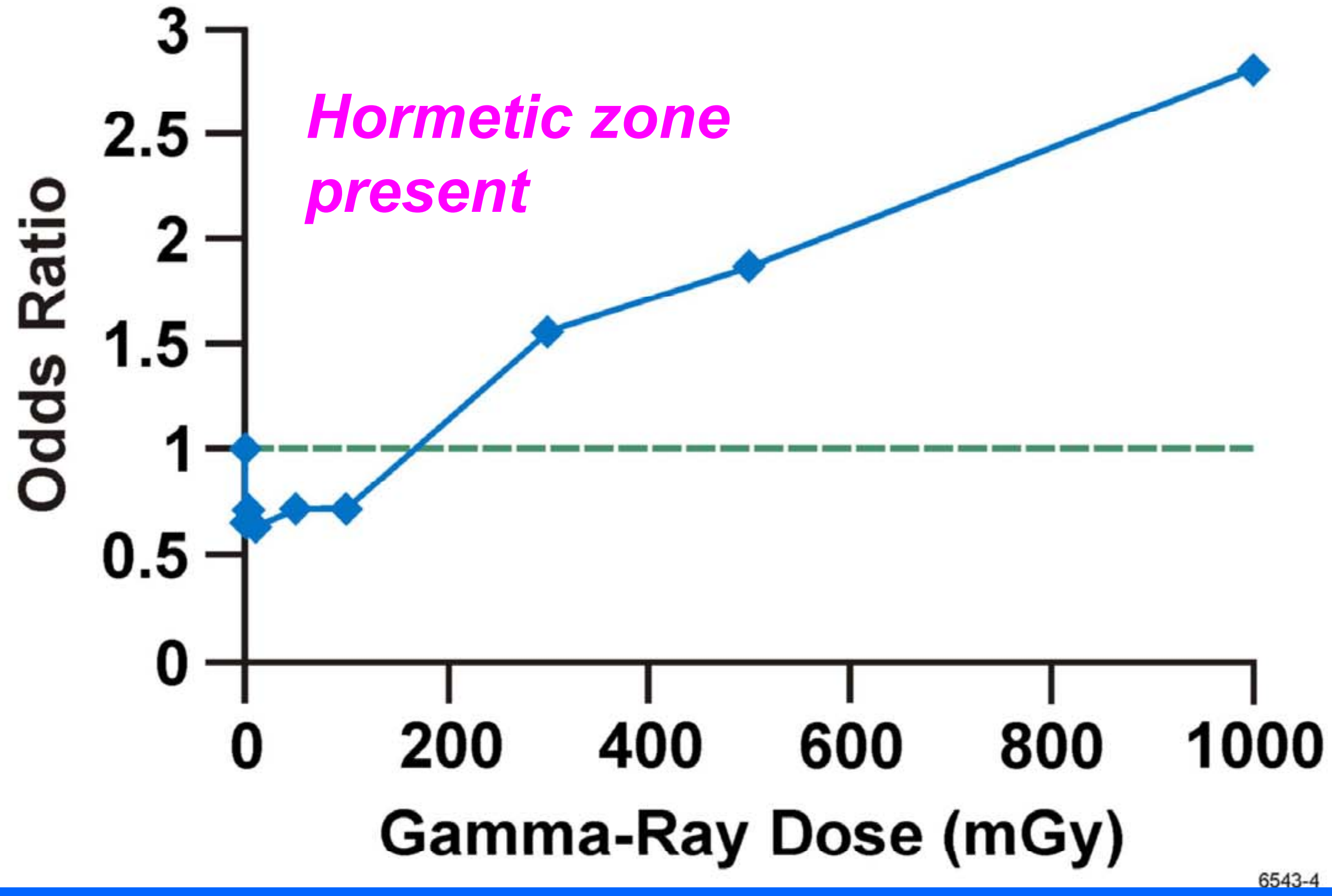
LOW-DOSE VIEW



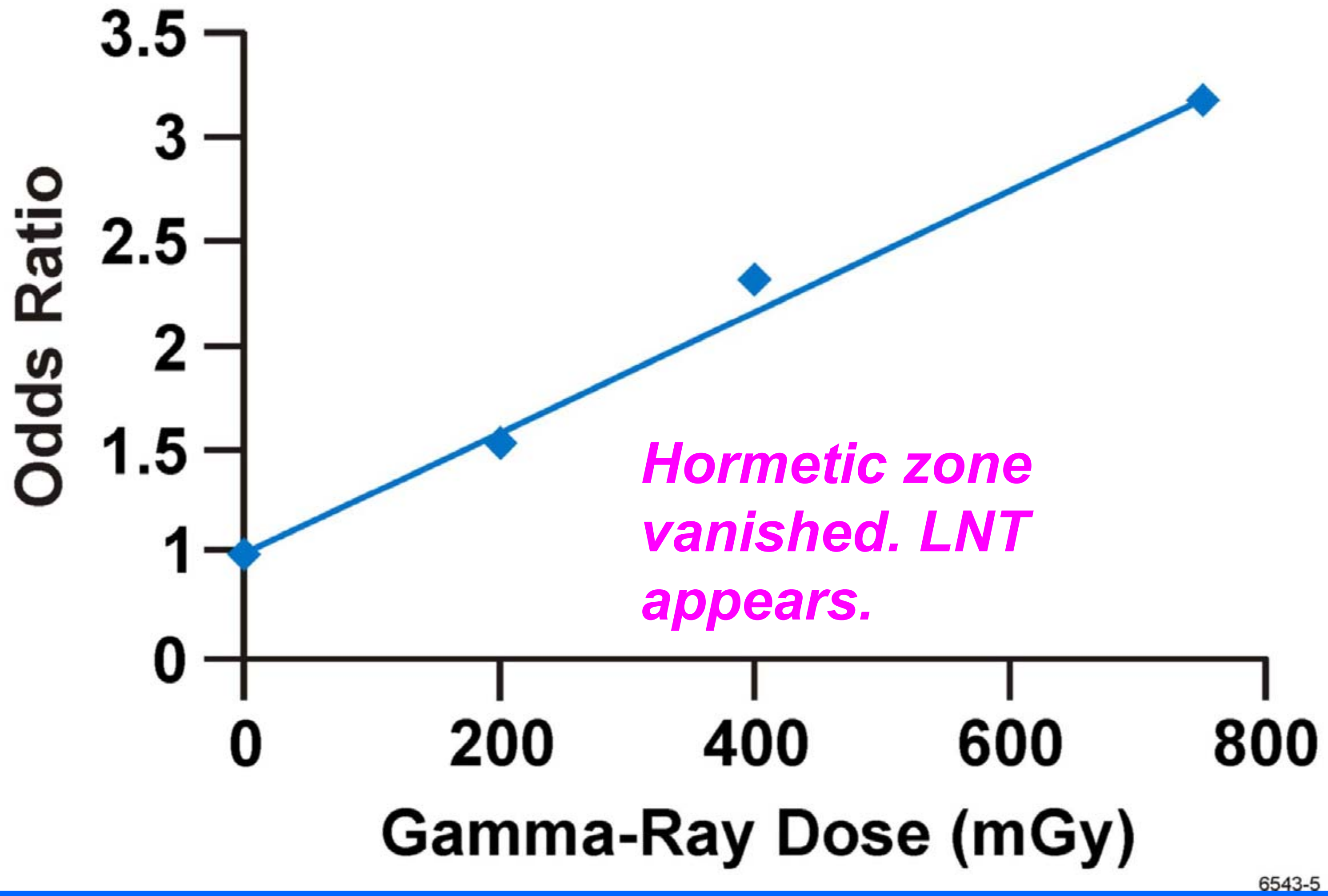
DOSE-LAGGING TRICK: 100-mGy LAG



NEOPLASTIC TRANSFORMATION ODDS RATIO



ODDS AVERAGING TRICK: NEOPLASTIC TRANSFORMATION DATA



Positive Slope Constraint Trick

- Constrain the dose-response curve slope to being positive (e.g., use LNT or linear-quadratic function with positive parameters)
- Include moderate and high dose data to prevent rejection of the model used.
- Ignore the low-dose data if hormesis is implicated.

LNT-Based Radiation Protection System

- **Equivalent dose:** A weighted tissue-specific dose that is intended to account for the different effectiveness of different radiation types.
- **Effective dose:** A weighted dose intended to relate non-uniform exposure to uniform gamma-ray exposure over the body.
- The indicated doses are justified based on the LNT hypothesis.
- **Typical dose units:** sieverts (Sv) and millisieverts (mSv)
