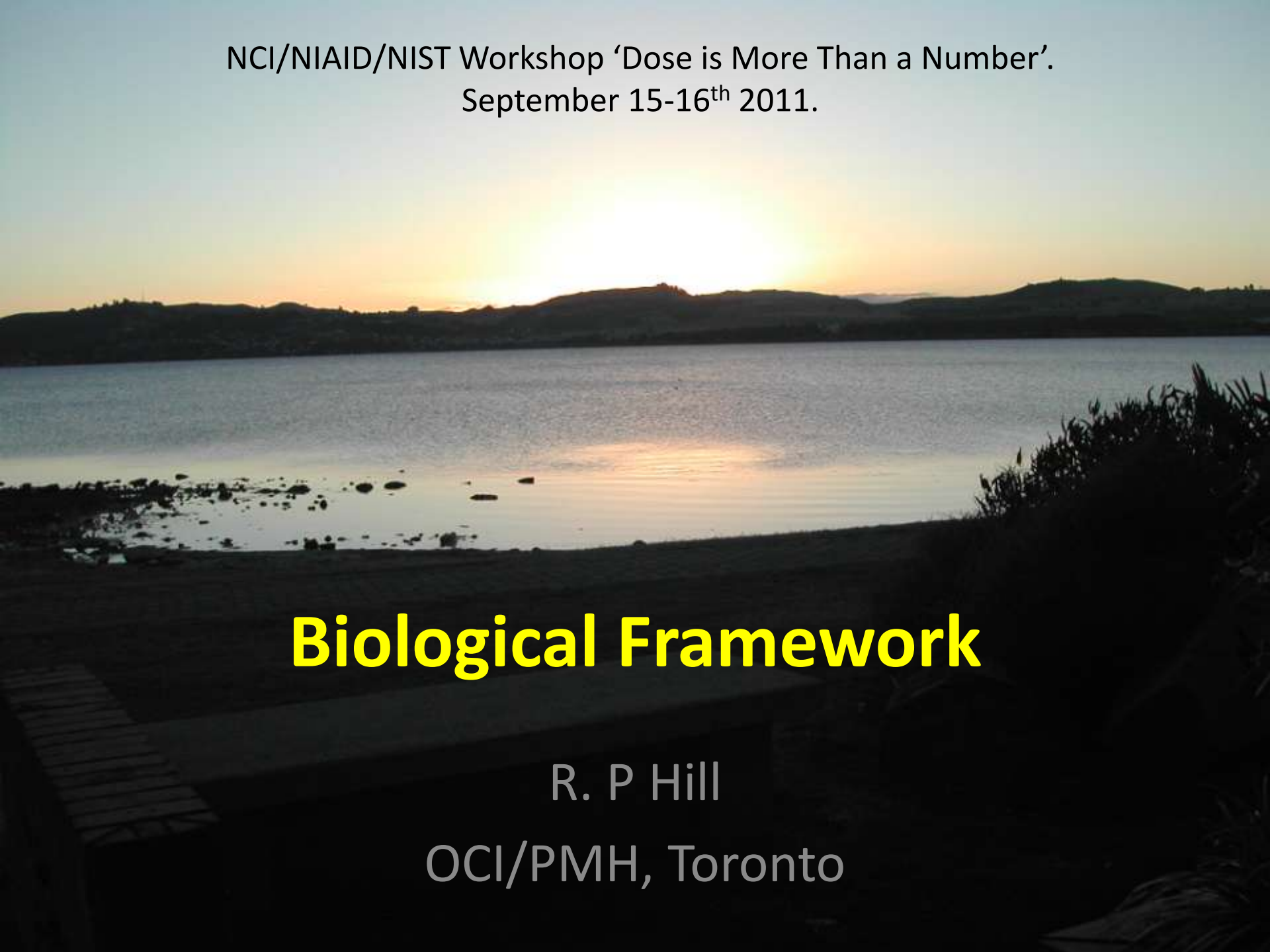
NCI/NIAID/NIST Workshop 'Dose is More Than a Number'.
September 15-16th 2011.



Biological Framework

R. P Hill

OCI/PMH, Toronto

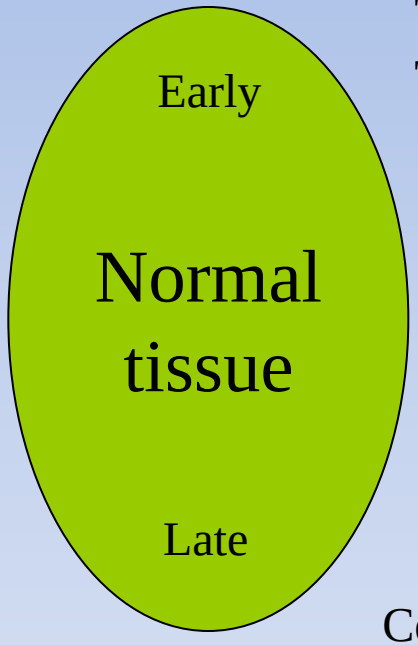
Normal tissue response to irradiation is multifactorial

Genetic susceptibility (DNA repair e.g. ATM, NBS1, Rad 51, DNA Pk, Ku). Tissue type specific expression?

Cytokine induction, e.g. TGF beta, IL-1, IL-6, TNF alpha, bFGF.

Induced Differentiation

Cellular sensitivity



Tissue related factors

Multiple cell types
Parenchymal cells
Endothelial cells
Inflammatory cells

Cell-Cell Contact

Cell-Matrix Interactions

Induced Apoptosis
DNA/Membrane damage

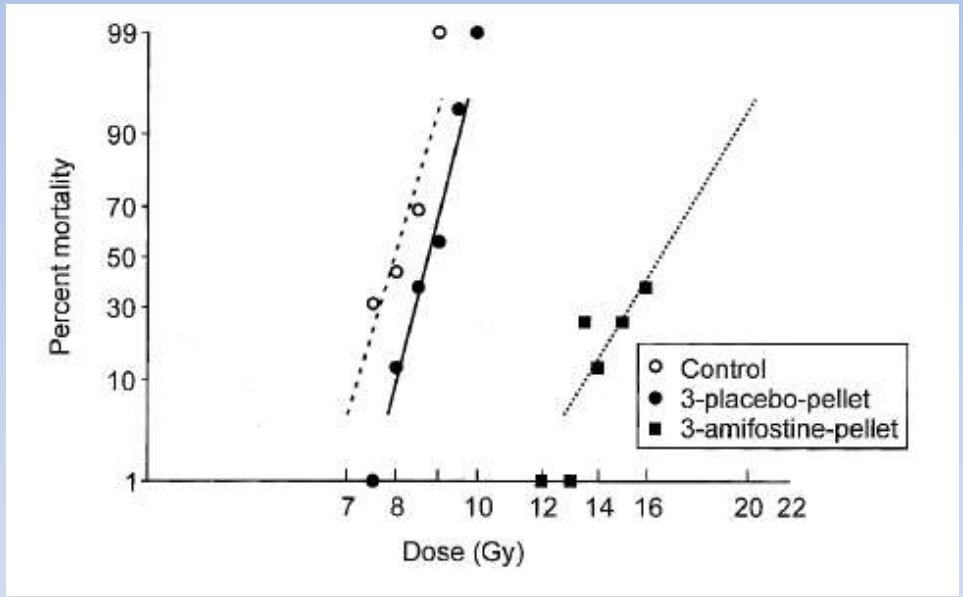
Radical Scavengers e.g.
GSH, MnSOD

Issues to be discussed

- Dose response
- Radiobiological effectiveness (RBE)
- Repair of radiation damage and consequent effect of dose rate.
- Differences in different endpoints
- Differences in different tissues

Dose response curves are steep

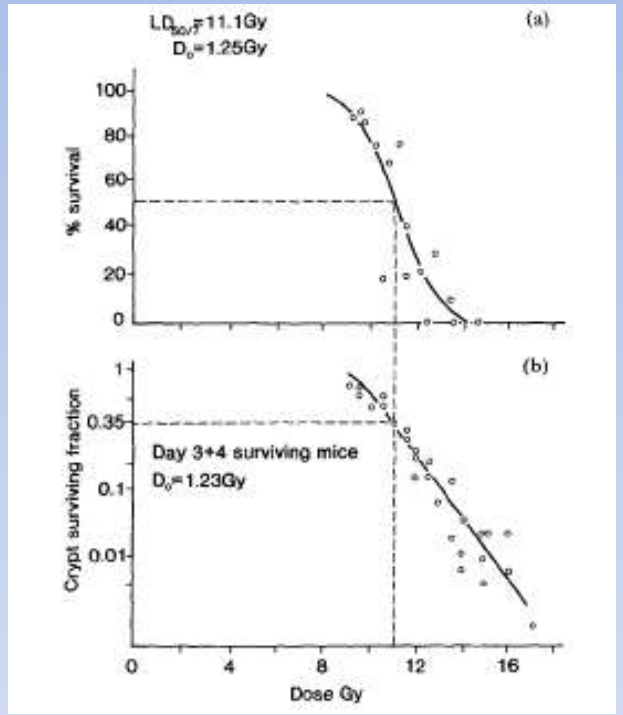
Lethality due to bone marrow failure (30 day survival)



