Paul Jonkergouw

Lage-dosiseffecten

Radboud Universiteit Nijmegen

Inhoud

- Validiteit LNT-model
- Lage-dosis effecten:
  - Adaptieve respons
  - ‘Bystander’ effecten
  - (Genomische instabiliteit)
- Belang voor de stralingsbescherming

ICRP

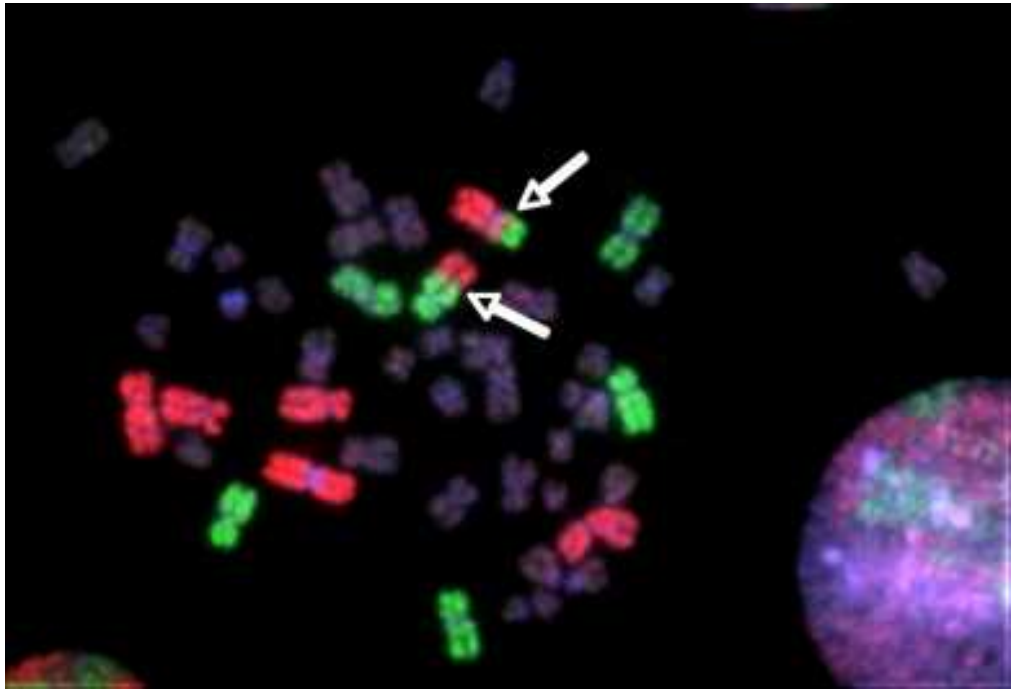
- Publicatie 103 (2007)
- Publicatie 99 (2005)

Standpunten:

1. LNT-model is de meest praktische benadering voor het omgaan met stralingsrisico's
2. LNT-model biedt vooralsnog een veilige basis voor de stralingsbescherming
3. ICRP erkent dat bij lage dosis (< 100 mSv) de onzekerheid groot is

Moleculaire effecten

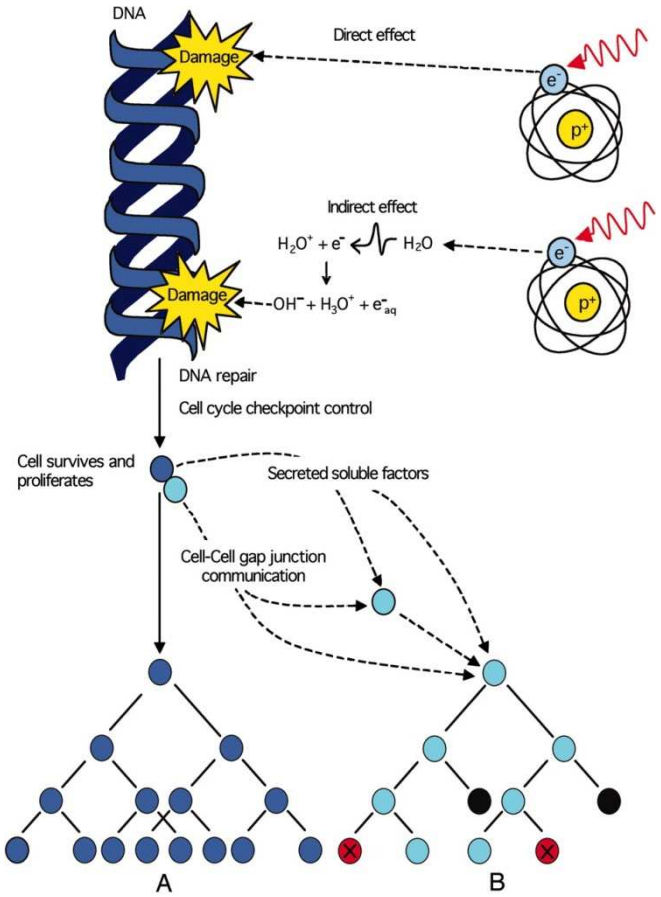
Chromosomale aberratie



Sigurdson et al (2008)

