How Does the Concept of Adaptive Response in Radiation Relate to the Concept of Radiation Hormesis?

Ron Mitchel

Atomic Energy of Canada Limited

Chalk River, Canada

mitchelr@aecl.ca

HORMESIS

A dose–response phenomenon characterized by a low dose stimulation (usually assumed beneficial) and a different response (often opposite) at high dose

ADAPTIVE RESPONSE

Exposure
of cells or animals to radiation
at a low dose and dose rate
induces mechanisms that protect
against the detrimental effects
of other events or agents,
including radiation

STRESS RESPONSES

- **Adaptive response to radiation is part of a general stress response**

- **Other stress can modify radiation risk, and visa versa**

RADIATION-INDUCED ADAPTIVE RESPONSE IN YEAST

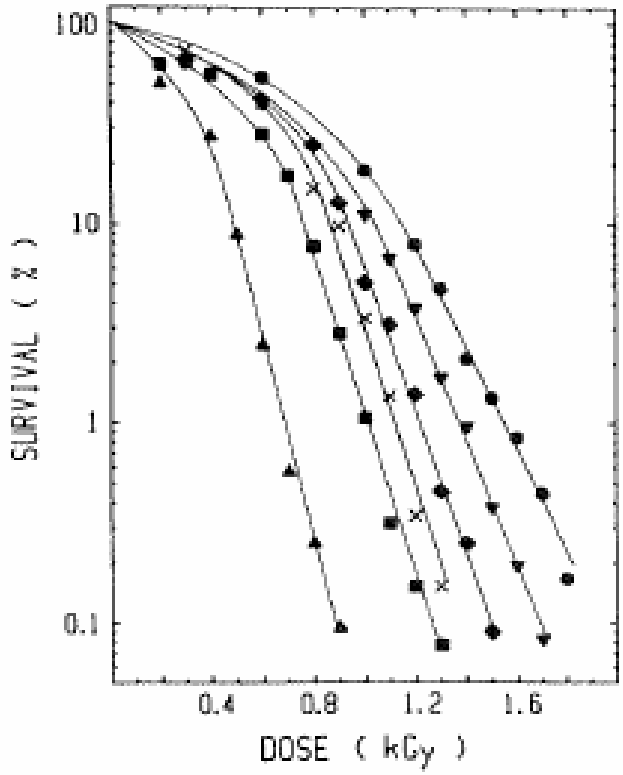


FIG. 1. Radiation survival curves of *Saccharomyces cerevisiae* induced to increased radiation resistance. Cells in exponential growth phase received an initial 200-Gy oxic dose of ^{60}Co γ radiation and were then tested for changes in resistance for further oxic irradiation. Radiation resistance was tested immediately ▲; and after 1, ■; 2, X; 3, ◆; 4, ▼; or 5 hr, ●, of incubation in nutrient medium at 23°C.

Mitchel and Morrison *Radiat. Res.* 100, 205, 1984

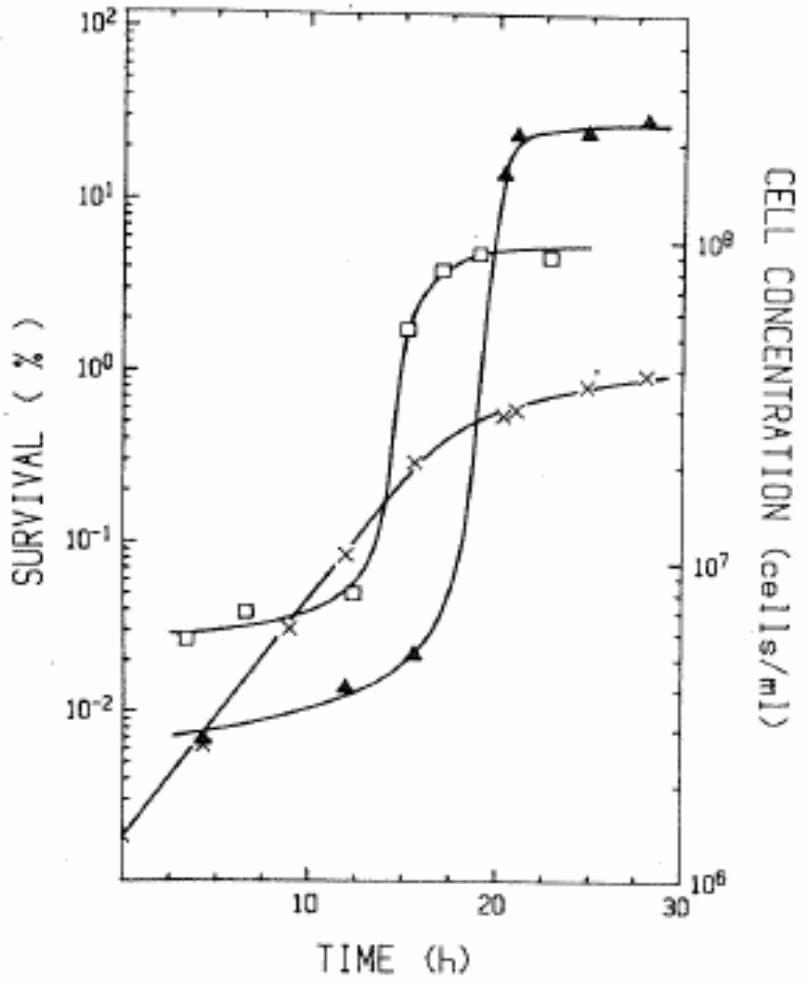


FIG. 4. Induction of resistance in *Saccharomyces cerevisiae* upon entering stationary growth phase. Cell growth at 23°C, ×; thermal resistance (52°C, 15 min), ▲; radiation resistance (400 krad, anoxic), □.

Mitchel and Morrison, Radiat. Res. 90:284-291 (1982)

RADIATION DOSE AND LIMITS TO ADAPTION

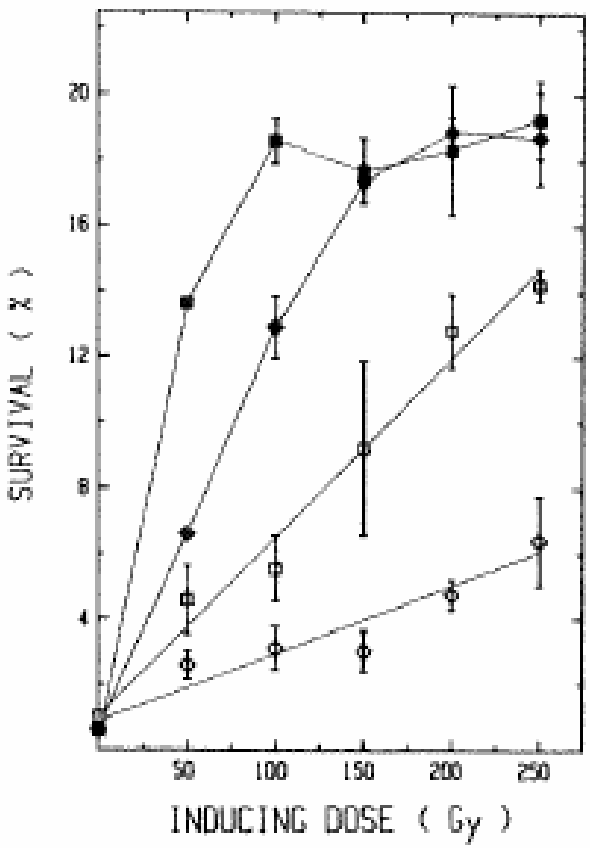


FIG. 3. The effect of oxygen on the level of radioresistance induced in *Saccharomyces cerevisiae* by various doses of γ radiation. Resistance was measured as percentage survival after exposure to 1 kGy in O_2, following 2 (open symbols) or 5 hr (closed symbols) of incubation at 23°C in nutrient medium. Inducing doses were delivered in the presence (□, ■) or absence (◇, ◆) of oxygen.