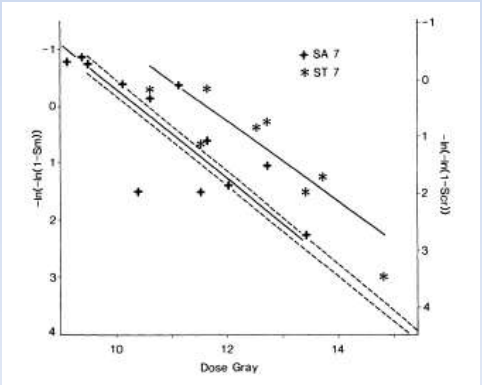
Co-60 γ-rays 1 Gy/min

From Srinivasan et al 2002

Crypt cell survival and GI tract lethality

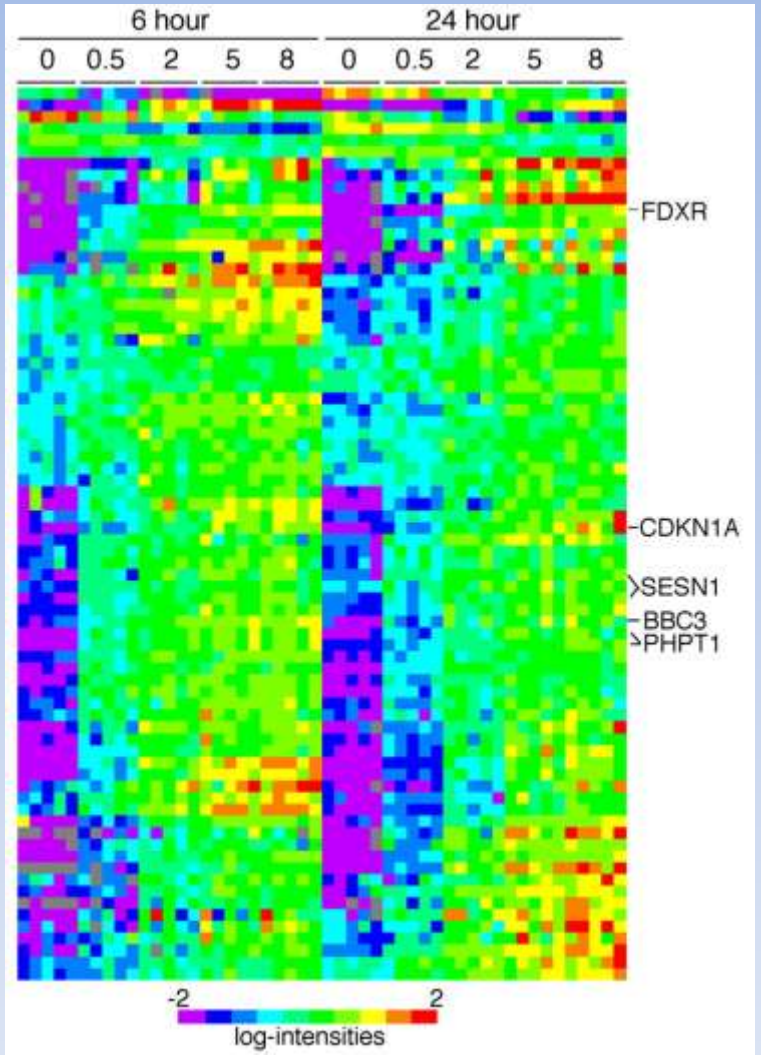


10 MeV electrons 20 Gy/sec
Or Cs γ-rays at 4.5 Gy/min

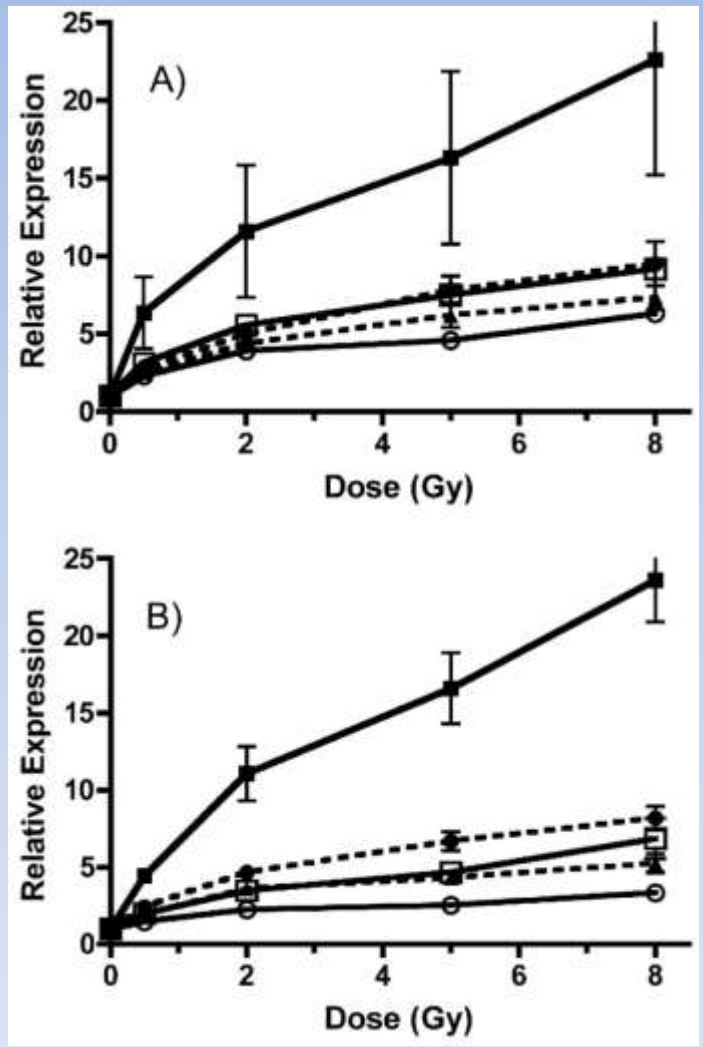


From Hendry et al 1983
Potton 2003

Expression of specific genes in irradiated human blood from different donors at 6 or 24 hrs after irradiation

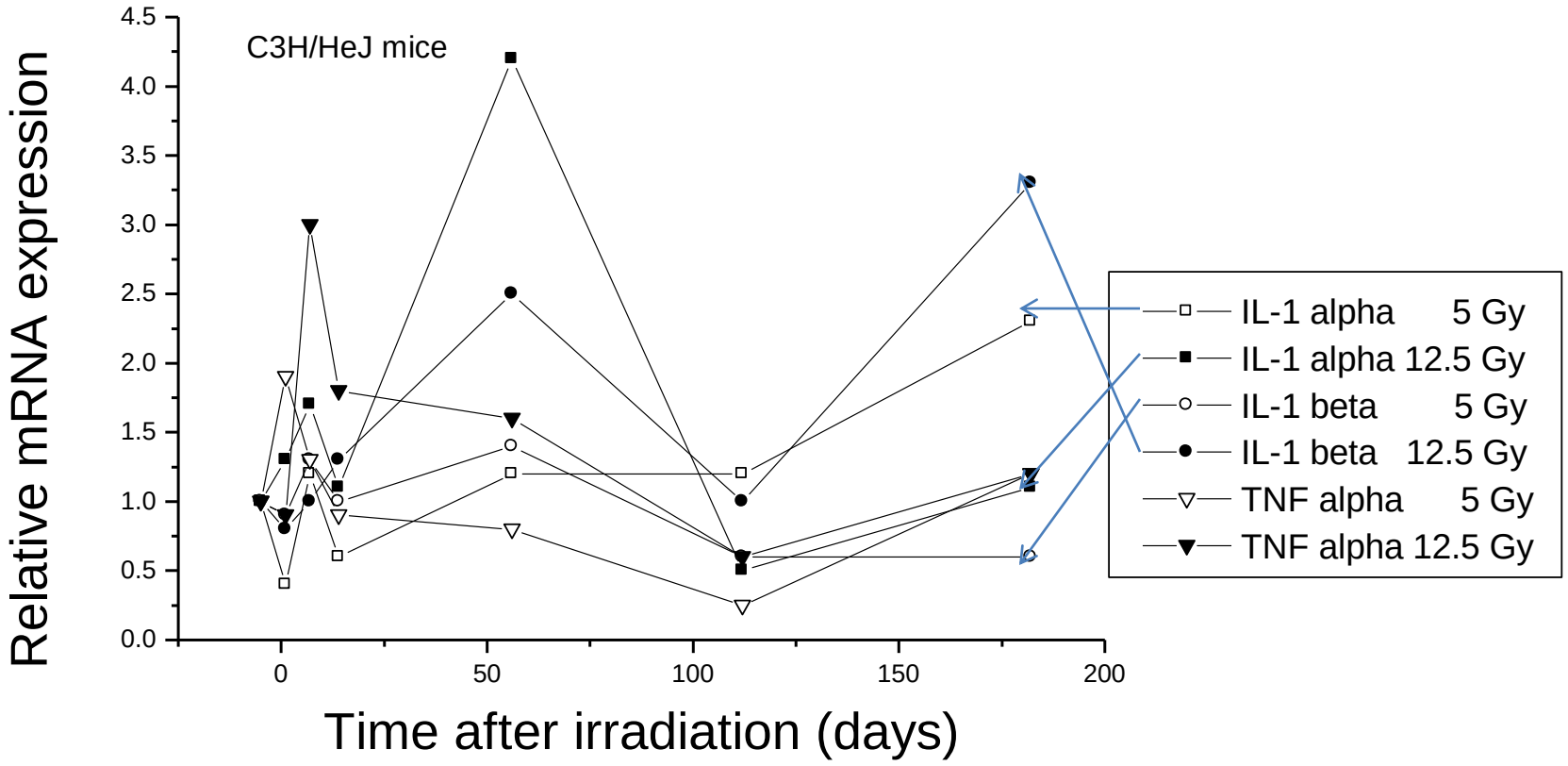


Relative expression of FDXR (■), CDKN1A (●), PHPT1 (□), BBC3 (▲) and SESN1 (○) at A) 6 and B) 24 hours after irradiation as measured by qRT-PCR.