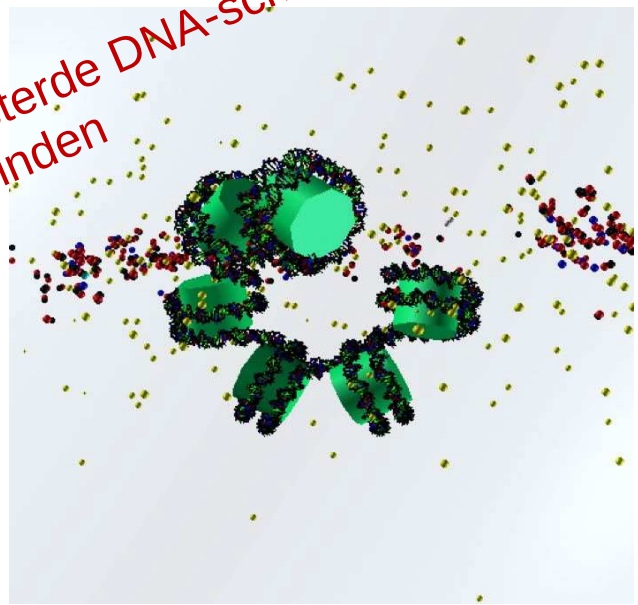
Reciproke translokatie

DNA-schade

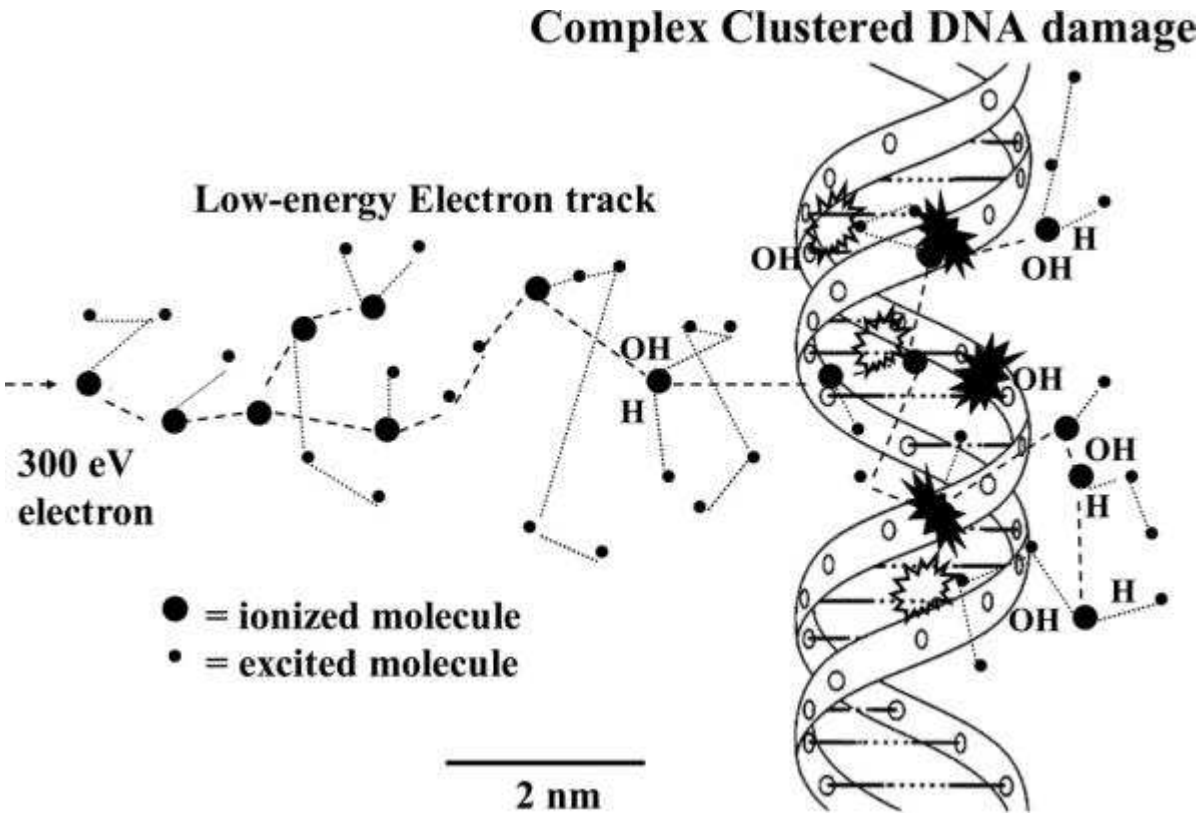


Morgan W F, Sowa M B PNAS 2005;102:14127-14128