Mitchel and Morrison *Radiat. Res.* 100:205-210, 1984

ADAPTION AND DNA REPAIR PATHWAYS

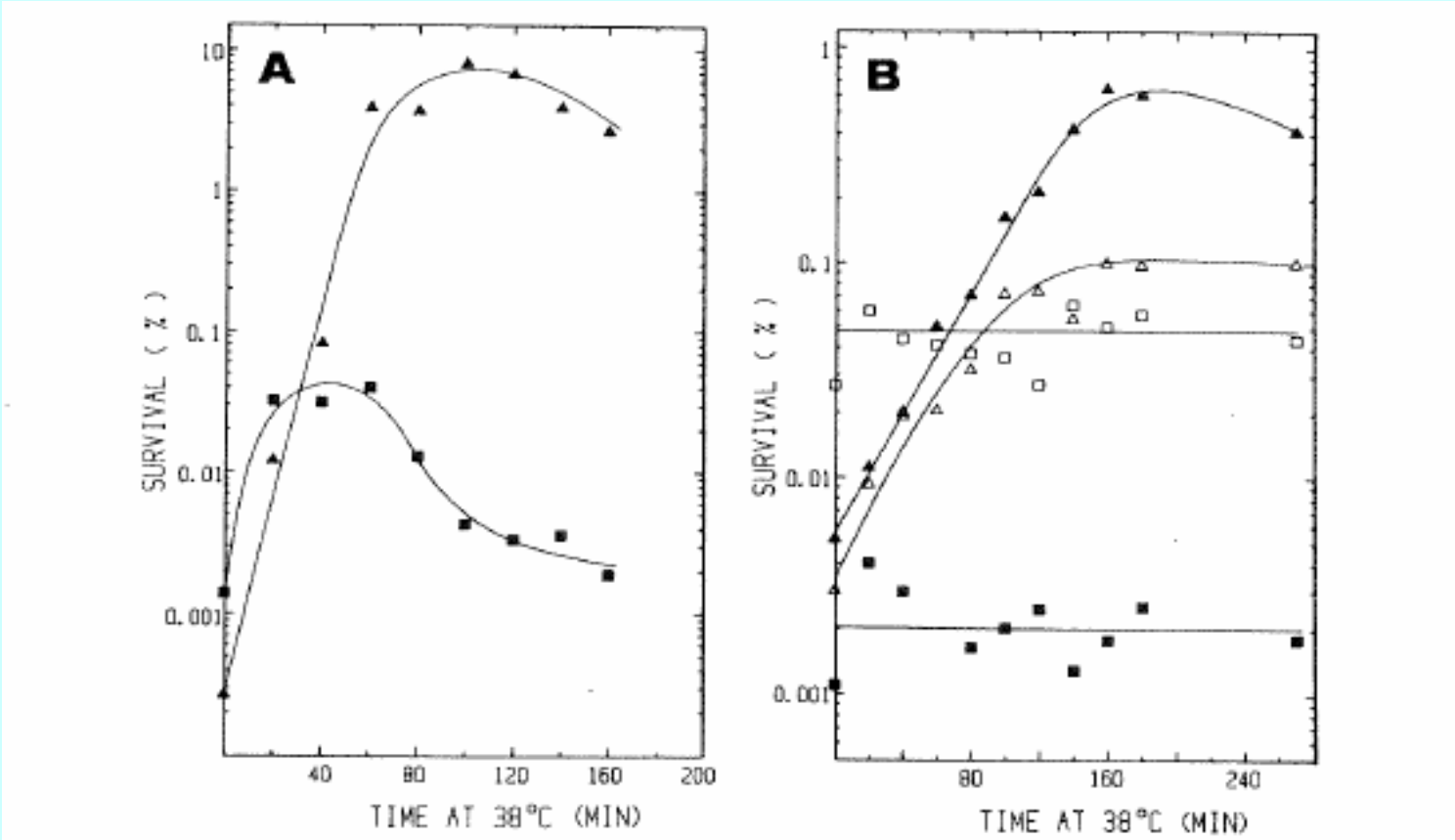
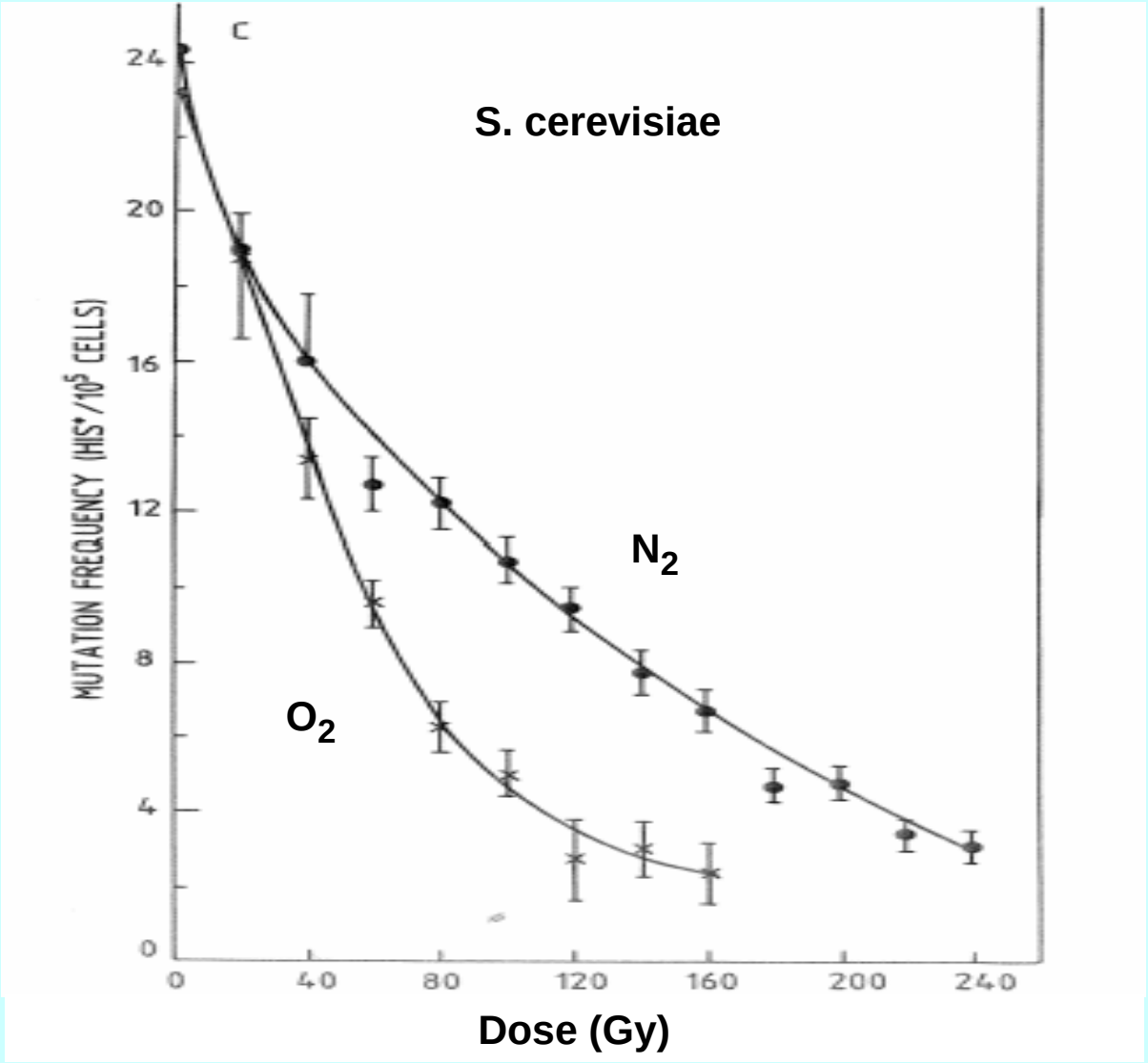


FIG. 1. Heat-shock induction of resistance to the lethal effects of ionizing radiation and heat in *Saccharomyces cerevisiae*. (A) Strain D7.3, defective in excision repair. Survival after heating at 52°C for 6 min, ▲; survival after exposure to 3 kGy delivered anoxically, ■. Heat shock at 38°C. (B) Strain MS31, open symbols; strain MS32, solid symbols; both defective in recombinational repair. Survival after heating at 52°C for 15 min, triangles; survival after exposure to anoxic γ irradiation (800 Gy), squares. Heat shock at 38°C.

Mitchel and Morrison, Radiat. Res 92:182-187, 1982

Radiation-Induced Resistance to MNNG Mutation



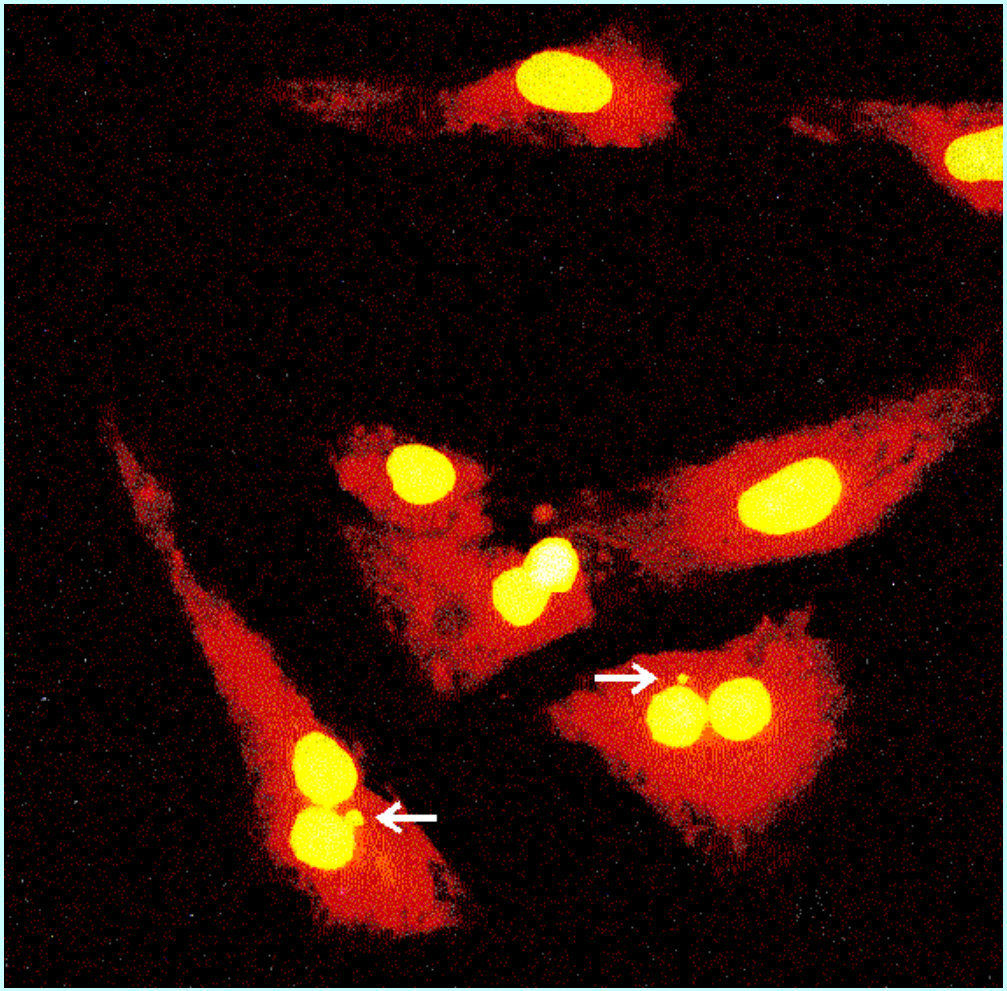
Mitchel and Morrison Mutat. Res. 183:149-159 (1987)

Adaption to radiation shown in:

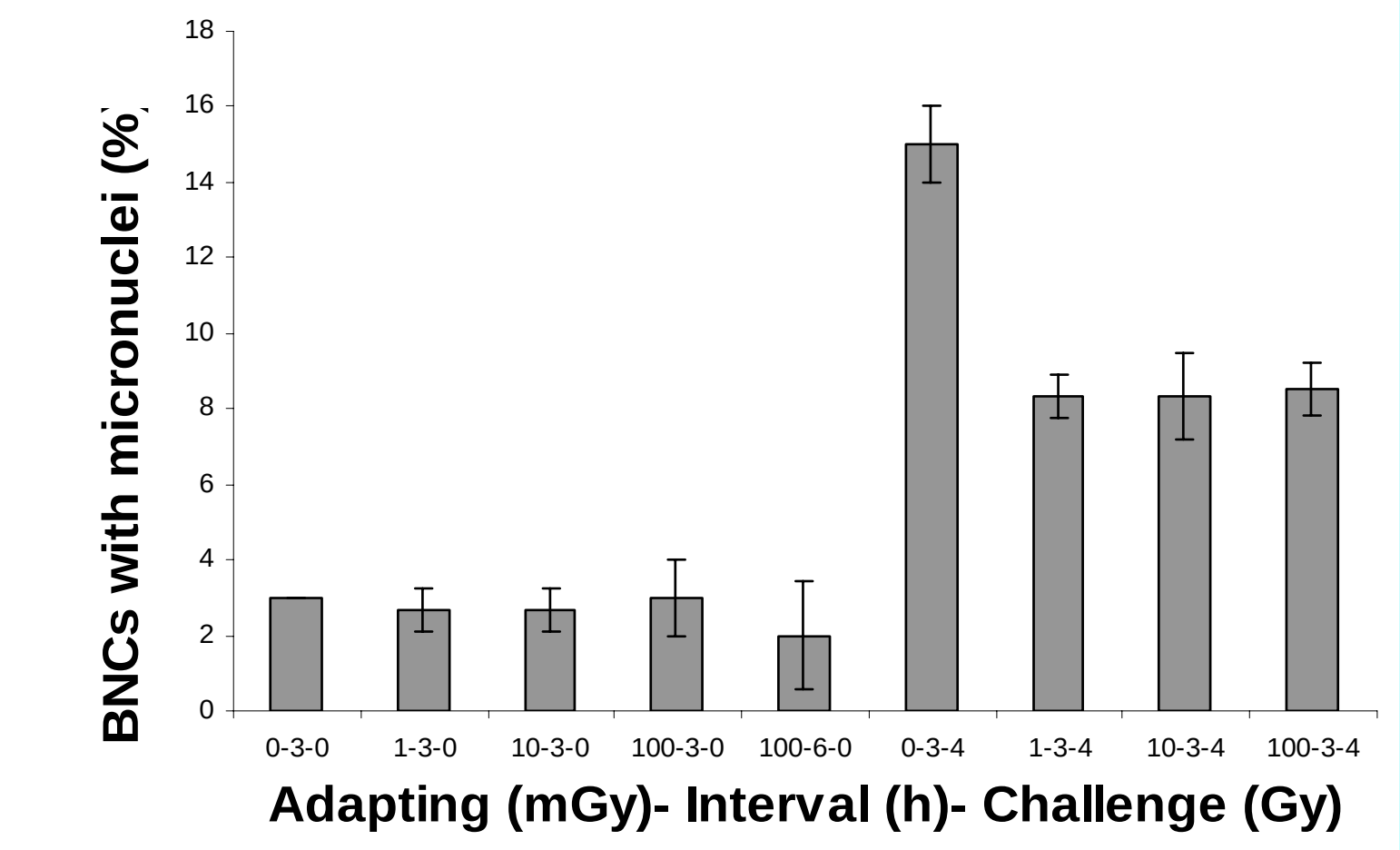
- Single cell organisms
- Insects
- Plants
- Lower vertebrates
- Mammalian cells including human
- Mammals