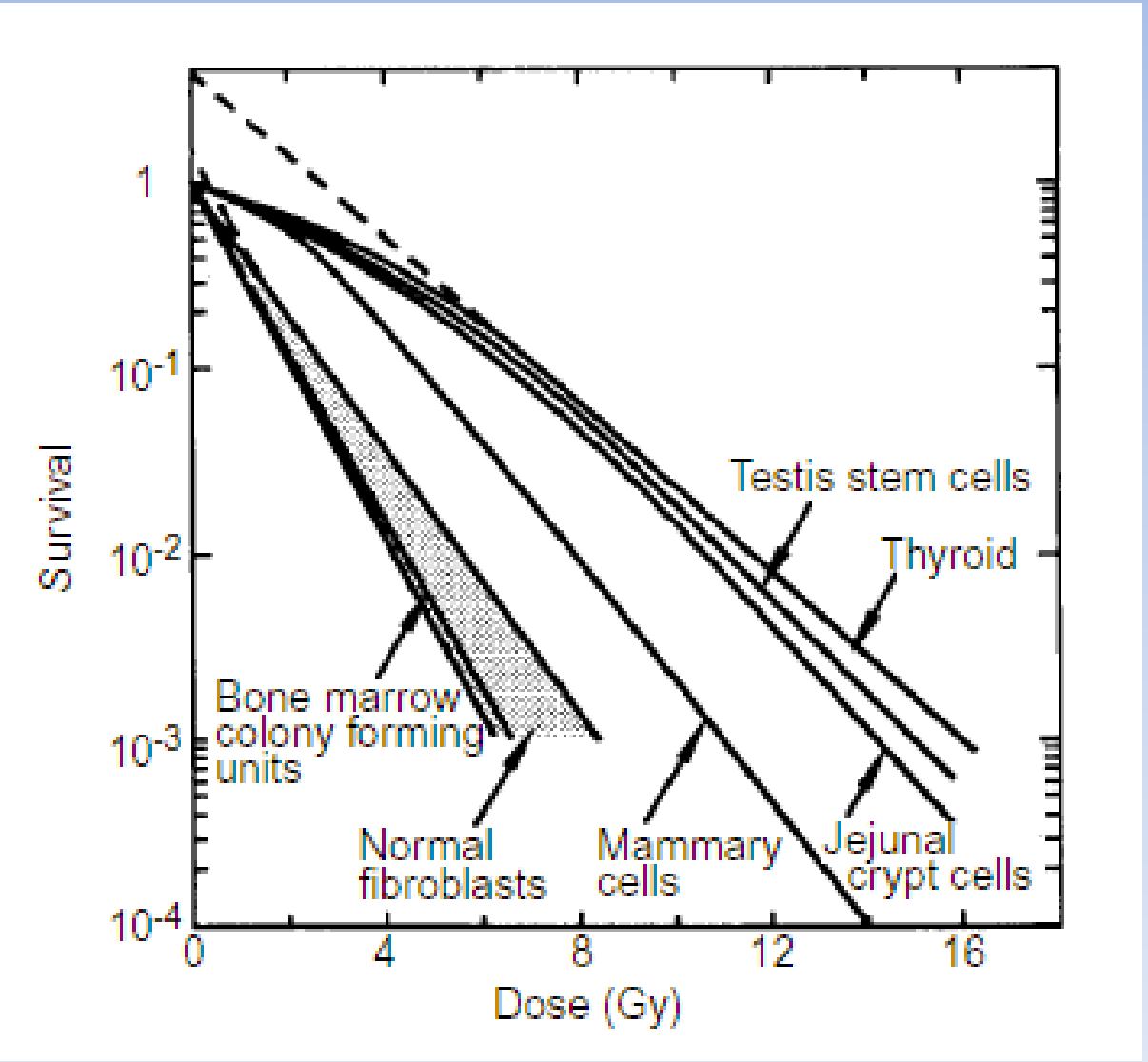
From Paul and Amundson 2008

Cytokine mRNA levels in lung after irradiation



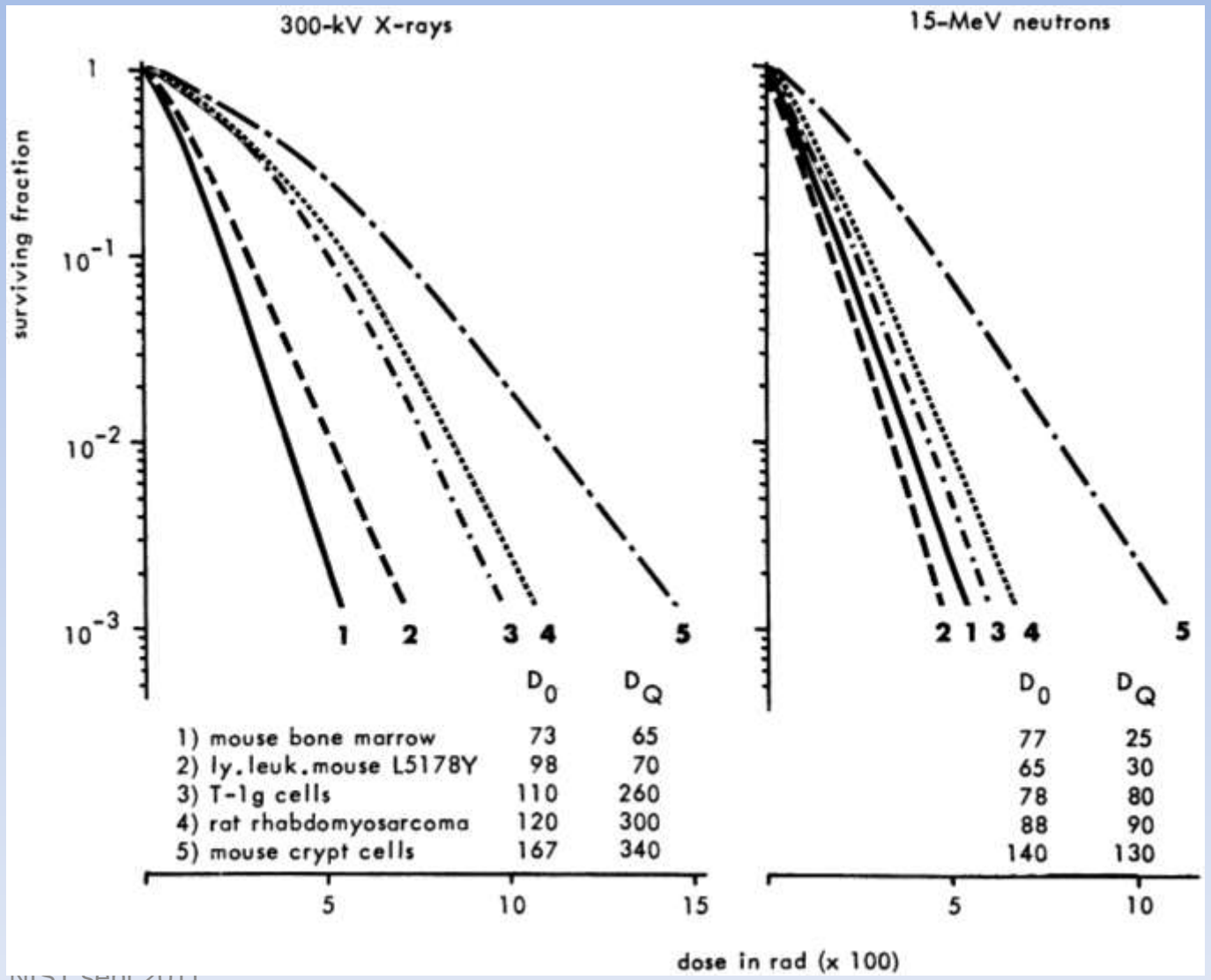
From Johnston et al 1996

Survival curves for different normal tissue cells



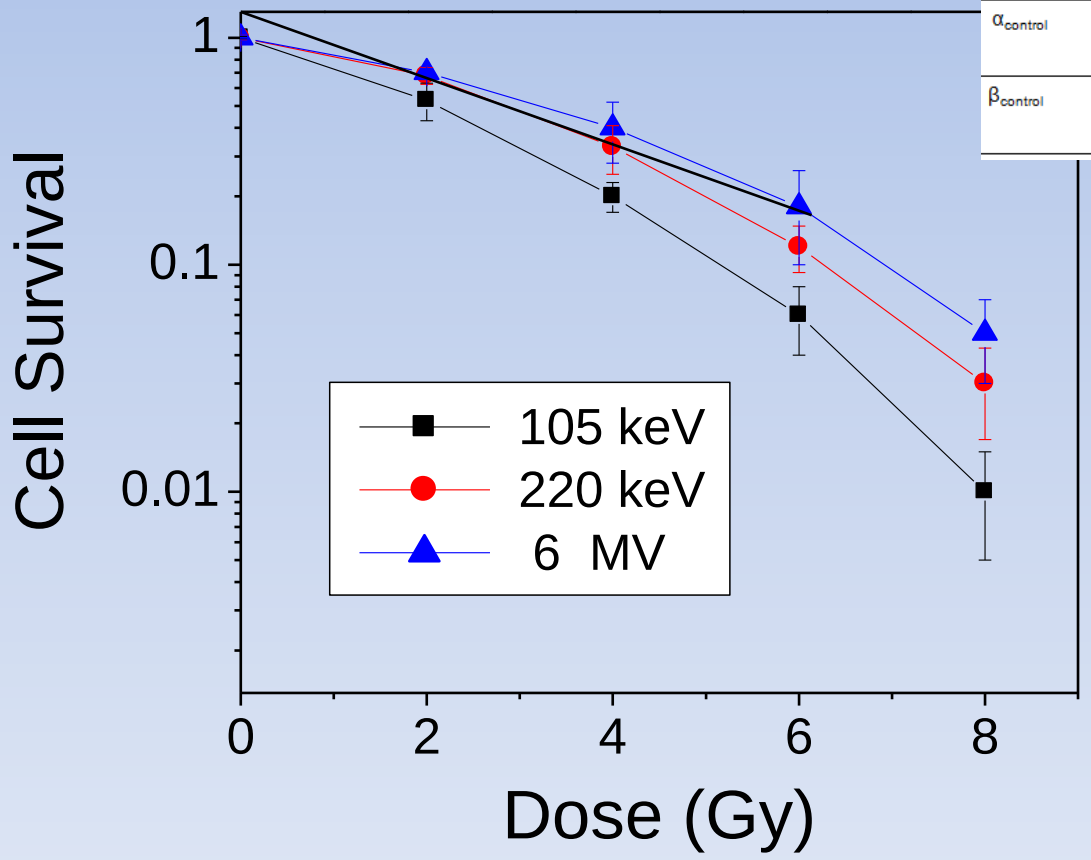
Modified from Hall, 1988

Dependence of RBE on type of cell irradiated



From Steel 2002

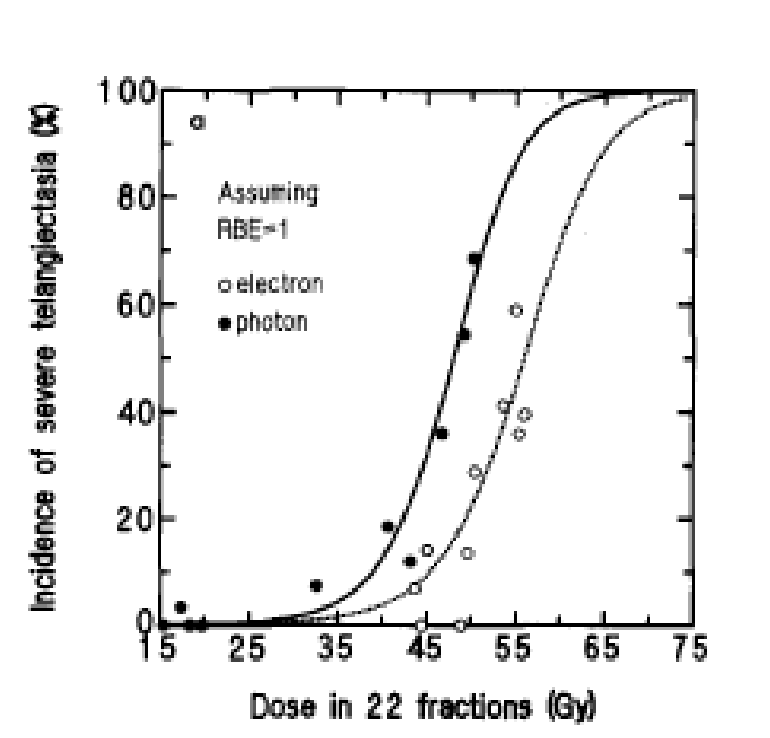
Cell survival following treatment with different sources (RBE effects)

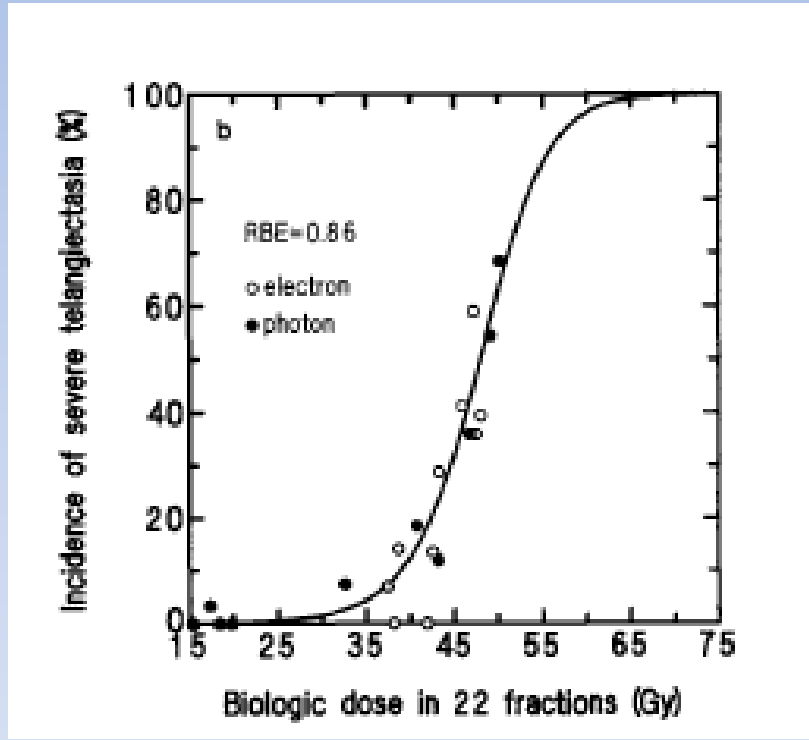


	105 kVp	220 kVp	660 kV	6 MV
$\alpha_{control}$	0.237 ± 0.005	0.150 ± 0.004	0.119 ± 0.013	0.110 ± 0.0080