m.n. geclusterde DNA-schade en DSB's met 'rafelige' einden

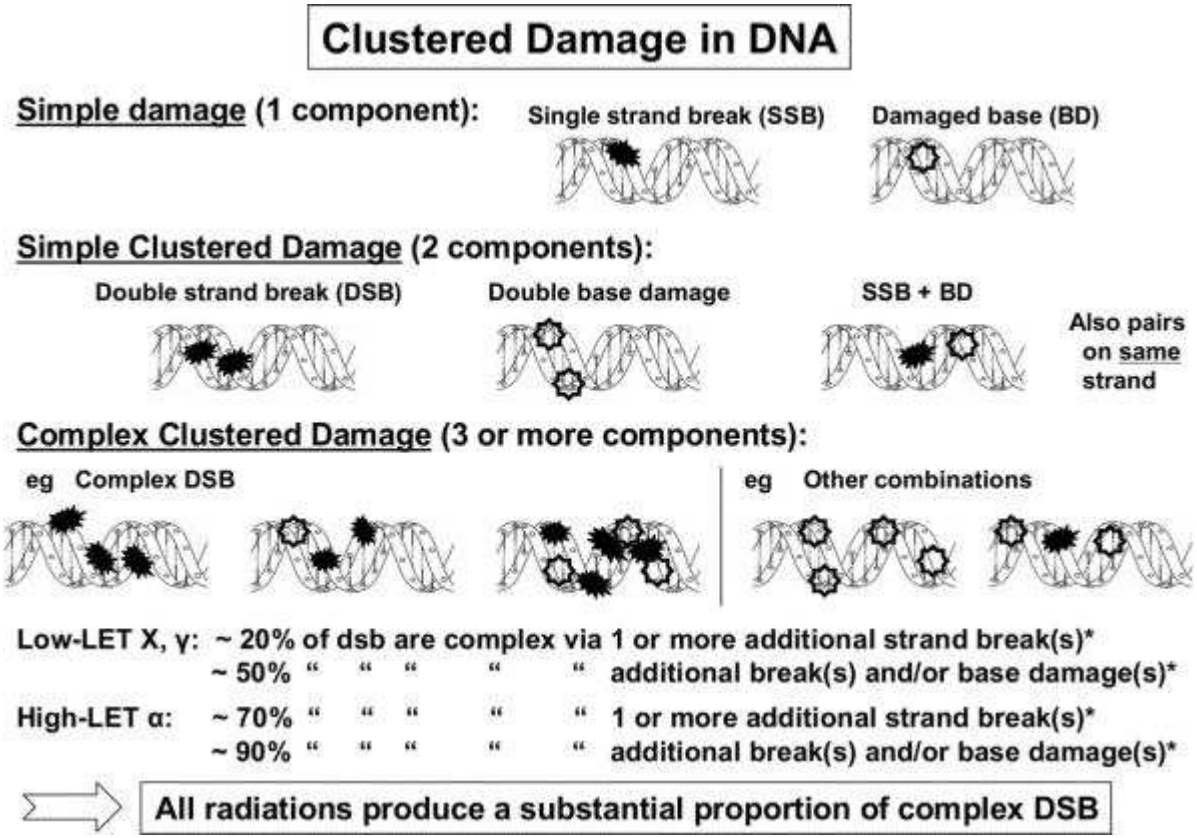


Validiteit LNT-model



Goodhead, Dudley
Health Physics. 97(5):394-406, November 2009.