- Humans are protected by limiting effective dose.

Radiation Limits (Metting 2006)

- **Public drinking water (EPA): 0.04 mSv/y**
- **Releases to air (EPA): 0.1 mSv/y**
- **Security personnel scanners (ANSI): 0.25 mSv/y**
- **Public exposure (DOE, NRC): 1 mSv/y**
- **DOE administrative control: 20 mSv/y**
- **Worker exposure (DOE, NRC): 50 mSv/y**

Natural background radiation, Ramsar, Iran: around 200 mSv/y

LNT-Associated Harm

- The LNT concept promulgates fear of all radiation and produces laws which have no basis in mammalian physiology (T.D. Luckey, 2006).
- After the Chernobyl accident, adverse health effects and vast material losses were induced in the former USSR by practical implementation of LNT-based radiation protection recommendations (Z. Jaworowski, 1997).
- The LNT concept leads to poor health unreasonable medicine and oppressed industries (T.D. Luckey, 2006).

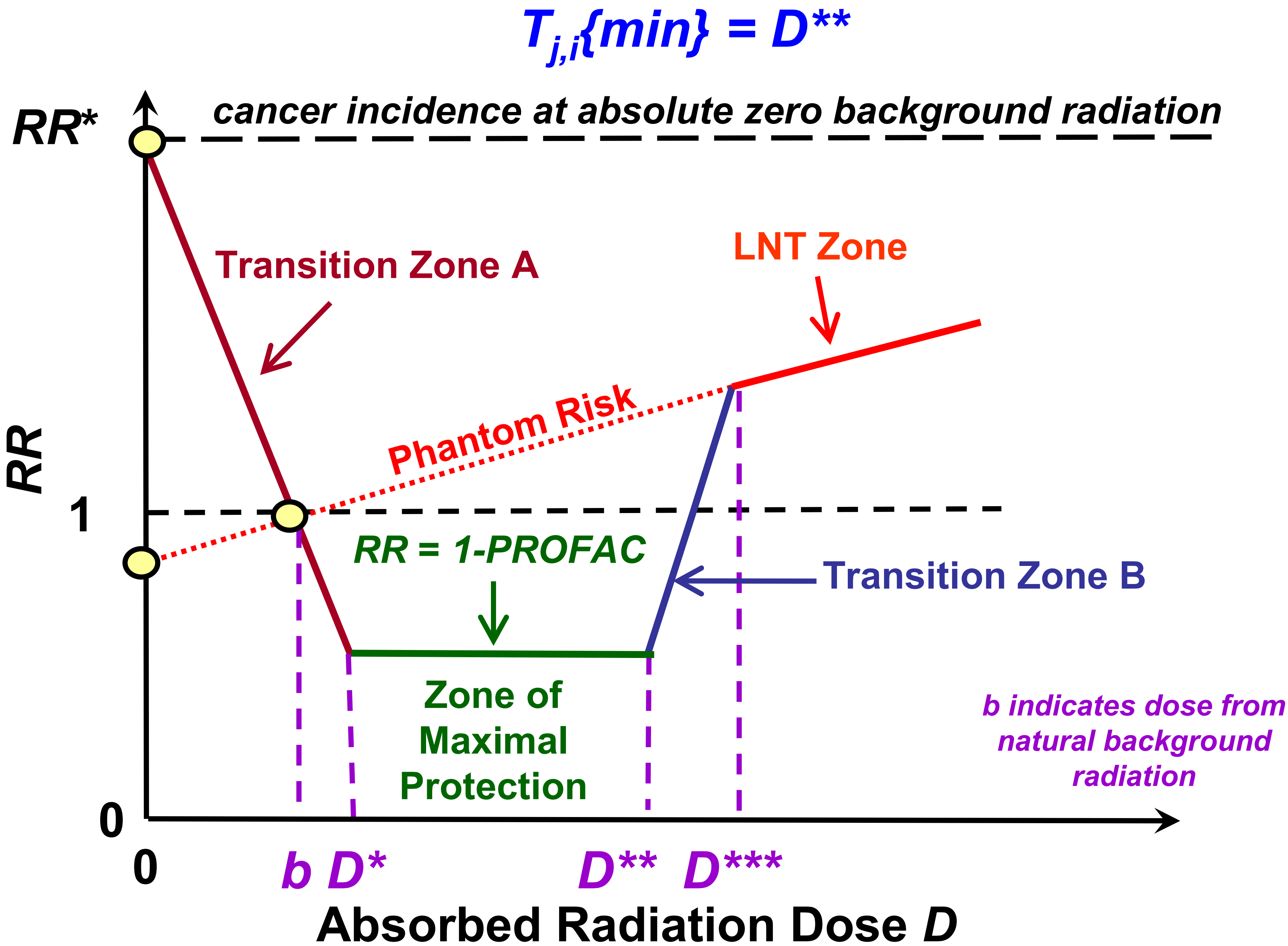
A Need for Revision in Radiation Regulatory Policy