$\beta_{control}$	0.041 ± 0.002	0.041 ± 0.001	0.04 ± 0.003	0.029 ± 0.0019

From Chithrani et al Rad Res 2010

Dose response – teleangiectasia in human skin (Breast Ca patients)





8 MV photons
8-10 MeV electrons
Dose was estimated at 0.1 mm depth.

Bentzen and Overgaard R and O 1991

RBE effects for different tissues

Fractionation

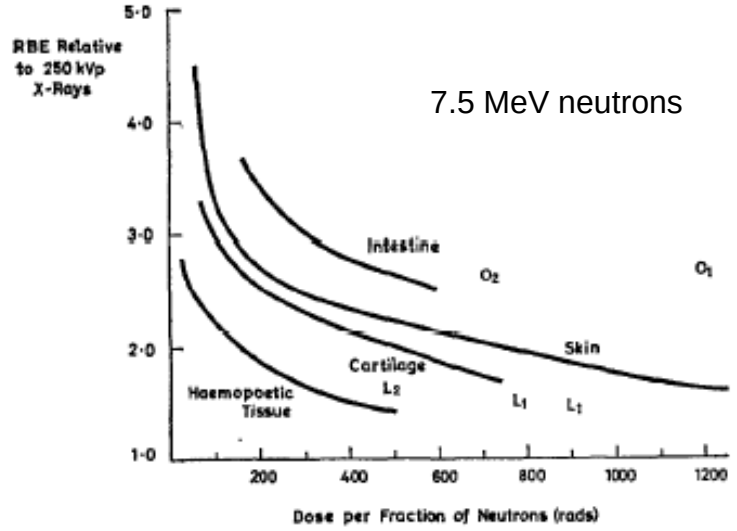
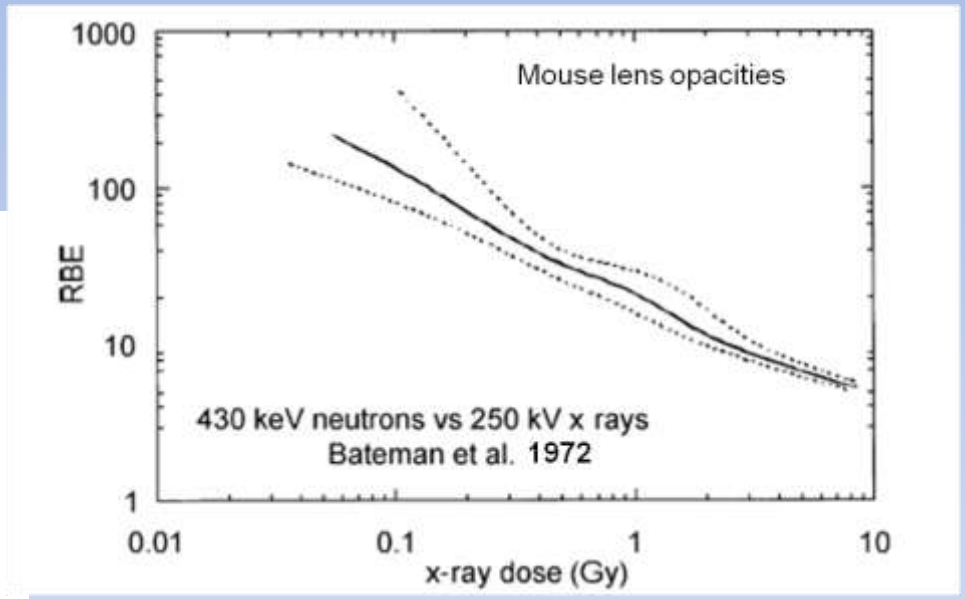


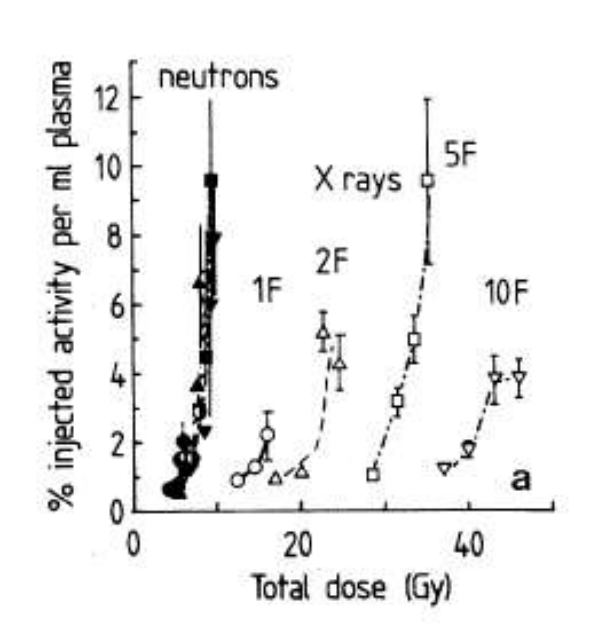
Fig. 2. RBE of Hammersmith cyclotron neutrons for different tissues, as a function of dose per fraction. O_1 and O_2 represent values for single doses and two fractions for oesophageal death, L_1 and L_2 represent values for lung death.