This is an Evolutionarily Conserved Response

Micronuclei from Unrepaired Chromosomes

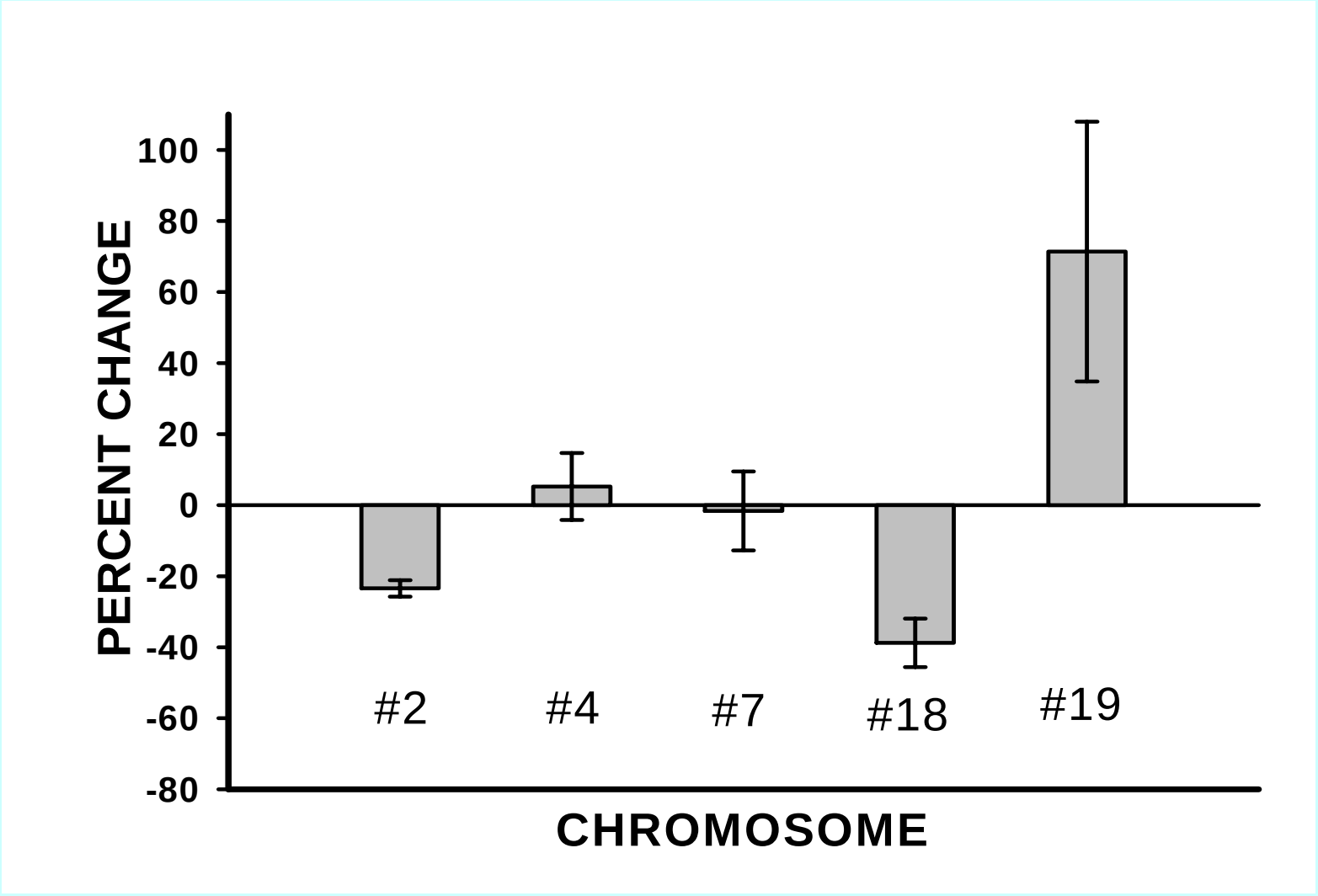


Adaption in Whitetail Deer Cells



Ulsh, Miller, Mallory, Mitchel, Morrison, and Boreham
***J Environ Radioact* 74, 73-81 (2004)**

Change in Micronuclei Containing Chromosome Fragments in Adapted Human Fibroblasts



Broome, Brown, and Mitchel, IJRB 75:681-690, 1999

Low Doses Protect Cells Against Malignant Transformation by High Doses

Treatment	Transformation Frequency ($\times 10^{-4}$)
Control	3.7
4 Gy (high dose rate)	41
100 mGy (low dose rate) +24h + 4 Gy (high dose rate)	16

Azzam, Raaphorst and Mitchel *Radiat. Res.* 138: S28-S31, 1994

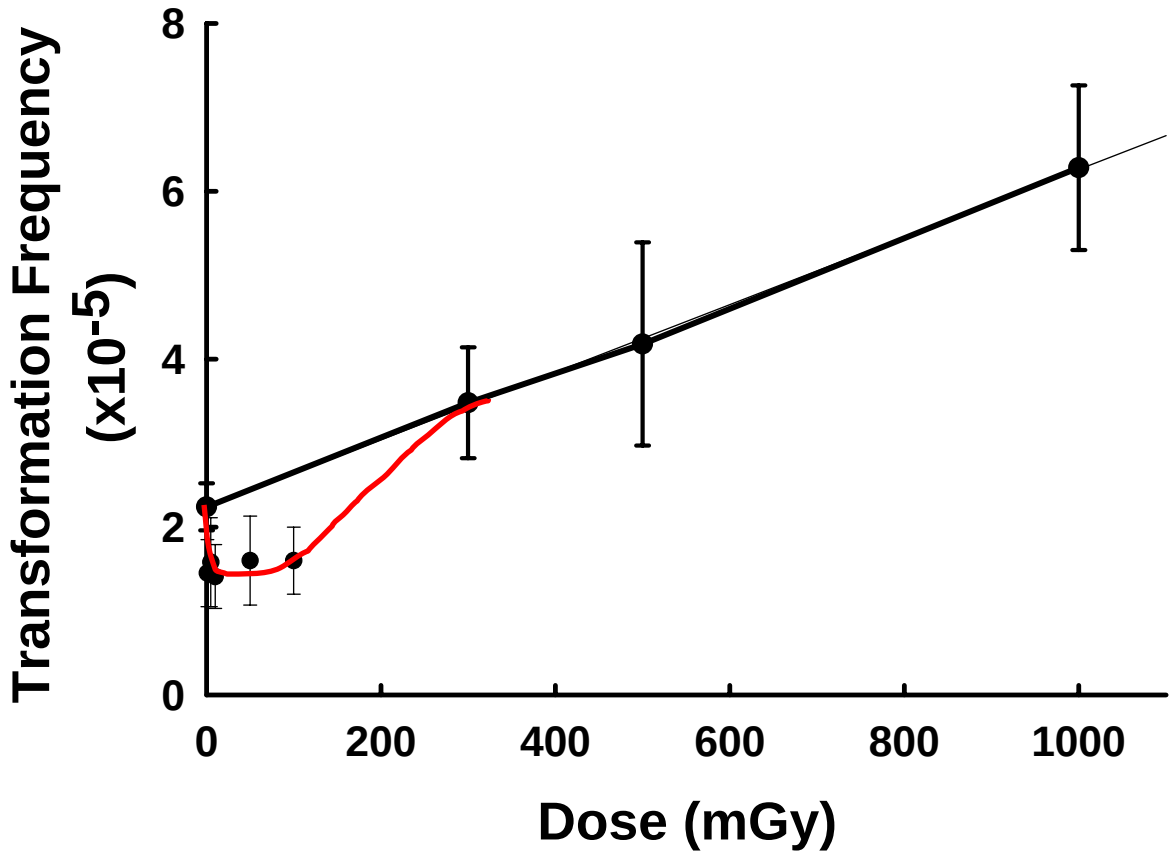
The Influence of Low Doses On the Risk of Spontaneous Malignant Transformation

Treatment	Transformation Frequency ($\times 10^{-3}$)
Control	1.8
1.0 mGy	0.53
10 mGy	0.42
100 mGy	0.53