A revision of the current approach to managing the risks of ionizing radiation is needed for the public interest.

Z. Jaworowski, 1997

Regulatory Radiation Absorbed Dose Threshold (REGRADT) for Preventing Excess Cancers

- **A proposed REGRADT is $T_{j,i}\{min\}$ which is the tissue-j-specific minimum for the stochastic absorbed-dose thresholds, $T_{j,i}$, for radiation type i, for Transition Zone B.**
- **$T_{j,i}\{min\}$ for a given radiation type may depend on absorbed dose rate and microdose distribution.**
- **$T_{j,i}\{min\}$ is population-specific and may be influenced by variability in genetic characteristics (e.g. polymorphisms).**



$T_{j,i}\{min\} = D^{**}$
cancer incidence at absolute zero background radiation
RR*
RR
1
0
Transition Zone A
LNT Zone
Phantom Risk
RR = 1-PROFAC
Transition Zone B
Zone of Maximal Protection
b indicates dose from natural background radiation
0
b D*
D**
D***
Absorbed Radiation Dose D

Stochastic-Effects-Associated Normalized Dose Limit (NDL): $S_j < 1$

The NDL $S_j < 1$ can be used to limit excess cancers for each tissue j, where:

$$S_j = (D_{j,1}/T_{j,1}\{min\}) + (D_{j,2}/T_{j,2}\{min\}) + \ldots + (D_{j,m}/T_{j,m}\{min\}).$$

If the NDL is not exceeded, cancer RR $\leq$ 1, is expected. Not essential to evaluate risk.

NDLs could be applied to populations or individuals.

What Does S_j Mean?

- $S_j = 0.5$ means that the radiation exposure is ½ of that needed to reach the exposure level where adaptive protection is lost by the most sensitive member of the population.
- The indicated normalized dose can be obtained by a variety of combinations of different radiation doses and dose rates for the different radiations of interest.

What About Genetic Effects?

Radiation-Induced Genetic Effects

There is no direct evidence of radiation-induced genetic effects in humans, even at high doses. Even the BEIR VII Report acknowledged that the risk of genetic effects is much lower than for cancer.

Cartoon source: Environ. Health & Safety, Princeton University

http://web.princeton.edu/sites/ehs/

Cancer REGRADTs Could be used in Limiting Genetic Effects

- Genetic effect risk << cancer risk.
- Cancer REGRADTs for the gonads could therefore be used in limiting genetic effects.
- The cancer-based NDL for the testes would apply to males.
- The cancer-based NDL for the ovary would apply to females.

Benefits of Acknowledging Hormesis/Thresholds

- **No increase risk of harm (relative to the spontaneous level) below the NDL.**
- **Reducing dose to well below the NDL can be quite expensive, e.g., "billions of dollars for environmental media containing radionuclides", while providing little if any benefit.**
- **Radiation-phobia-related loss of life (e.g., > 100,000 such lives were lost following Chernobyl accident) could be minimized through public education about benefits of low-level radiation and thresholds for excess harm.**

Conclusion

- **The LNT framework for regulating radiation exposure and for low-dose cancer risk assessment has outlived its usefulness.**
- **It’s time for a more scientifically valid system of radiation exposure regulation – one that encompasses hormesis.**
- **The use of REGRADTs and associated NDLs provides such a system.**