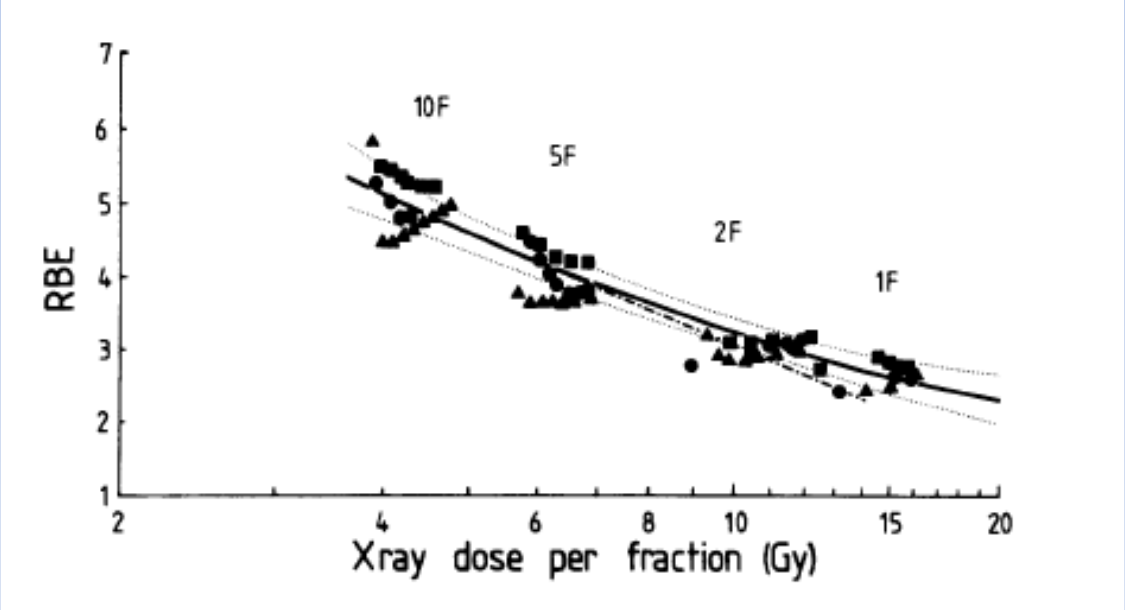
From Field and Hornsey, EJC, 1974



Low doses

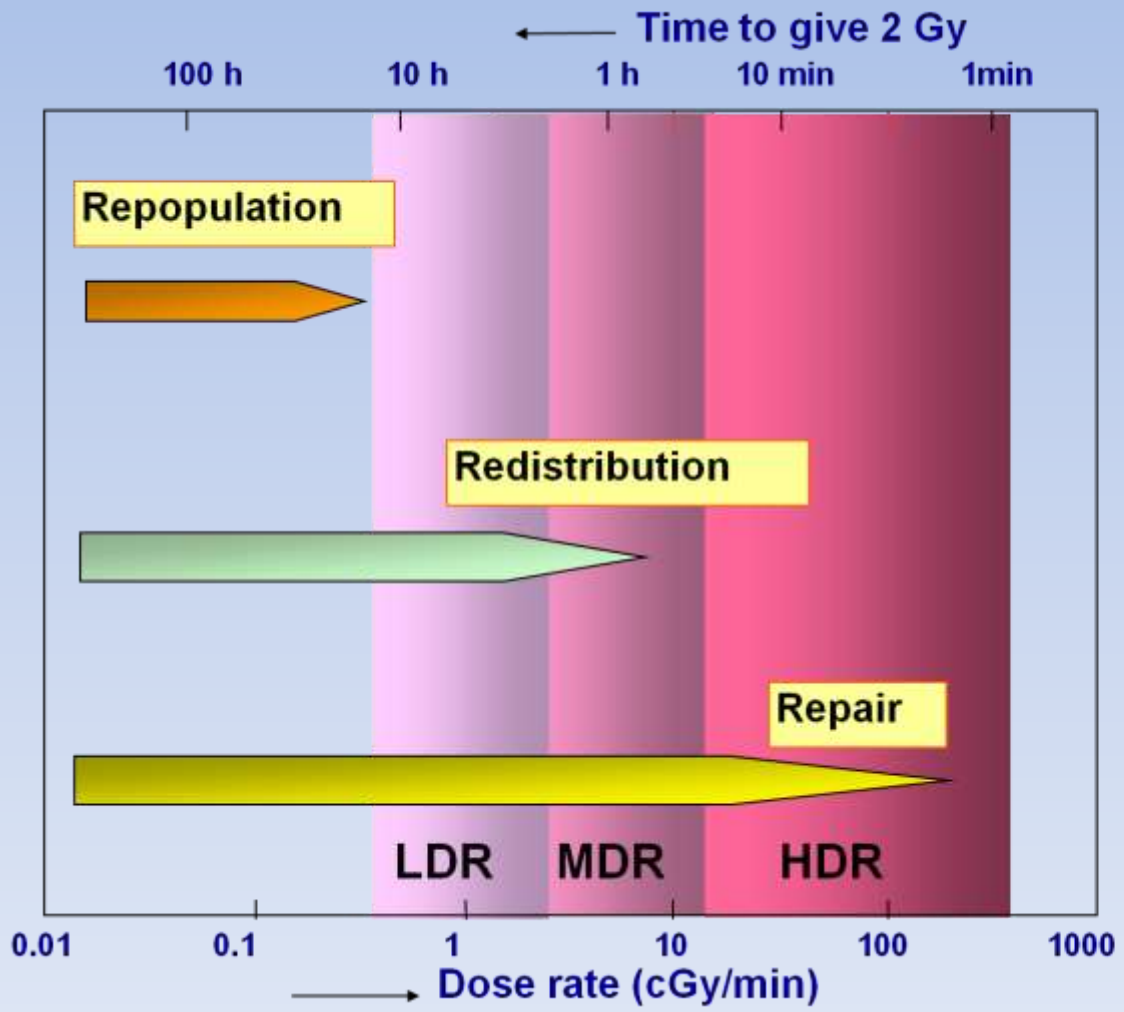
RBE and fractionation





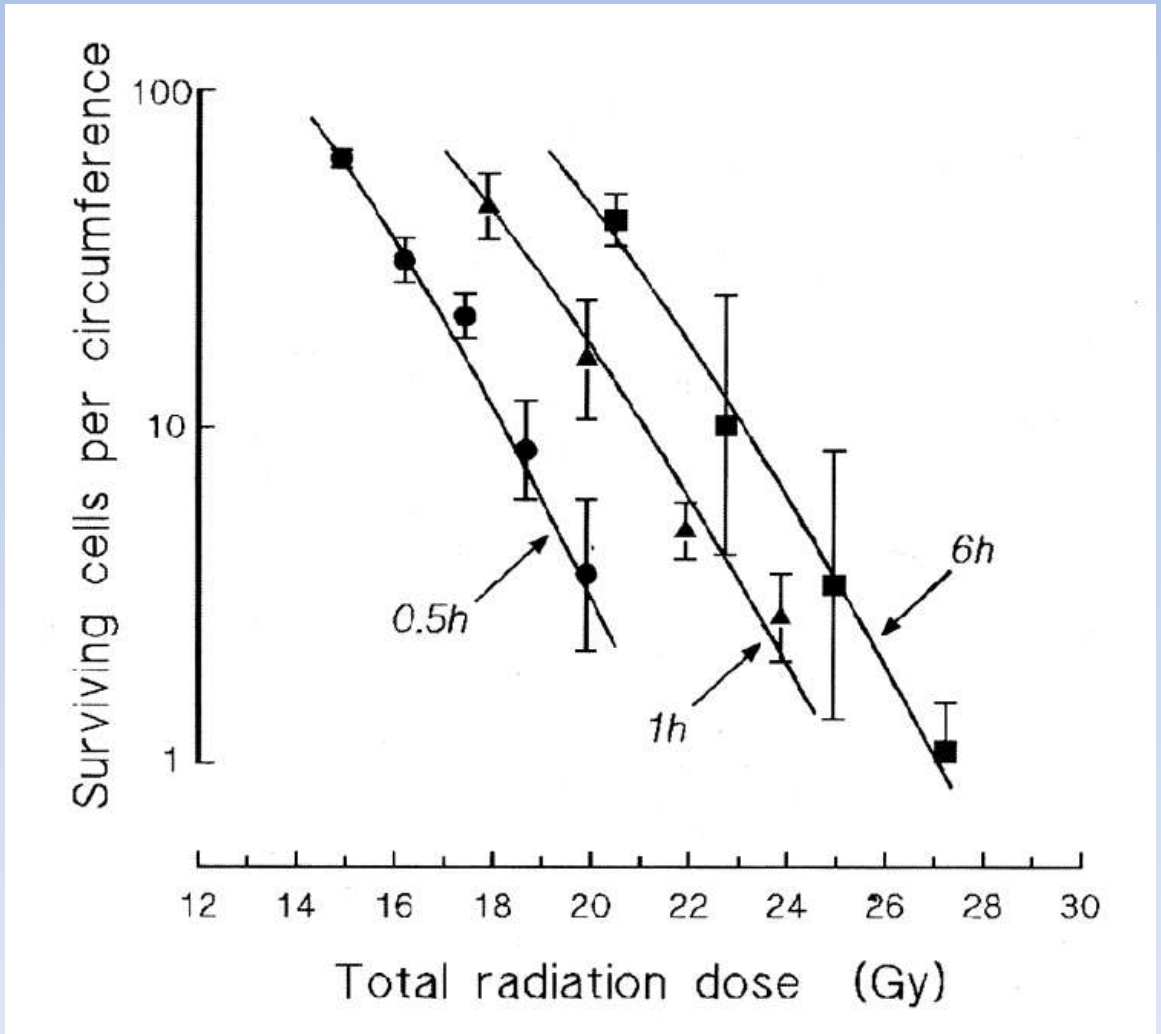
From Joiner and Johns Rad Res 1987

Radiobiological mechanisms underlying the dose rate effects in normal tissues.



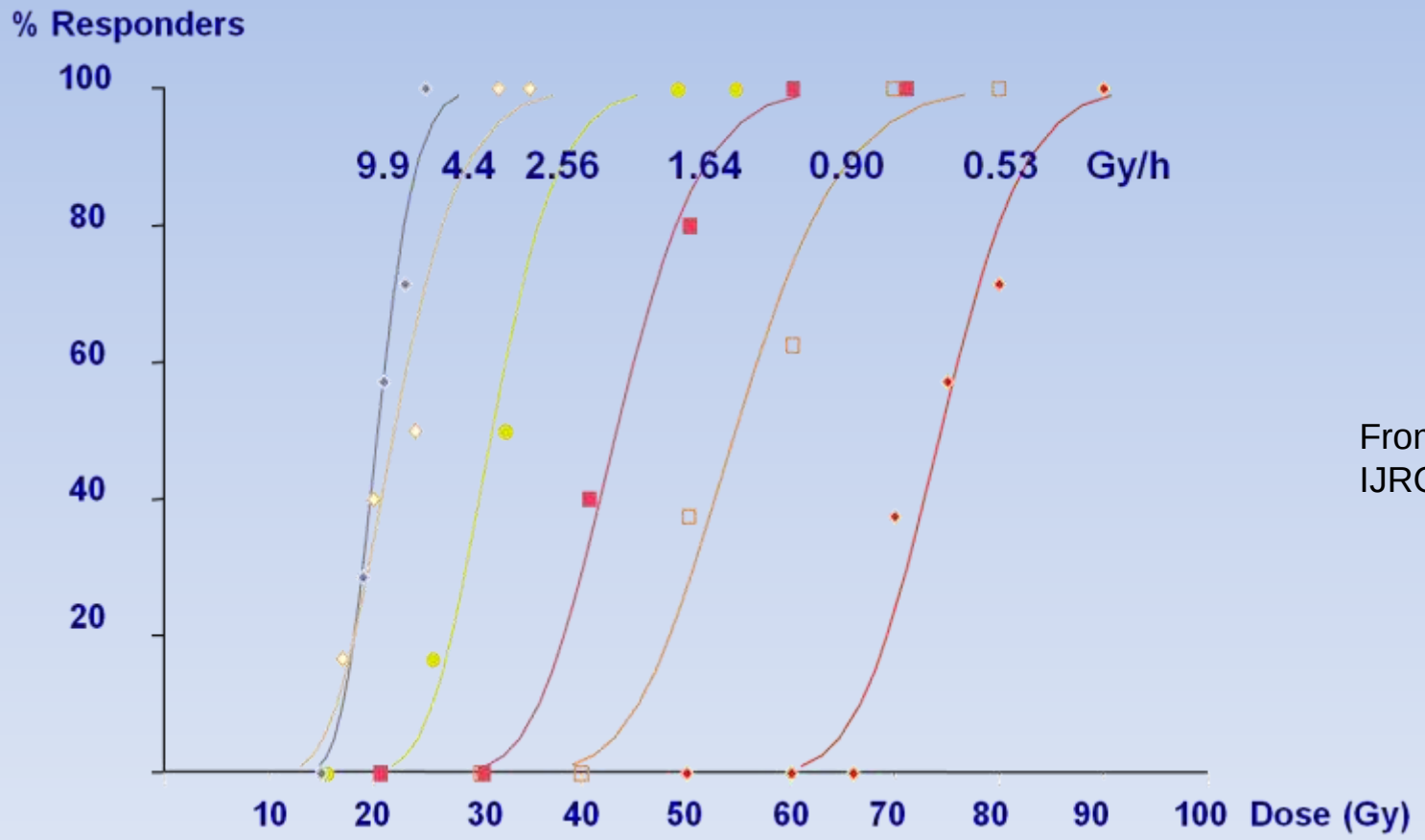