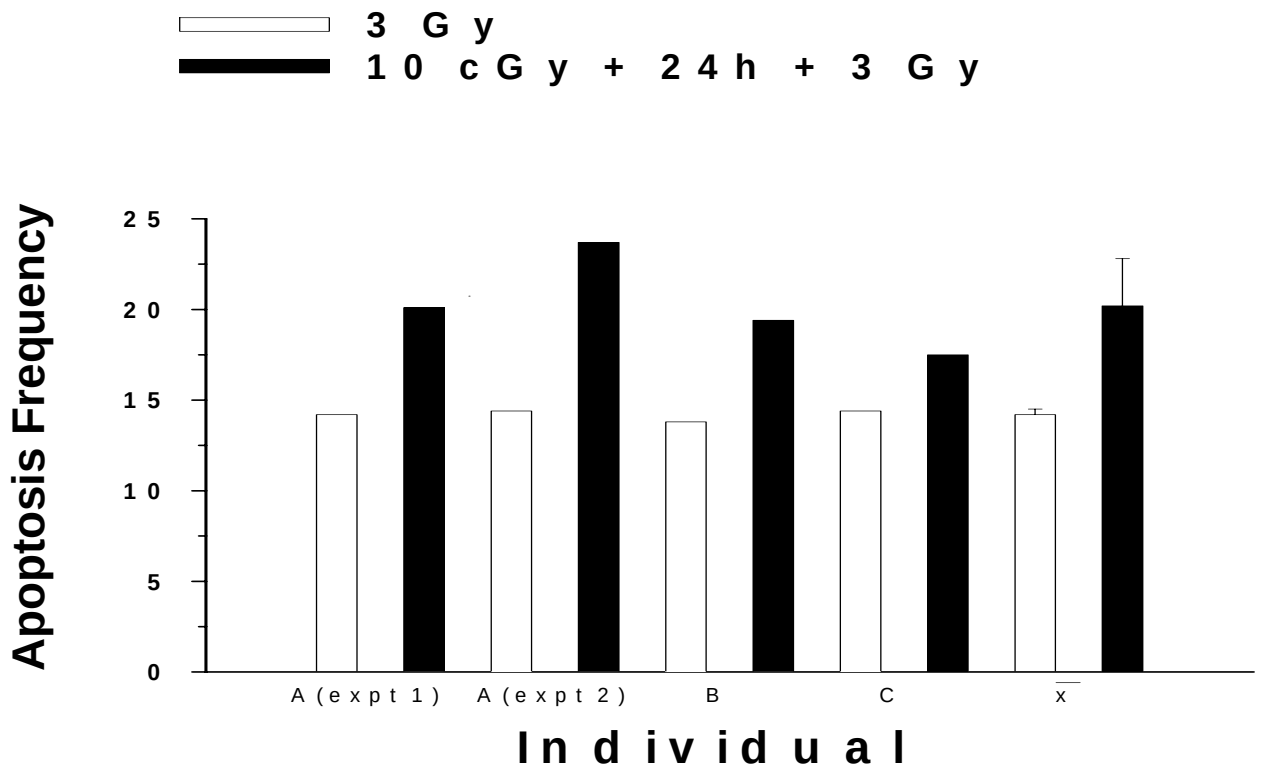
Azzam, de Tolido, Raaphorst and Mitchel, Radiat. Res. 146:369-373 (1996)

Transformation in Human Cells

J. L. Redpath and R.J. Antoniono,
Radiat. Res. 149, 517-520 (1998)



Low Doses Sensitize Non-Dividing Human Lymphocytes to Apoptosis



Cregan, Brown, and Mitchel, IJRB 75:1087-1094, 1999

ADAPTION IN THE IMMUNE SYSTEM

The Percentage of Human Lymphocytes Expressing IL-2 Receptors 24 h After Stimulation

Control Cells	Irradiated Cells (10 mGy)	50% Control Cells + 50% Irradiated Cells
7.7 ± 4.1	17.8 ± 3.3 p<0.01	22.6 ± 4.8 p<0.01

Y. Xu, C.L. Greenstock, A. Trivedi and R.E.J. Mitchel

Radiation and Environmental Biophysics 35: 89-93 (1996)

SOMETIMES HORMETIC EFFECTS ARE NOT BENEFICIAL

HORMESIS-AN UNDESIRABLE EFFECT!

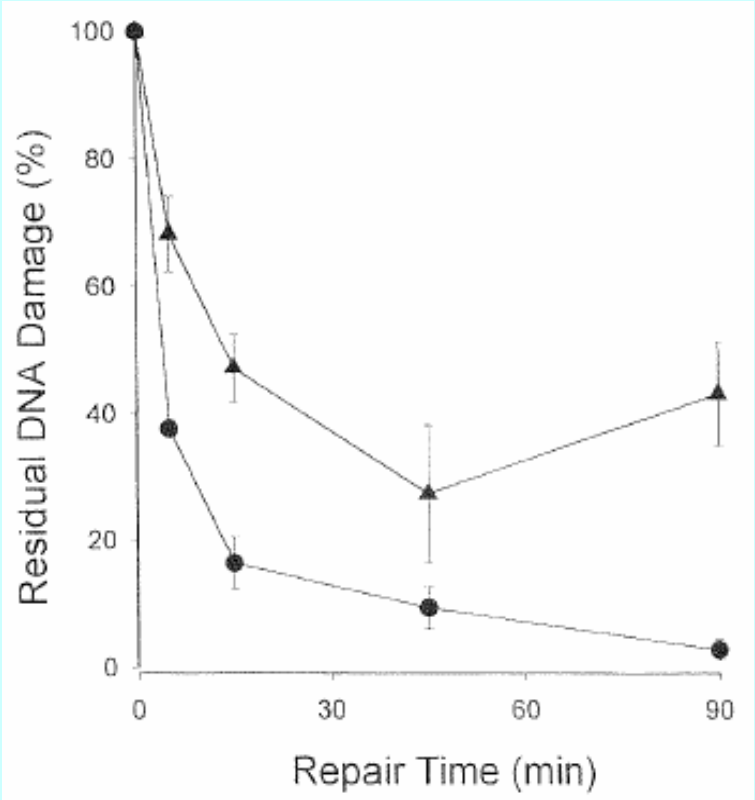


Figure 3. DNA strand break repair in AG1522 cells. Cells were treated with 10 μg/ml of cisplatin (for 30 min at 37°C) 24 h before (triangles) exposure to 4 Gy ^{60}Co γ-radiation. Control cells (circles) were not treated with cisplatin before irradiation.

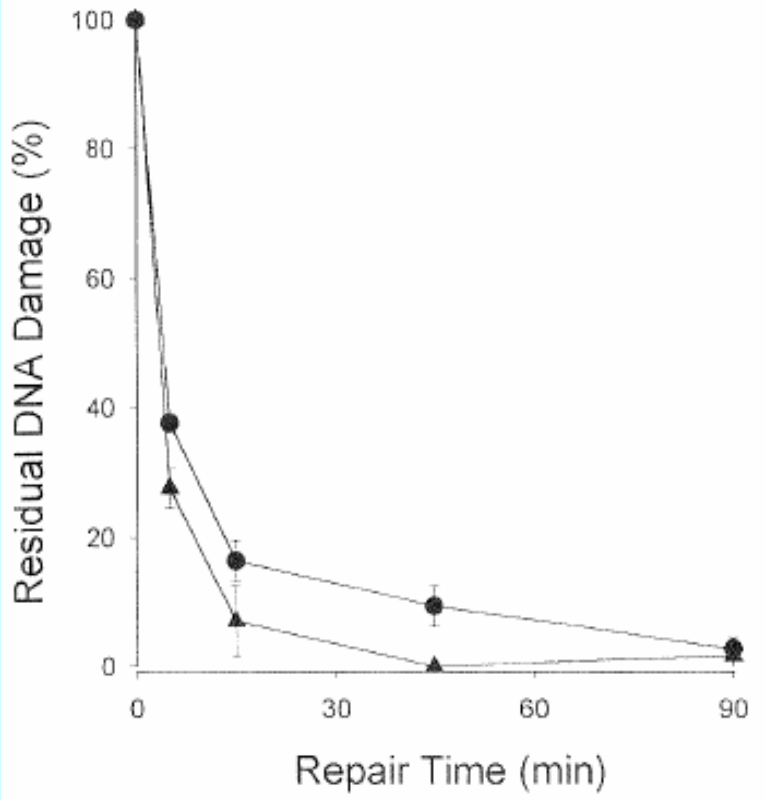


Figure 4. DNA strand break repair in AG1522 cells. Cells were treated with 1 μg/ml of cisplatin (for 30 min at 37°C) 24 h before (triangles) exposure to 4 Gy ^{60}Co γ-radiation. Control cells (circles) were not treated with cisplatin before irradiation.

Dolling, Boreham, Brown, Mitchel and Raaphorst, IJRB, 74:61-69, 1998

DO THESE RADIATION-INDUCIBLE ADAPTIVE PROCESSES PRODUCE HORMETIC EFFECTS *IN VIVO*??

DO RADIATION-INDUCED ADAPTIVE RESPONSES PRODUCE DESIRABLE HORMETIC EFFECTS FOR RADIATION RISK?

HOW DO WE MEASURE RADIATION RISK?

- Cancer
- Teratogenesis
- Heritable effects
- Other diseases

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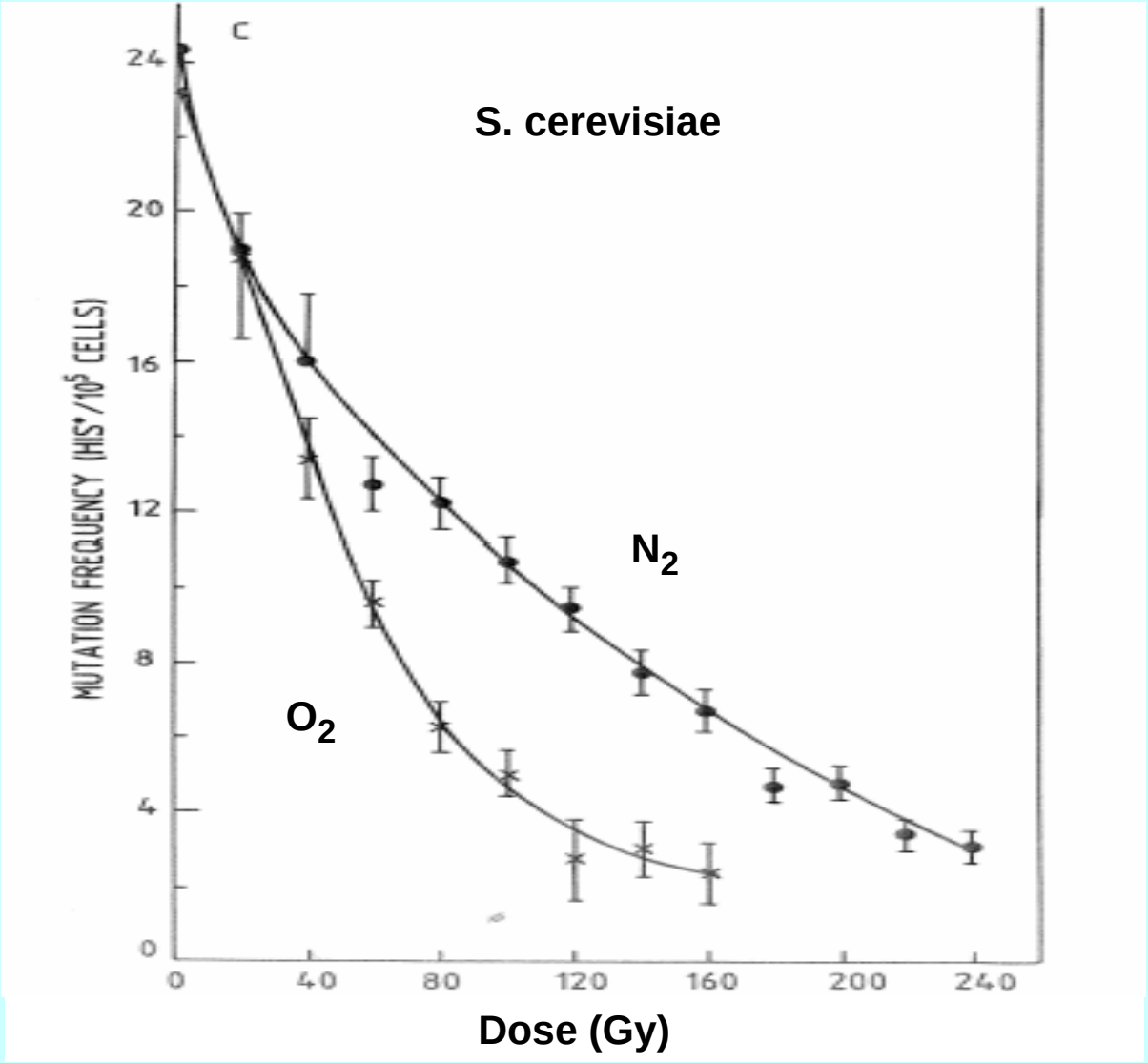