Acknowledgements

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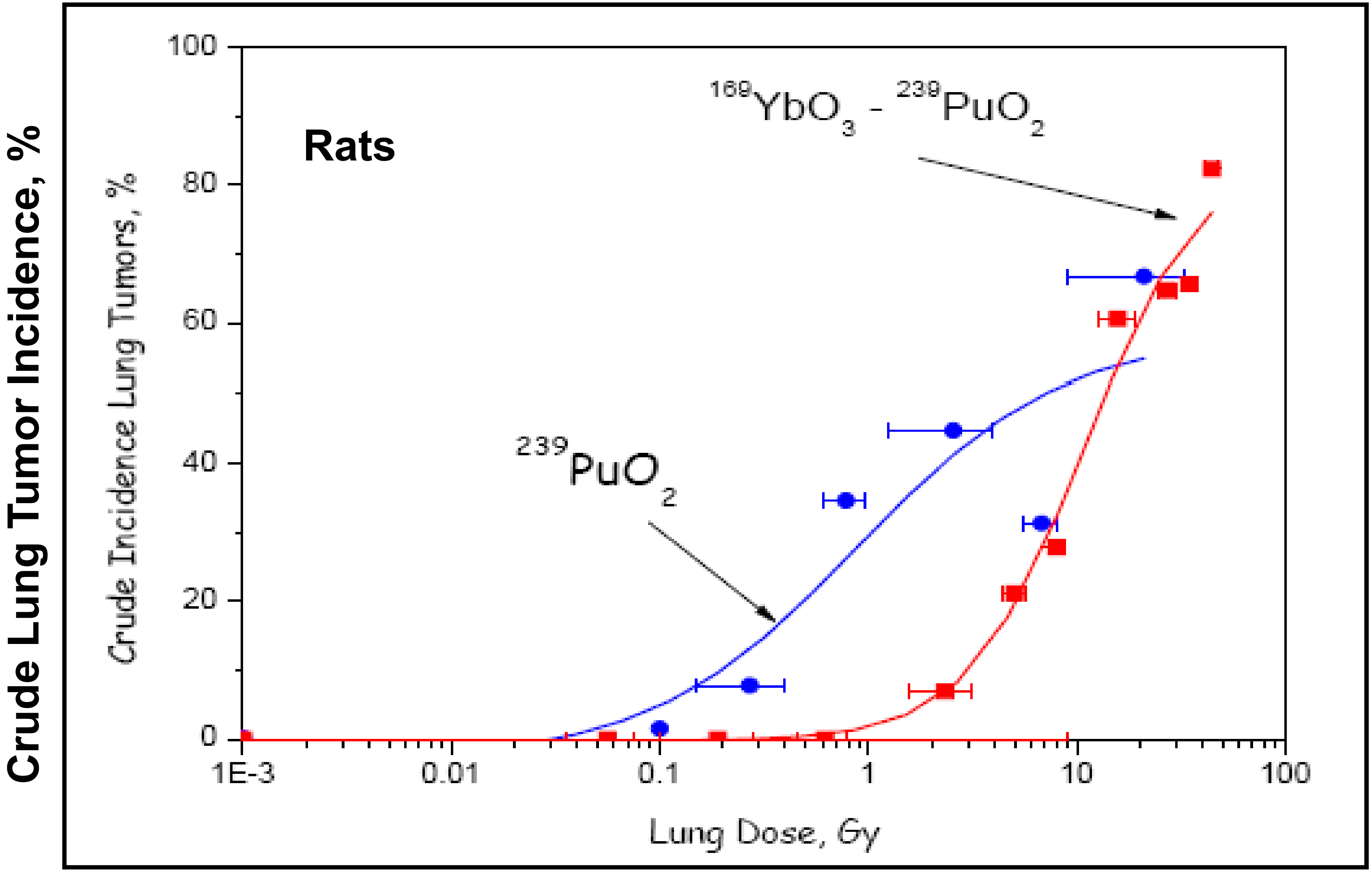
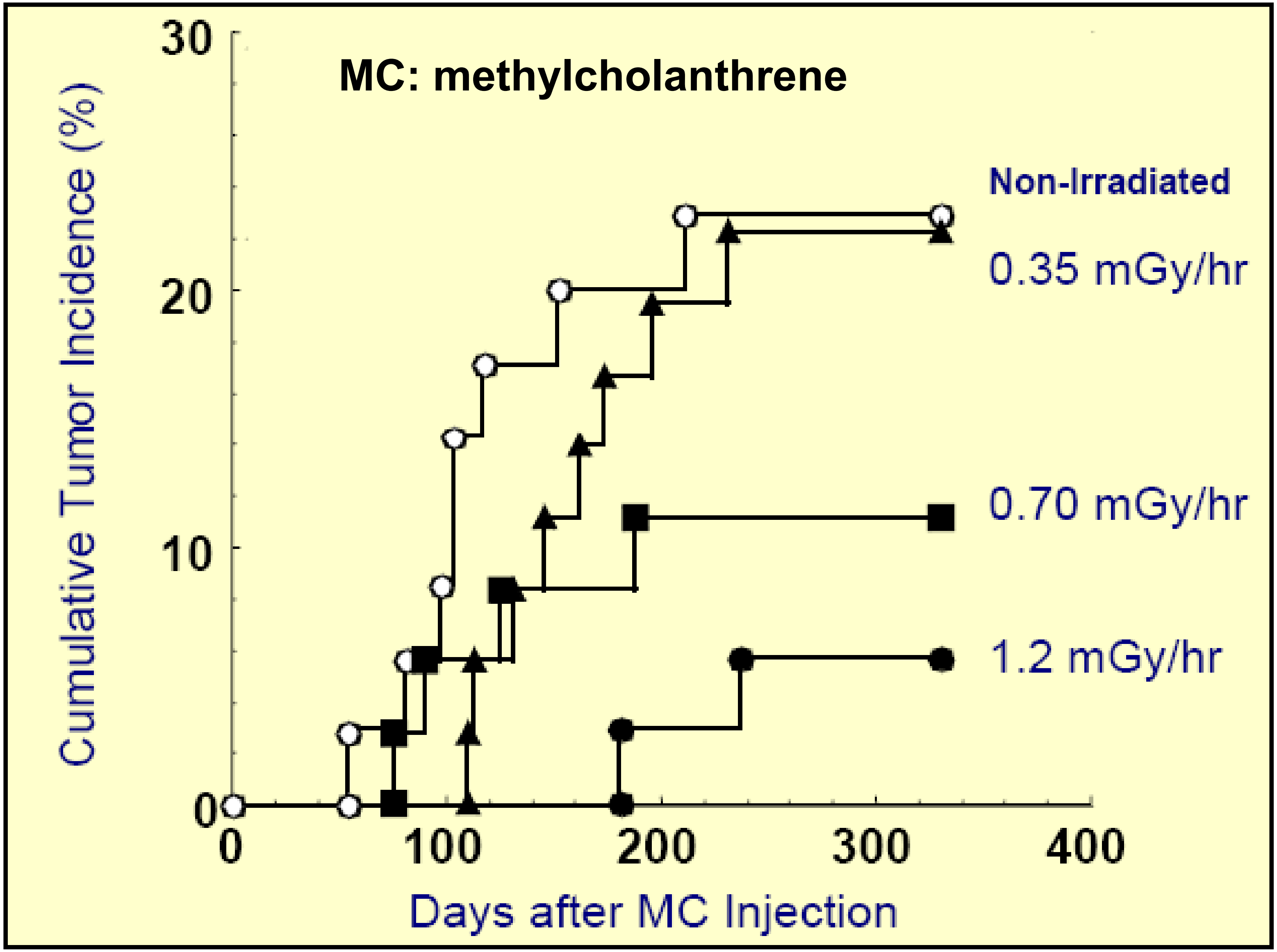
- **Jaworowski Z. Australasian Physical & Engineering Sciences in Medicine 20:125, 1997.**
- **Khokhryakov VF *et al.* Radiation Safety 2:51, 1996.**
- **Luckey TD. Dose-Response 4(3):169, 2006.**
- **Metting NF. Dose Ranges Chart, DOE 2006.**
- **Nyström L *et al.* The Lancet 359:909, 2002.**
- **Redpath JL *et al.* Radiat Res 156:700, 2001.**
- **Scott BR. Dose-Response, 2007, in press.**
- **Scott BR, Di Palma J. Dose-Response, 2007, in press.**