Modified from *Steel et al* (1986)

Crypt cell survival curves
(time between fractions)



From Steel 2002

Dose-rate effects in rat spinal cord: continuous irradiation using ^{192}Ir- wires (= 6 different constant dose rates)



From Pop et al.
IJROBP 1998

Dose-rate effect in murine normal tissues

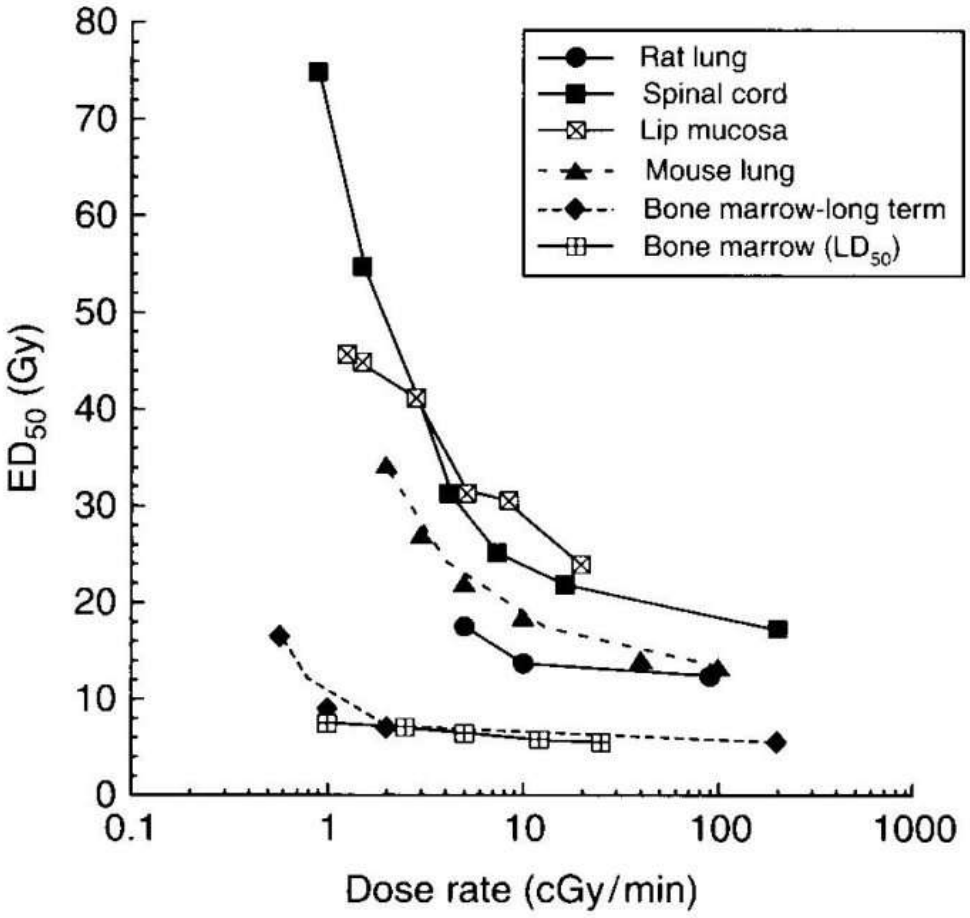
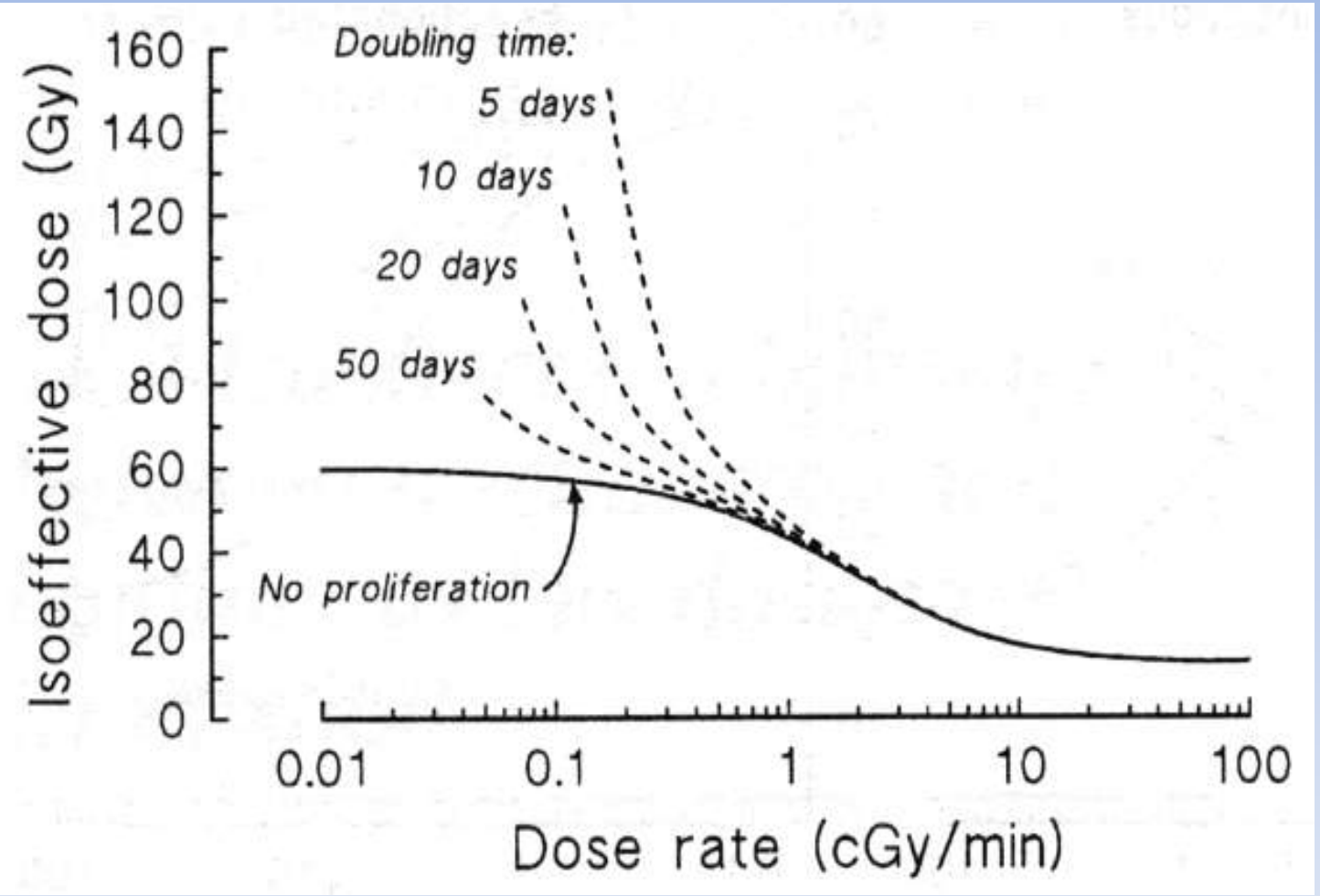