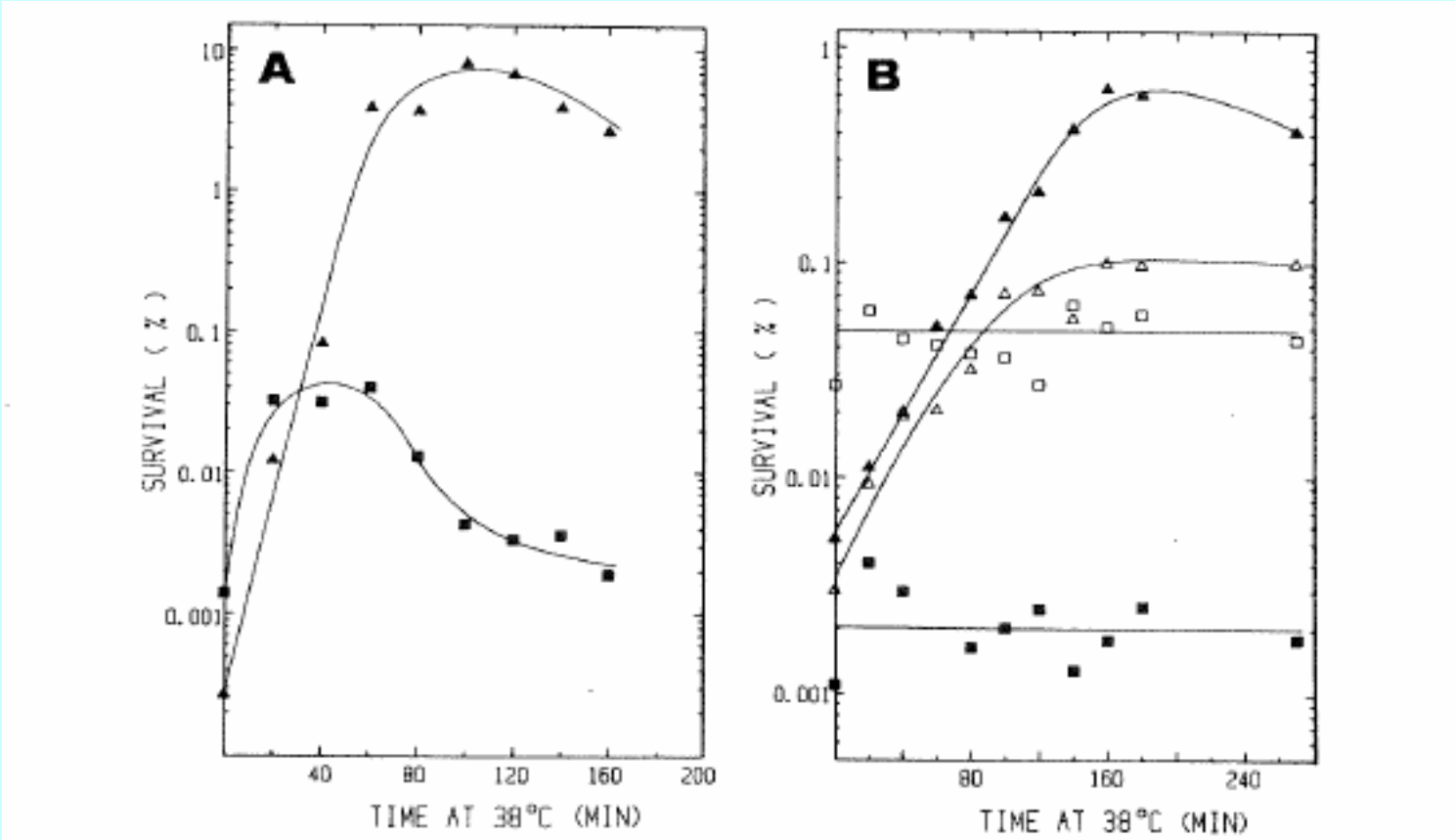
Mitchel and Morrison Mutat. Res. 183:149-159 (1987)

CHEMICAL-INDUCED SKIN TUMORS IN MICE

Protection by Radiation Against Chemical Tumor Initiation

Initiation Treatment	Tumors per Animal
MNNG	2.04
Beta Radiation (0.5 Gy)	0
Beta + MNNG	0.39

ADAPTION AND DNA REPAIR PATHWAYS



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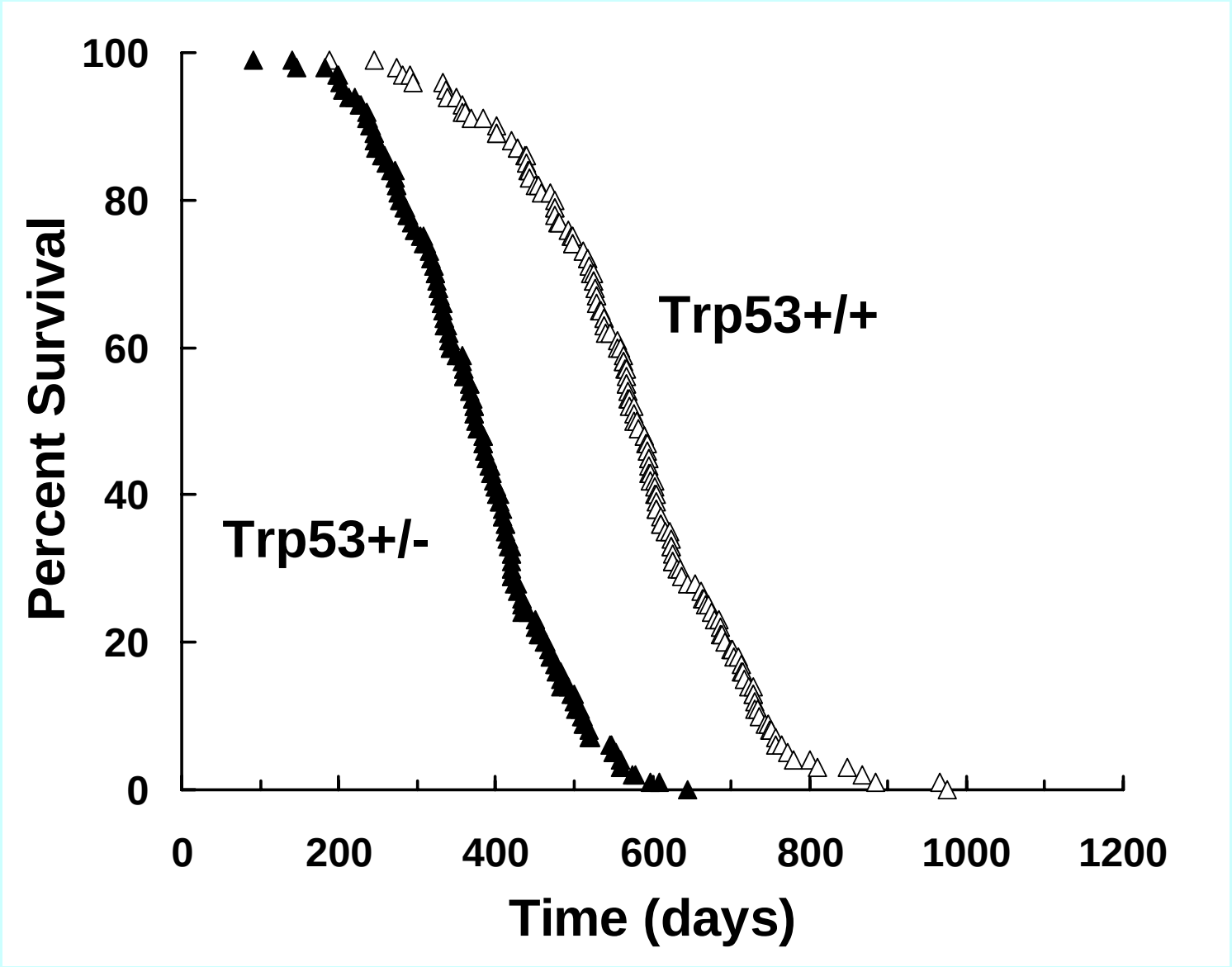
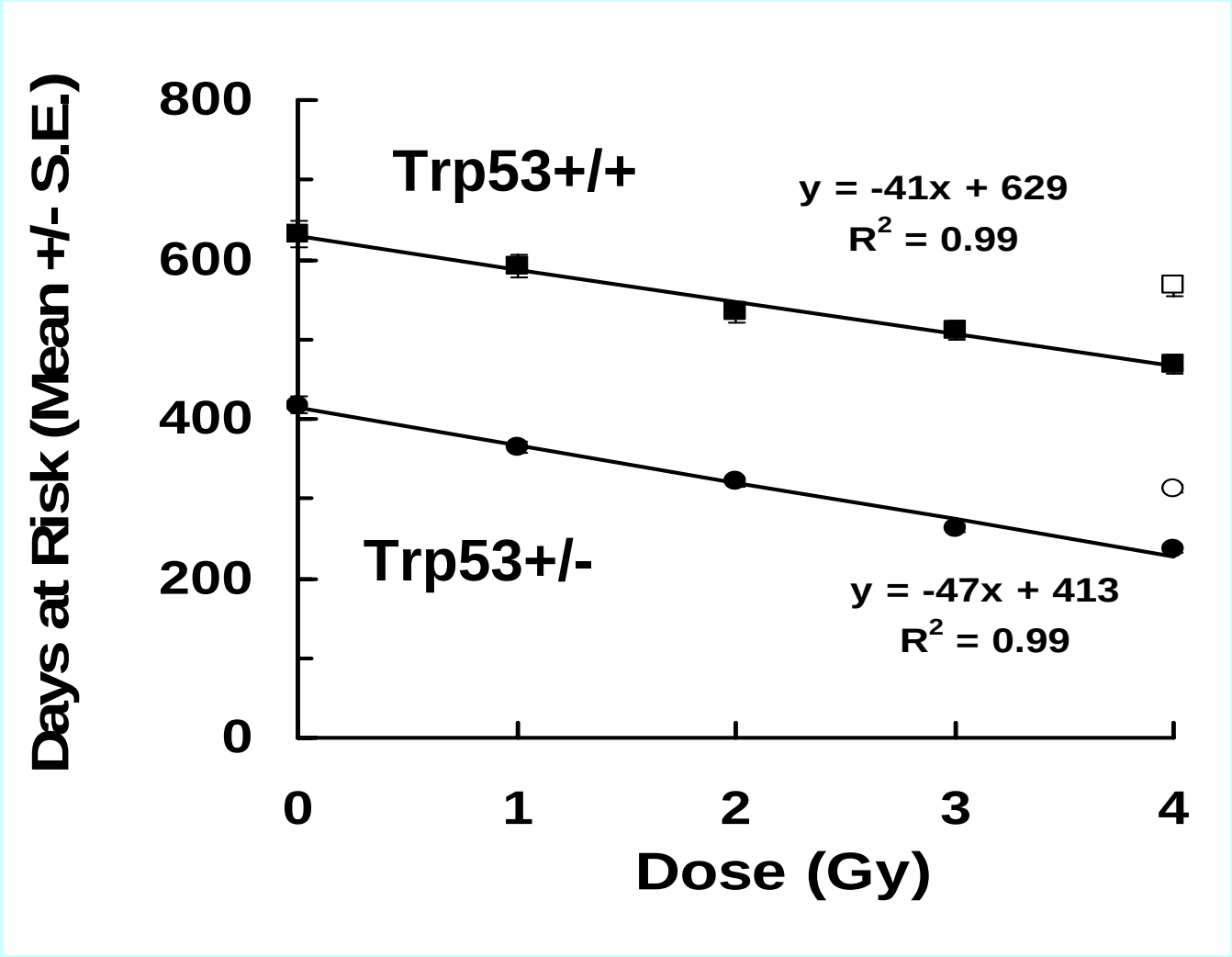
Mitchel and Morrison, Radiat. Res 92:182-187, 1982