Low-Dose-Rate Gamma Rays Prevented Alpha-Radiation-Induced Lung Cancers



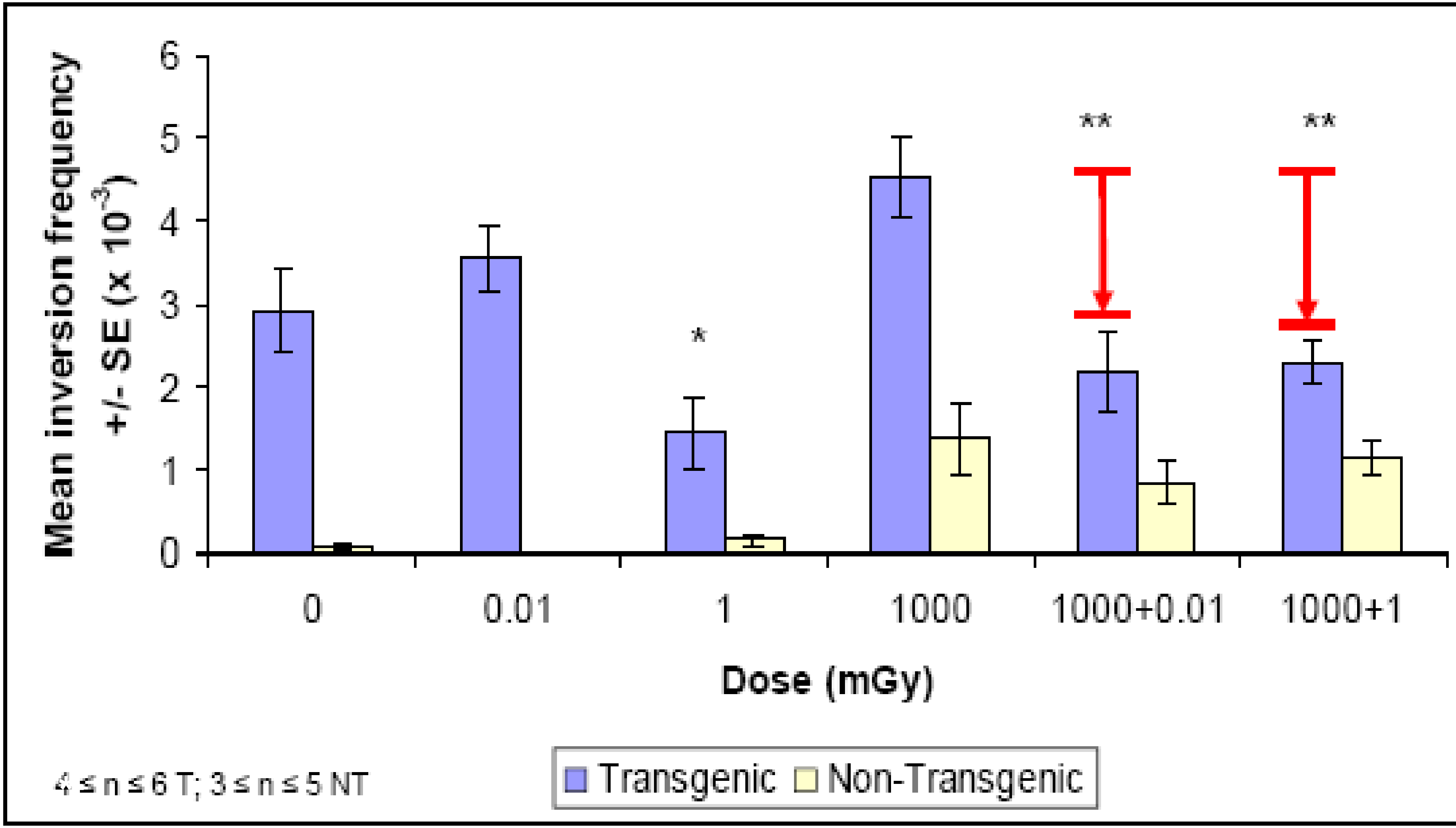
C. L. Sanders, International Hormesis Conference, 2006