Figure 12.6 The dose-rate effect in various rodent normal tissues: lung, spinal cord, lip mucosa and bone marrow.

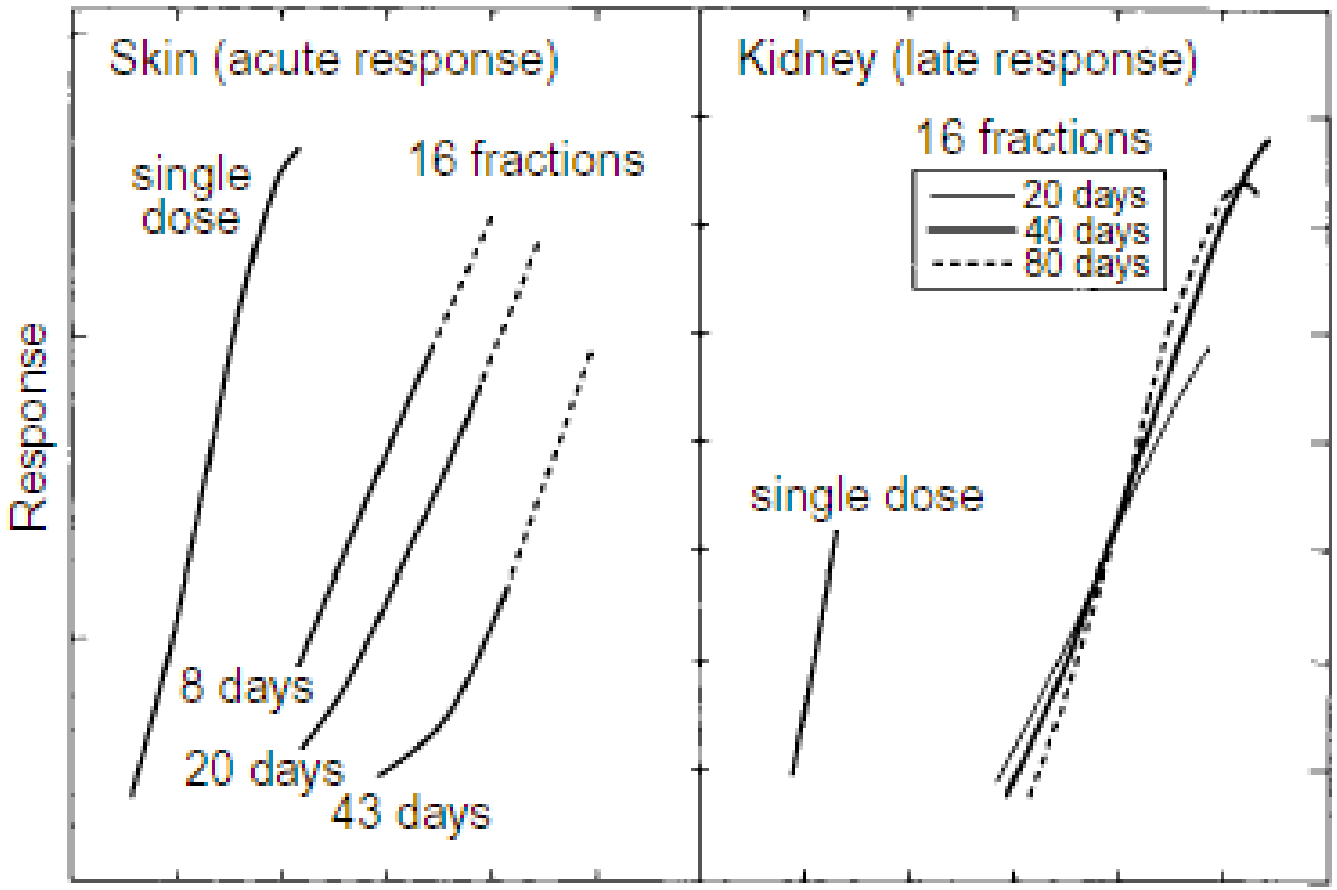
From Joiner and Van der Kogel
Basic Clinical Radiobiology
2009

Effect of (rate of) cell proliferation during LDR irradiation



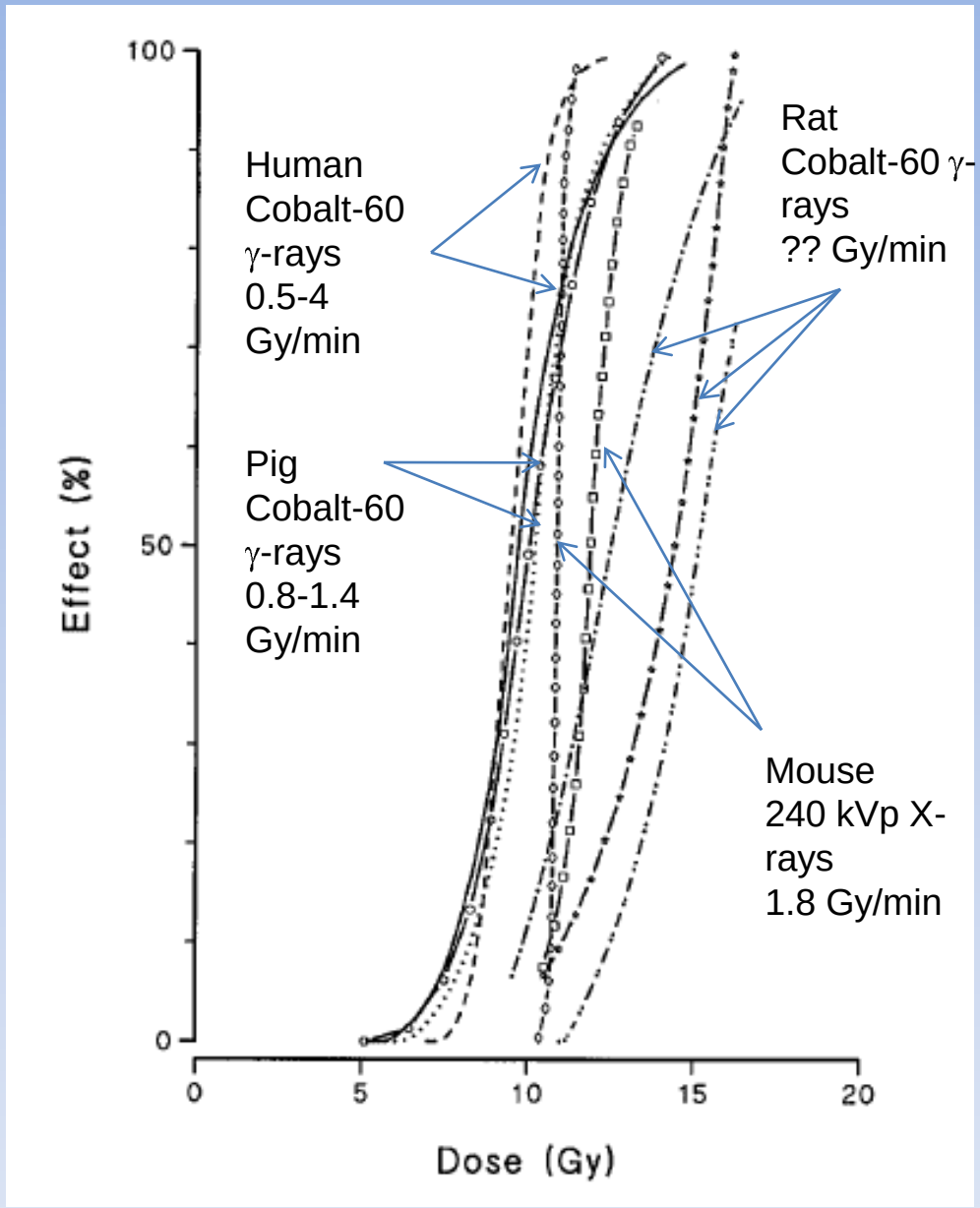
From Joiner and Van der Kogel
Basic Clinical Radiobiology
2009