SURVIVAL WITHOUT RADIATION EXPOSURE

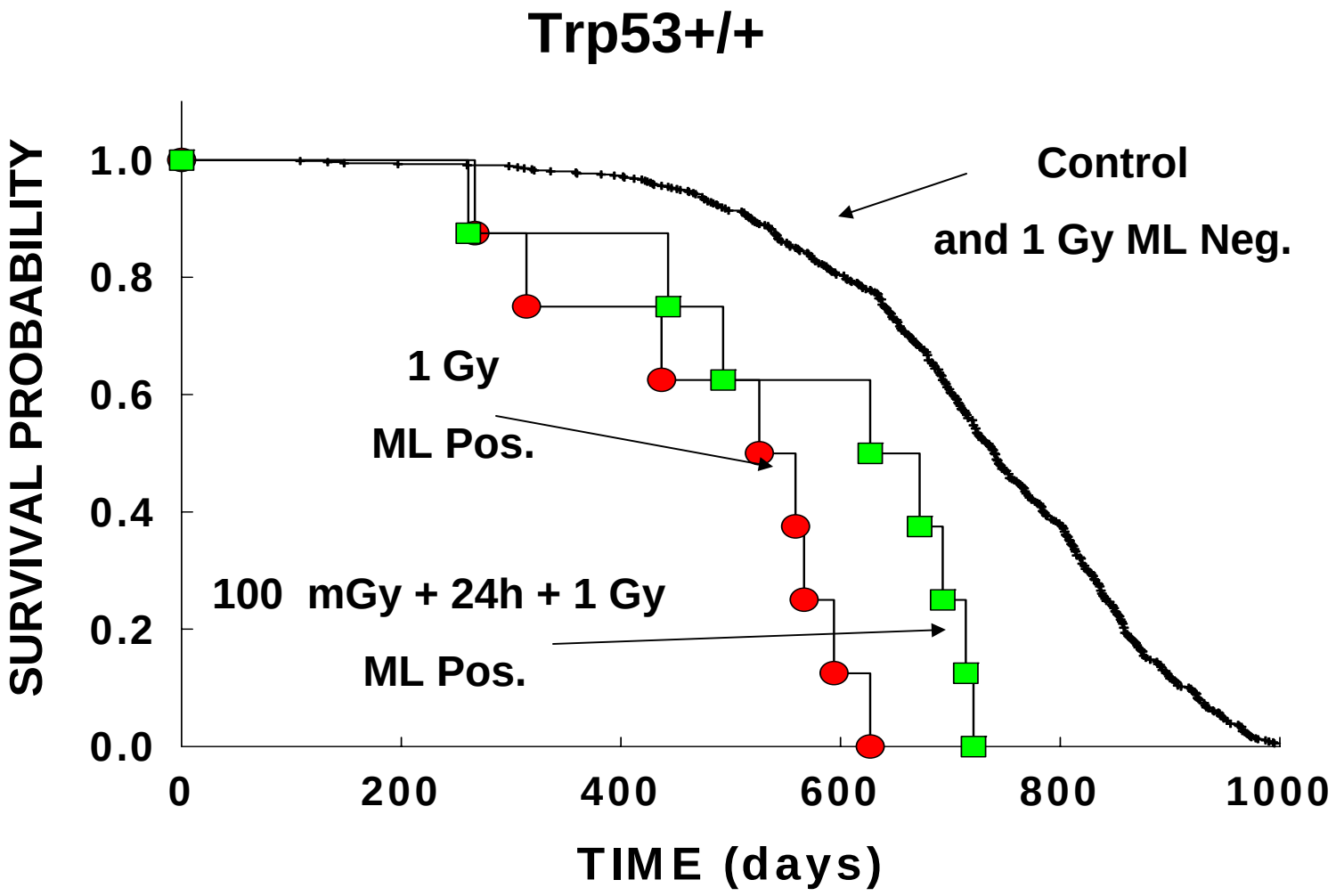


LOSS OF LIFE FROM HIGH DOSE EXPOSURE IN NORMAL AND TRP53 +/- MICE WITH CANCER



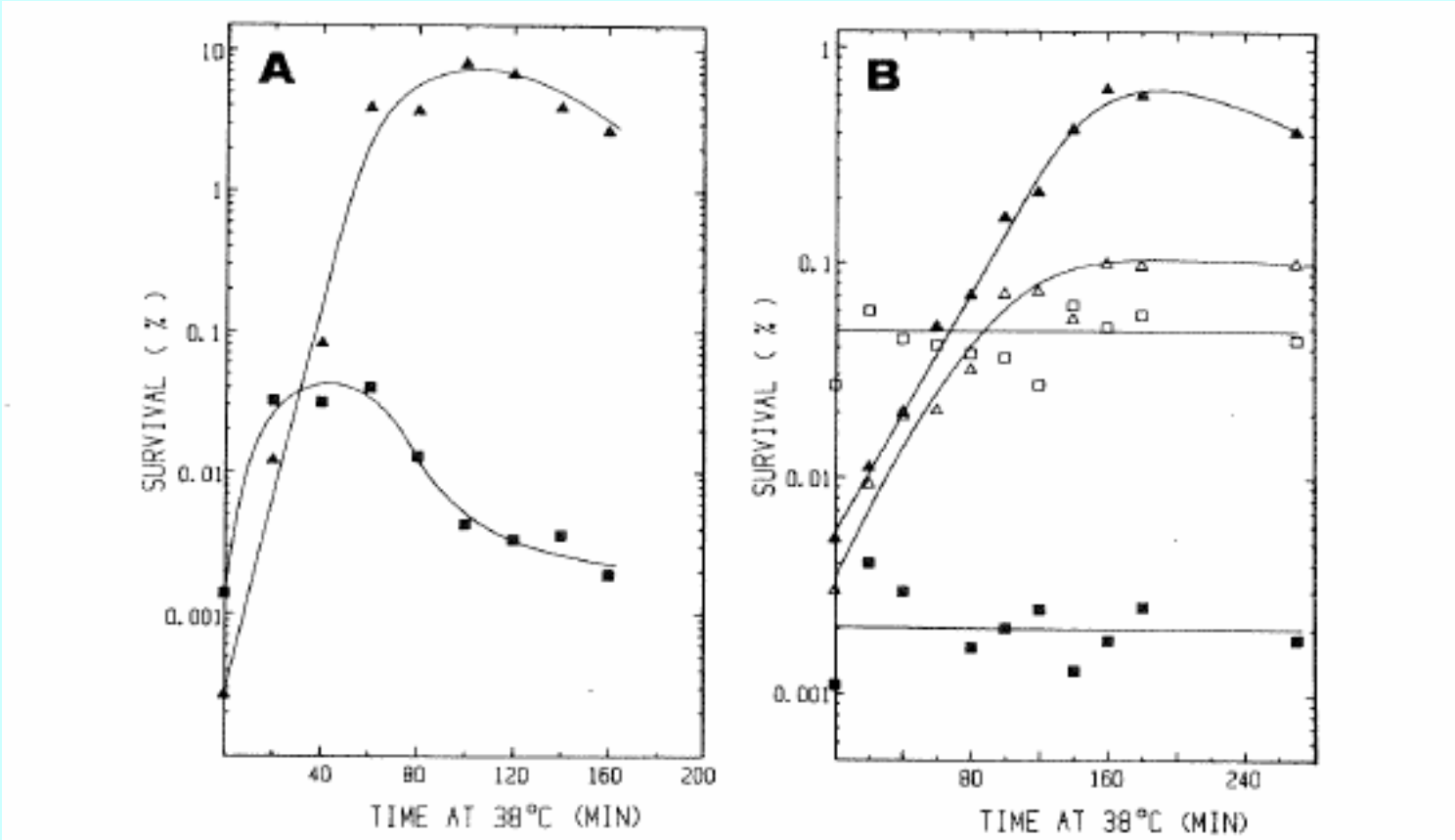
R. E. J. Mitchel et al. unpublished

Myeloid Leukemia in p53 Normal Mice



Mitchel, Jackson, McCann and Boreham, Radiat. Res. 152:273-279 (1999)