Low-Dose-Rate Gamma Rays Prevented MC-Induced Skin Tumors



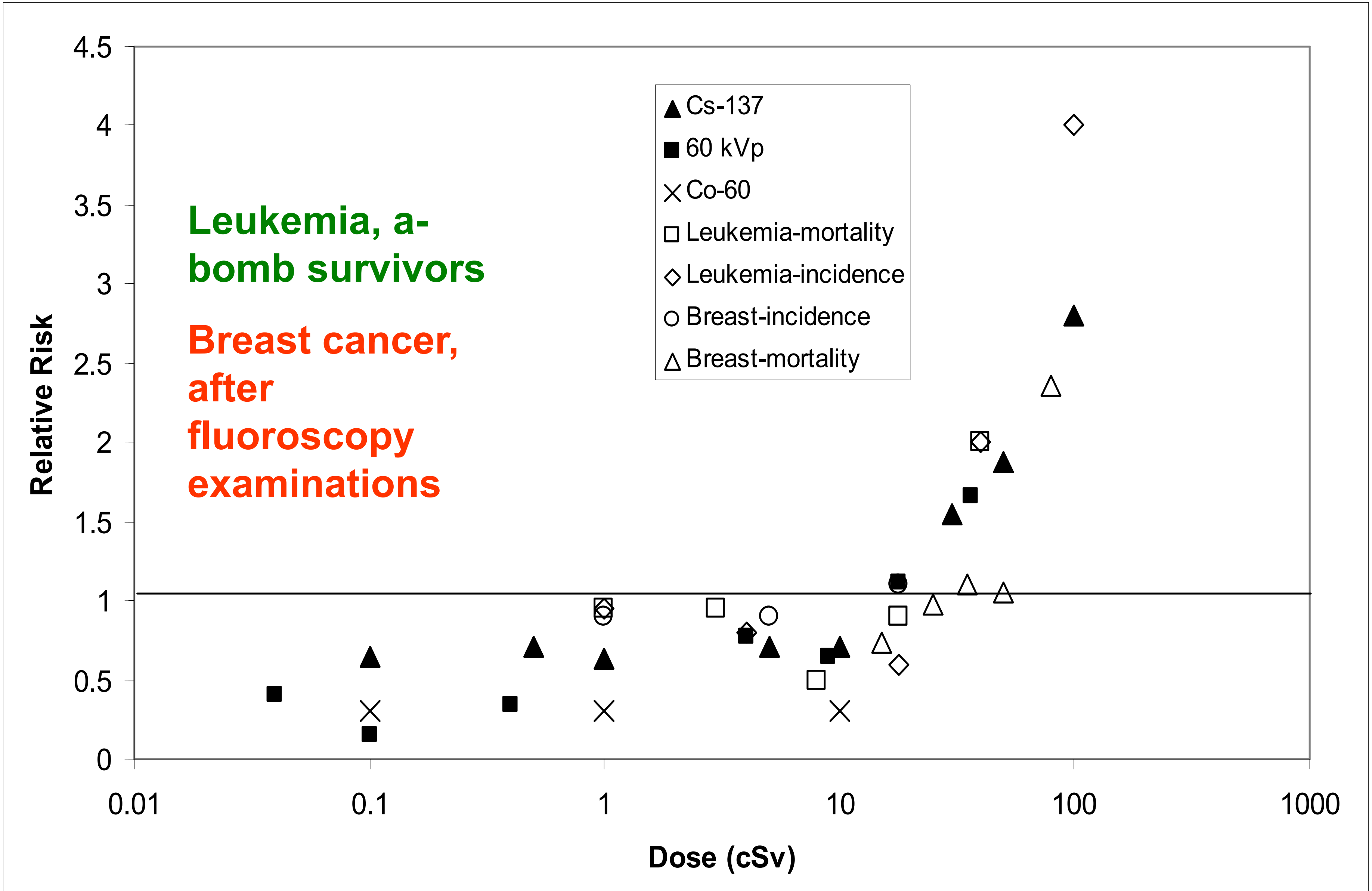
K. Sakai, International Hormesis Conference 2005