Dose response relationship for skin and kidney following fractionated irradiation



From Denekamp 1986

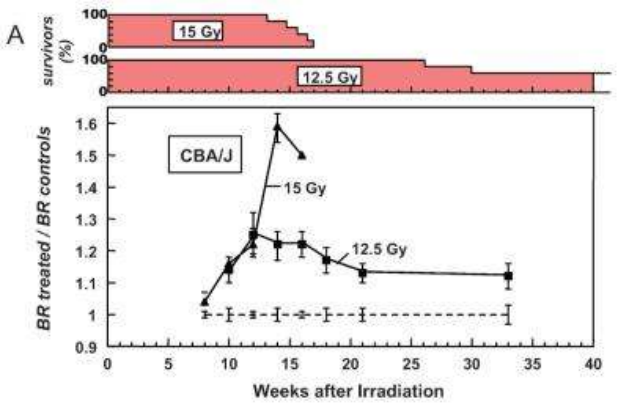
Dose response of lung in different animals

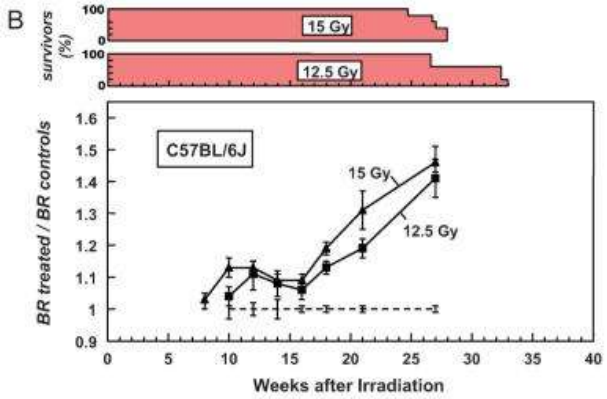


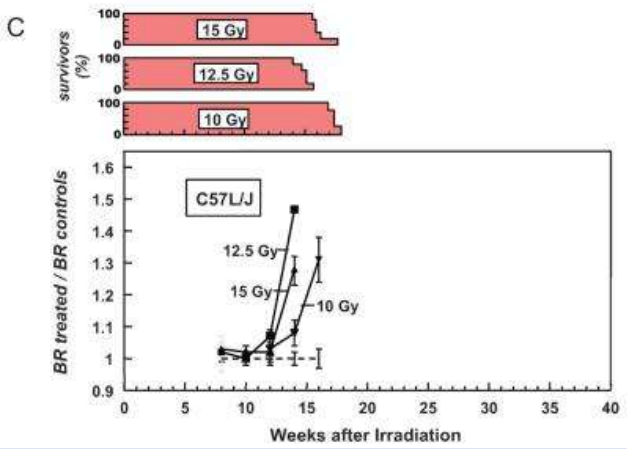
From Hopewell et al 2000

Figure 2. Dose-related incidence of lungs showing: (i) pneumonitis in patients (--- van Dyk *et al.* 1981); (_ Mah *et al.* 1987); and pigs (○ Herrmann *et al.* 1990, unpublished data). (ii) A ⩾ 15% loss of ventilation function in pigs after 13–26 weeks (--- Rezvani *et al.* 1989). (iii) Deaths within 40 and 196 days in mice (□ Parkins and Fowler 1985) or rats (–·–·– Lehnert and El-Khatib 1989). (iv) A > 20% increase in breathing rate at 28 weeks in mice (◇ Parkins and Fowler 1985) or 120 days in rats (☆ Lehnert and El-Khatib 1989). (v) A > 20% increase in lung density at 120 days in rats as determined by CT (–··–·· Lehnert and El-Khatib 1989).

Strain differences in response to lung irradiation







Mice (whole lung)
200 kVp X-rays
@ 0.44 Gy/min

Jackson et al 2010

Rats (hemi lung)
200 kVp X-rays
@ 0.66 Gy/min

Van Eerde et al 2001

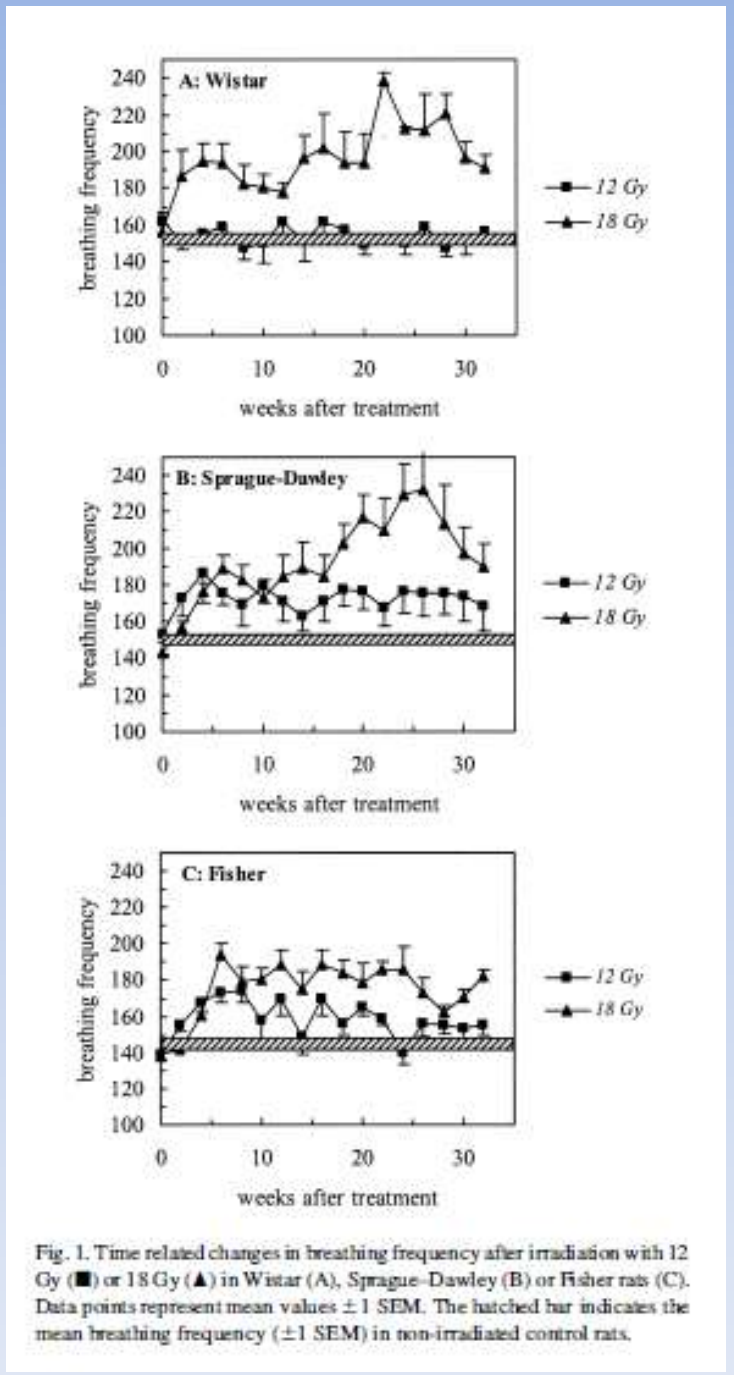


Fig. 1. Time related changes in breathing frequency after irradiation with 12 Gy (■) or 18 Gy (▲) in Wistar (A), Sprague–Dawley (B) or Fisher rats (C). Data points represent mean values ±1 SEM. The hatched bar indicates the mean breathing frequency (±1 SEM) in non-irradiated control rats.

Critical Issues

- Steep dose response curves for functional endpoints.
- Dose response may vary for different molecular endpoints.
- Different tissues/cells have different repair capacity. Leads to:
  - Differences in RBE effects
  - Differences in dose rate or fractionation effects.
- Functional tissue endpoints are usually multifactorial due to:
  - Different cell types in the same tissue
    - Parenchymal cells, Stromal cells, Vascular cells.
  - Inflammatory responses
  - Immune responses
  - Tissue ‘repair’ responses
- Strain differences
- Issues of husbandry in lethality studies