ADAPTION AND DNA REPAIR PATHWAYS



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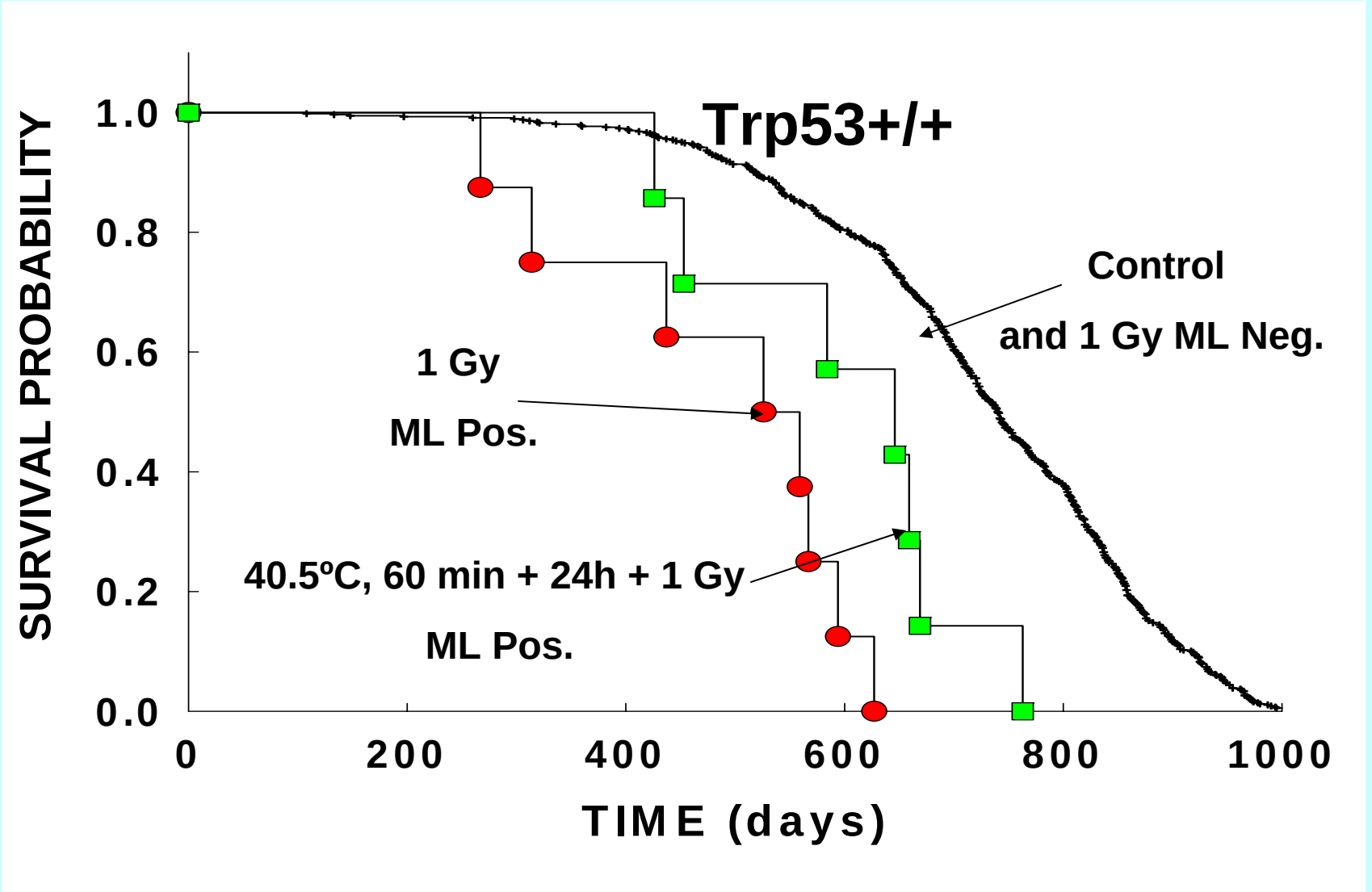
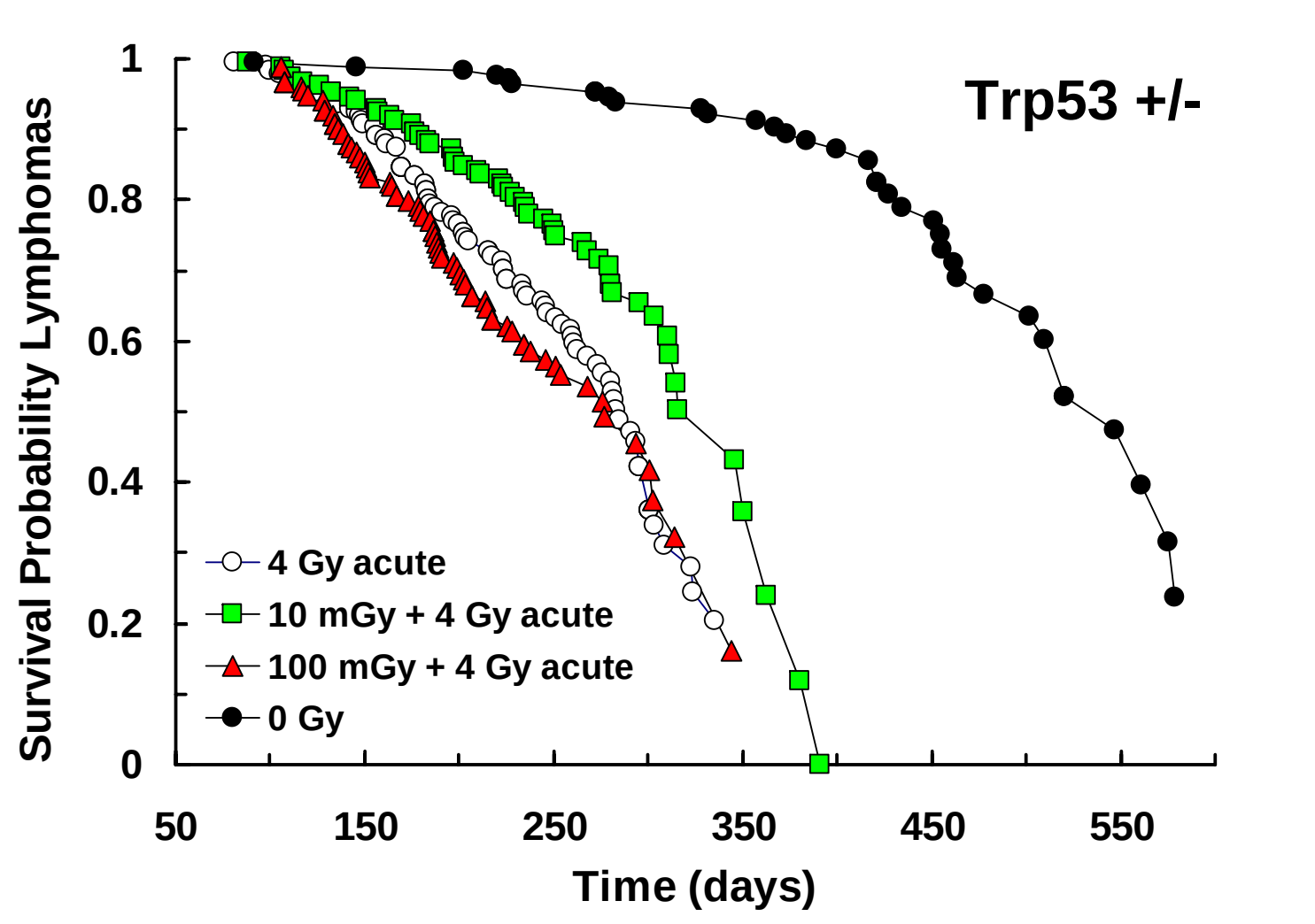


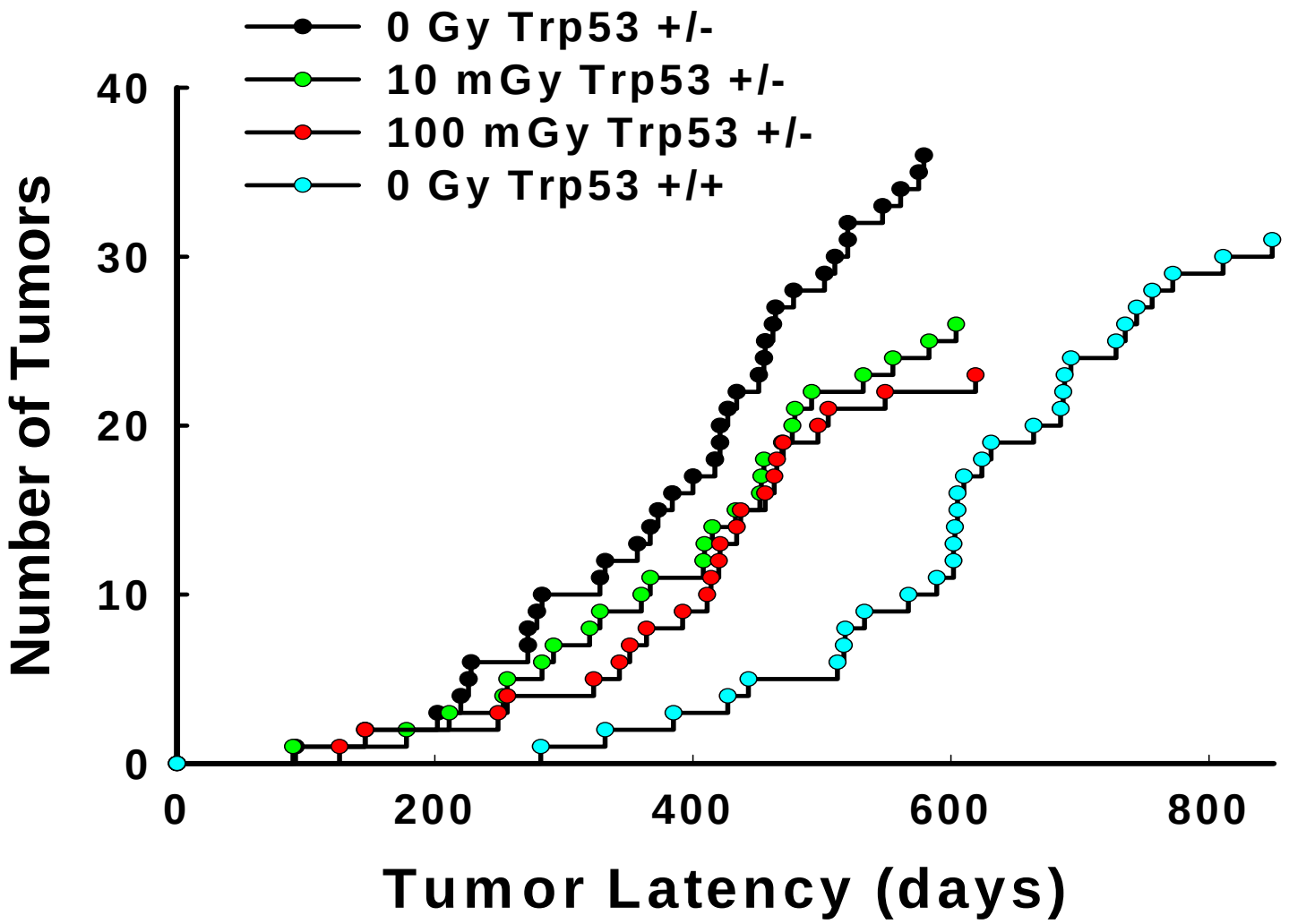
Mitchel, Jackson, McCann and Boreham, Radiat. Res. 152:273-279 (1999)