Low-Dose X-Rays Protected From Inversion Mutations in pKZ1 Mice

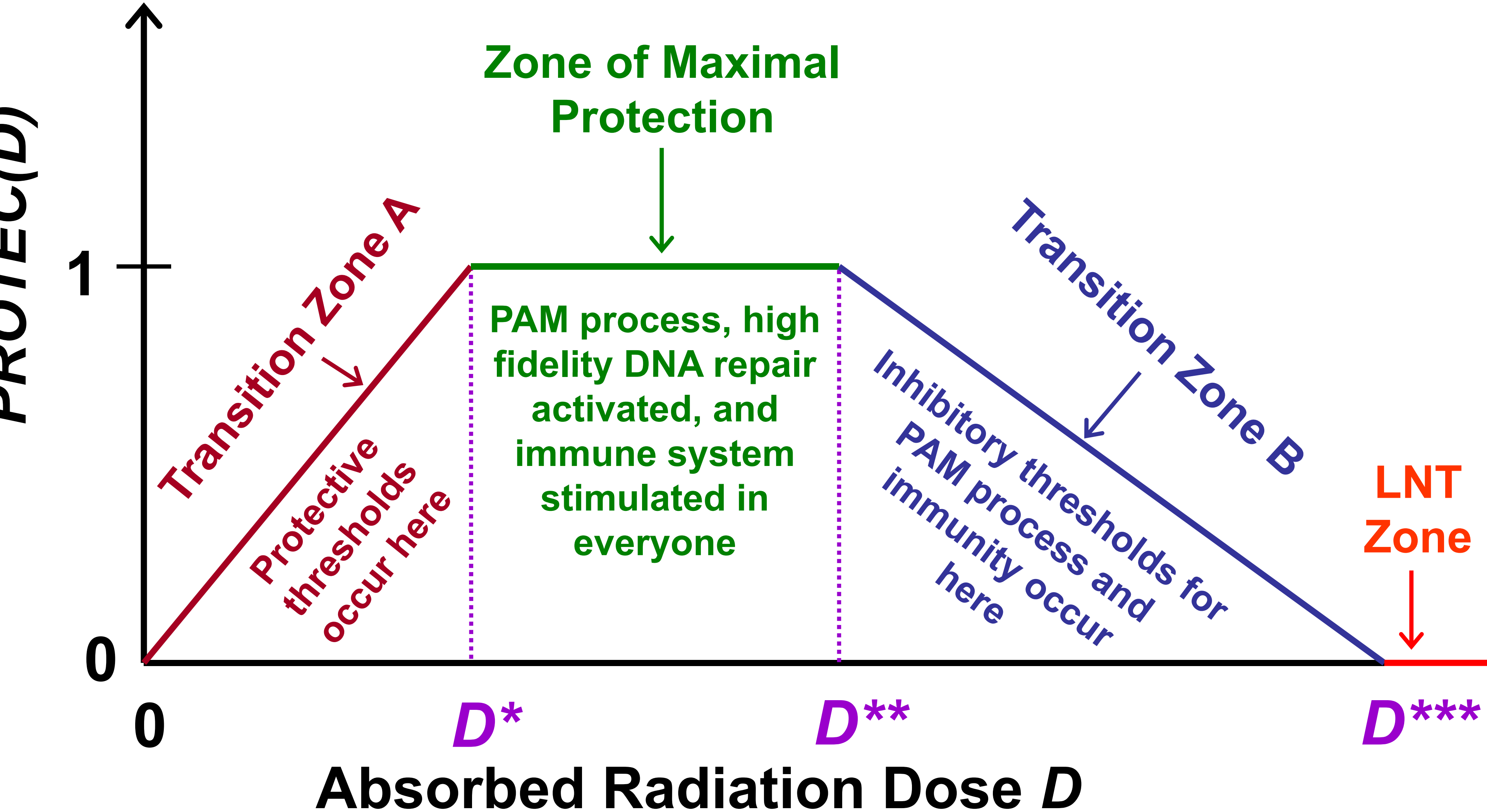


Small X-ray dose given hours after 1000 mGy dose protected.
T. Day, International Hormesis Conference 2006

Correspondence Between Neoplastic Transformation and Cancer (Redpath 2006)