Lymphomas in Cancer-Prone Mice



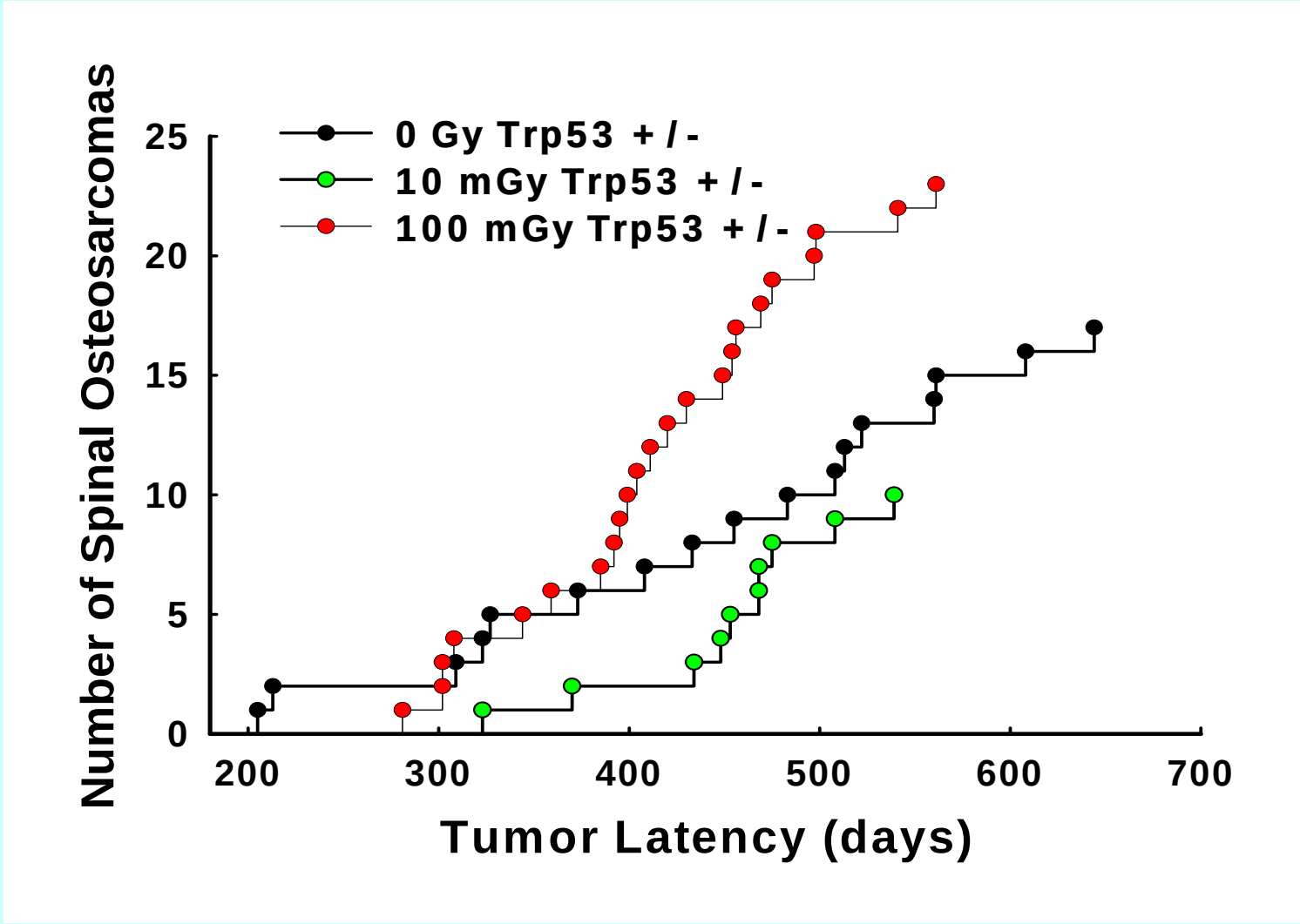
Mitchel, Jackson and Carlisle, Radiat. Res. 162:20-30 (2004)

Lymphoma Latency



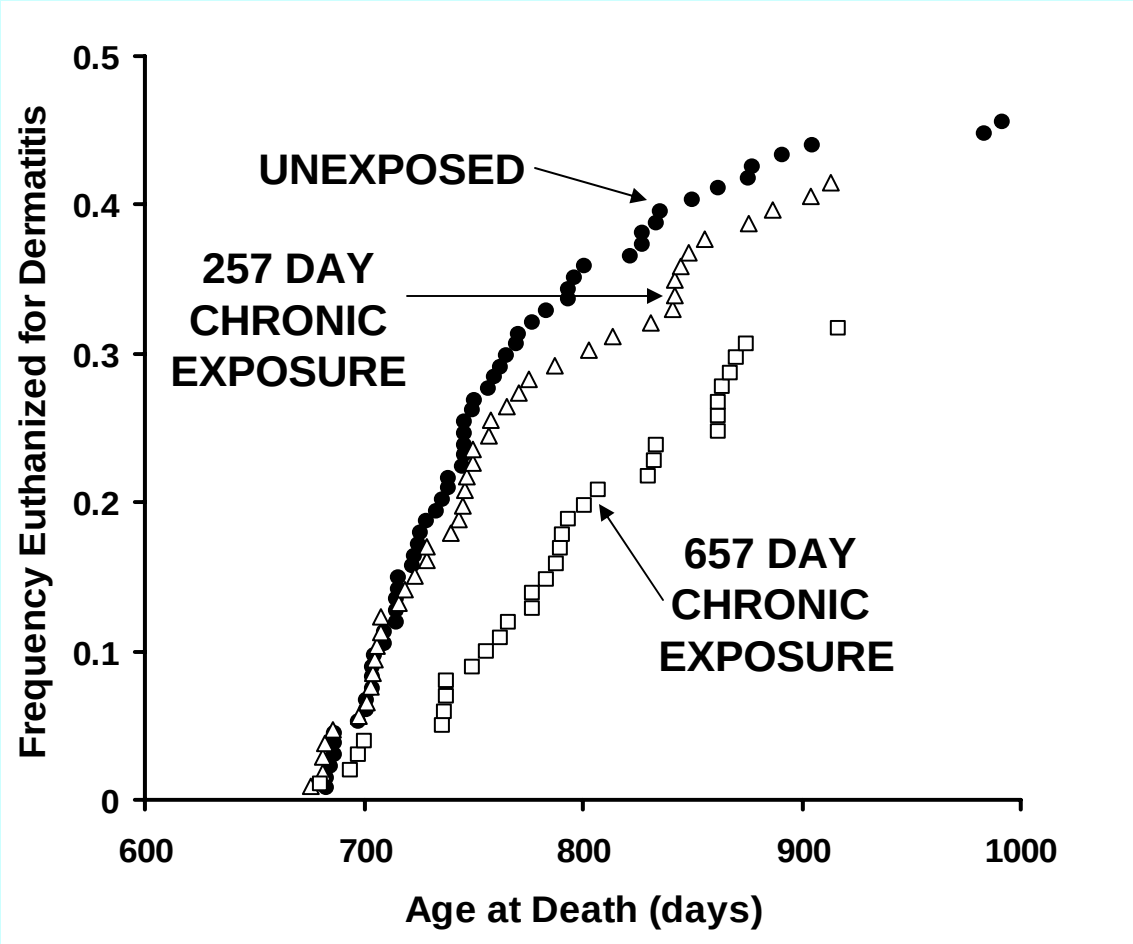
Mitchel, Jackson, Morrison and Carlisle, Radiat. Res. 159:320-327 (2003)

Spinal Osteosarcomas in Trp53+/- Mice



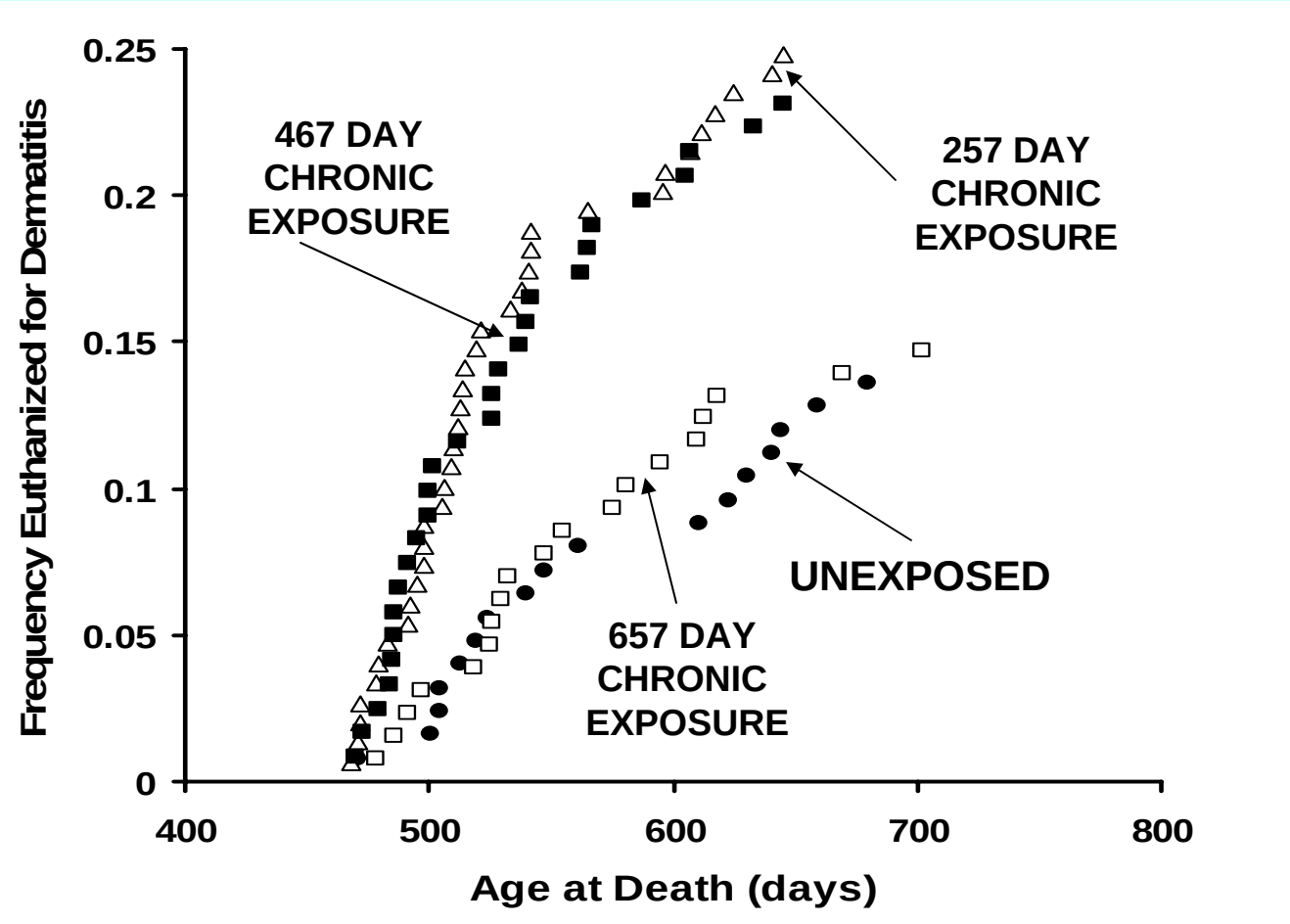
Mitchel, Jackson, Morrison and Carlisle, Radiat. Res. 159:320-327 (2003)

LOW DOSES AND ACUTE ULCERATIVE DERMATITIS IN MICE WITH NORMAL P53 FUNCTION (TP53+/+)



MITCHEL, BURCHART AND WYATT, UNPUBLISHED

LOW DOSES AND ACUTE ULCERATIVE DERMATITIS IN MICE WITH LOW P53 FUNCTION (TP53+/-)



MITCHEL, BURCHART AND WYATT, UNPUBLISHED

CONCLUSIONS

- **Adaptive responses to radiation induce hormetic effects**
- **Hormetic effects have mainly positive outcomes**
- **Abnormal genes can result in negative hormetic outcomes**

QUESTION

Do (all?) observed negative human outcomes from low dose radiation exposures result from hormetic effects in persons with abnormal gene function??