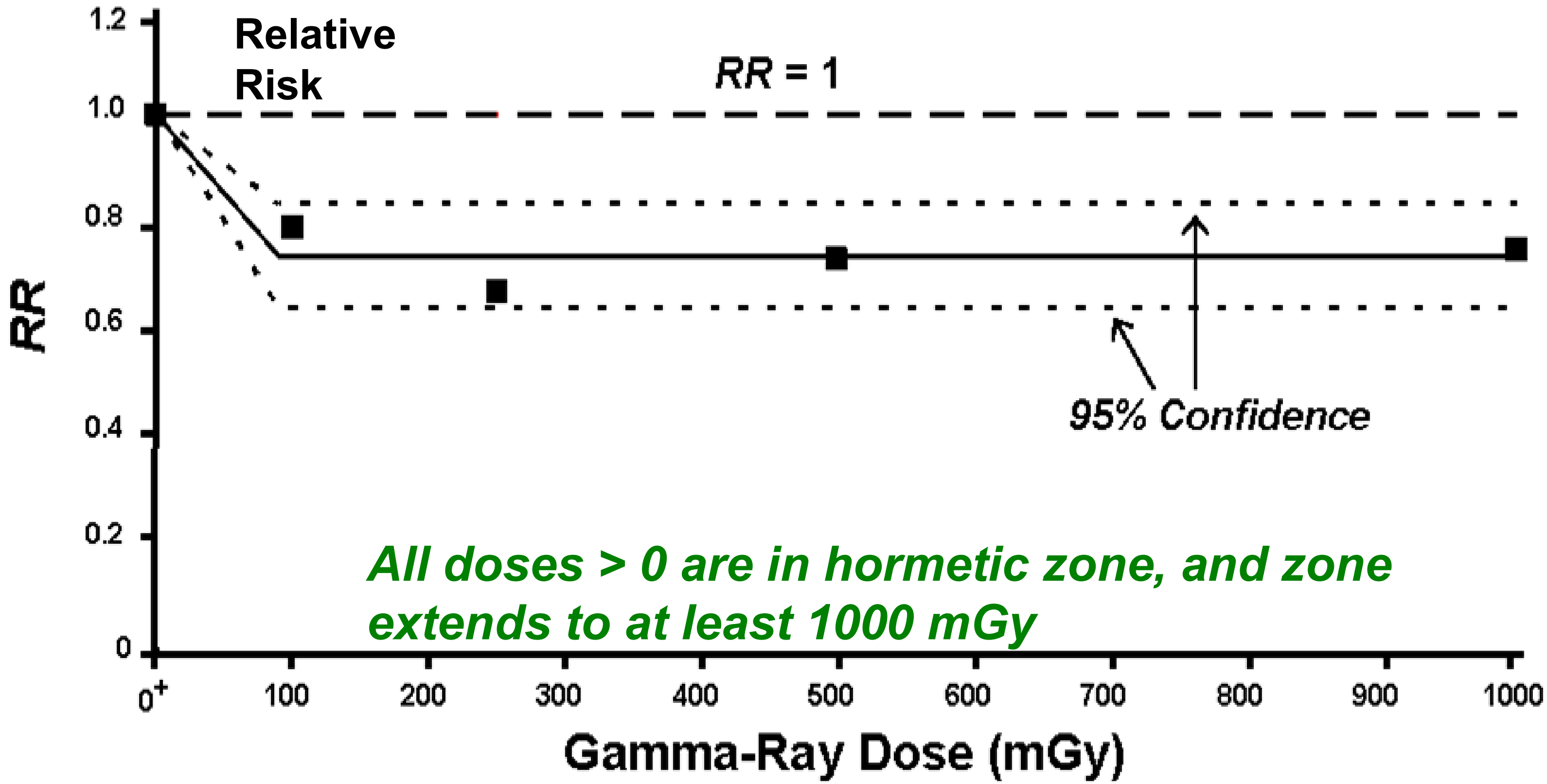


Protection Probability Function *PROTEC(D)*, A Consequence of Stochastic Modeling[a]



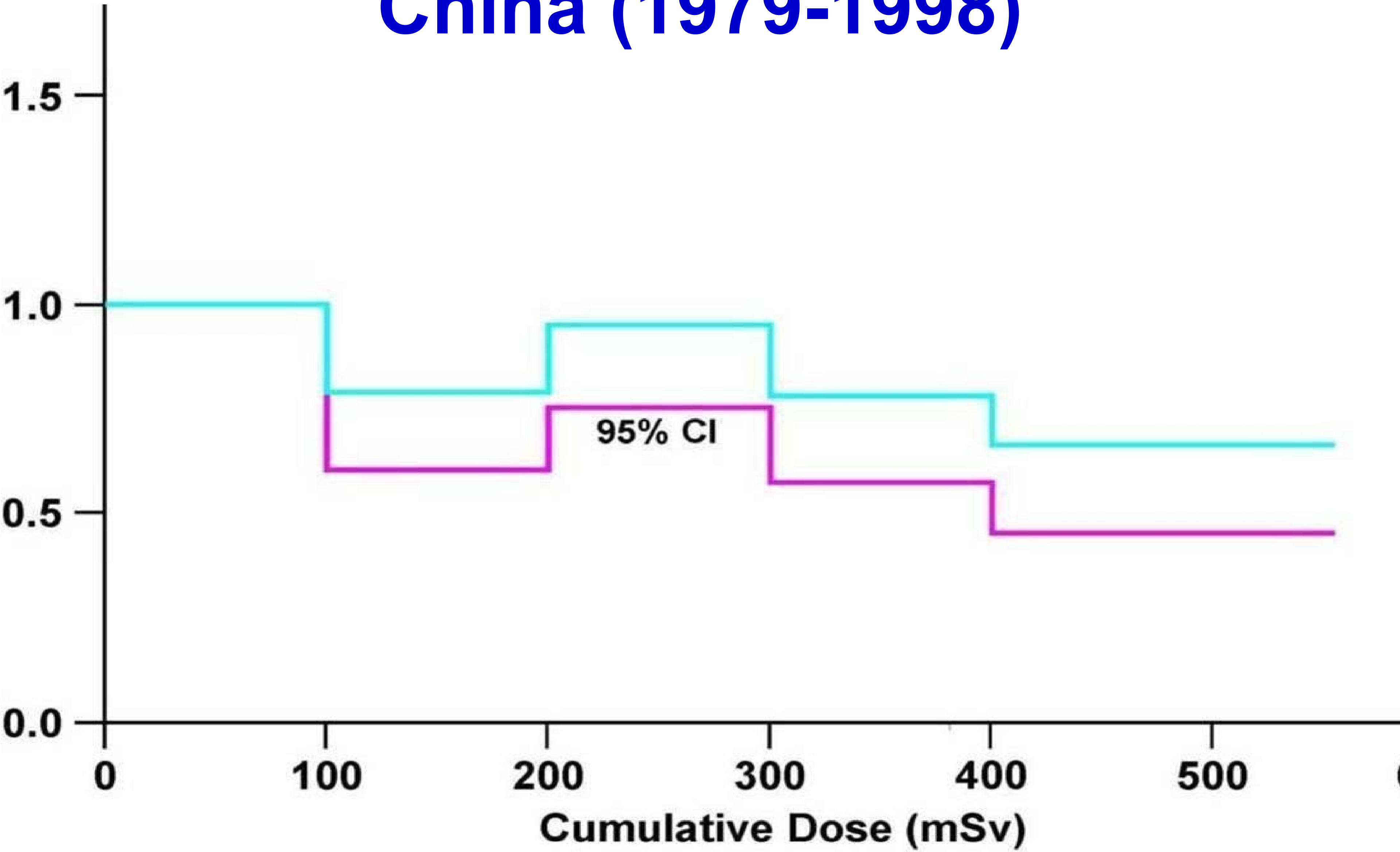
[a]Scott BR. Chapter, Nova Science Publishers, Inc. book on new research on
genomic instability (accepted, 2007).

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.

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



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

Why Hormetic Dose-Response Curves Not Reported in Epidemiological Studies

- **Little funding available for conducting epidemiological studies with a hormesis focus.**
- **LNT or other monotonically increasing risk-vs.-dose responses presumed by most researchers including grant reviewers.**
- **Epidemiological tricks employed that favor a LNT-type dose-response curve.**

Protective Processes Associated with $NEOTRANS_3$ 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.

Evaluating Cancer Risk for $S_j \geq 1$.

- Develop and employ a modified LNT framework.
- Genetic susceptibility and genetic resistance would be addressed.
- Subpopulation with similar genetic characteristics (e.g., sensitive, highly sensitive, resistant, highly resistant) would be assigned genetic-characteristics-specific, dose-response curve slopes.
- Other influences such as age and gender could also be addressed if needed.