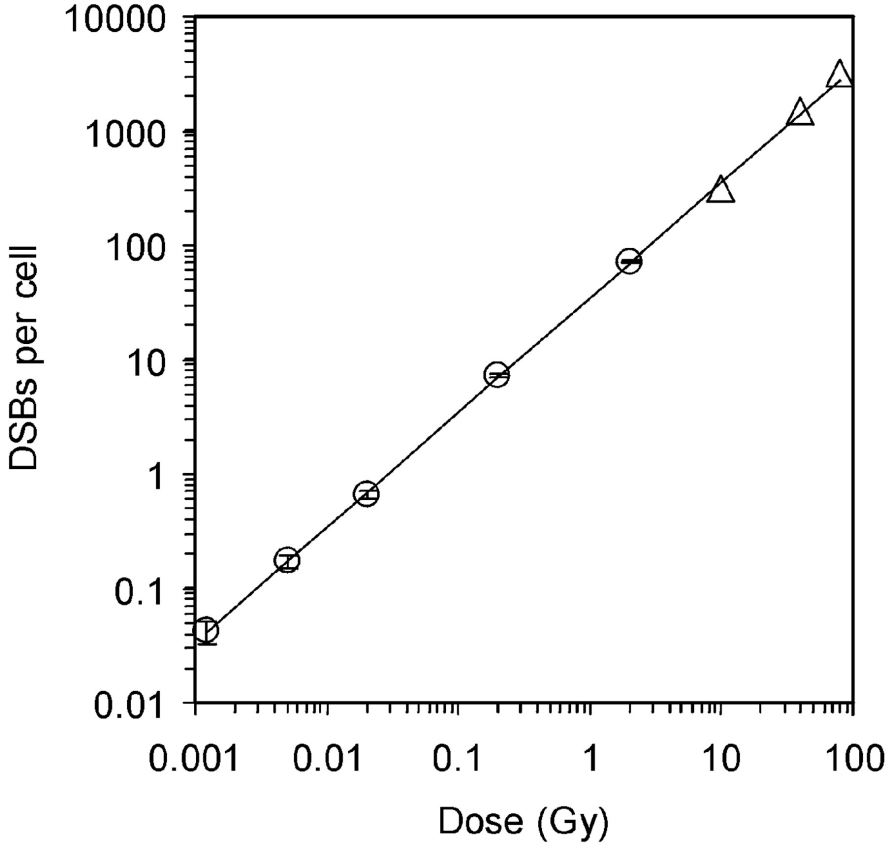
Validiteit LNT-model



Goodhead, Dudley
Health Physics. 97(5):394-406, November 2009.

Moleculaire effecten

Dubbelstrengs breuken

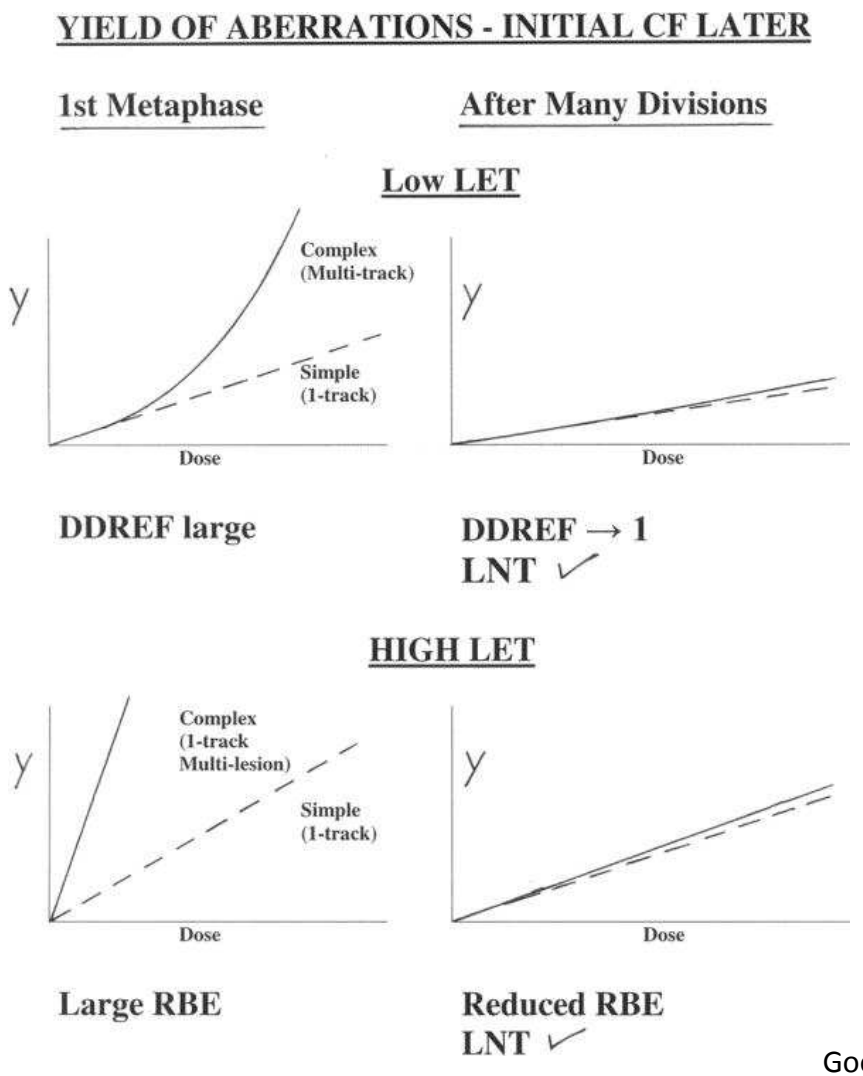


Geen drempeldosis

35 DSB's per cel Gy^{-1}

Rothkamm et al (2003)

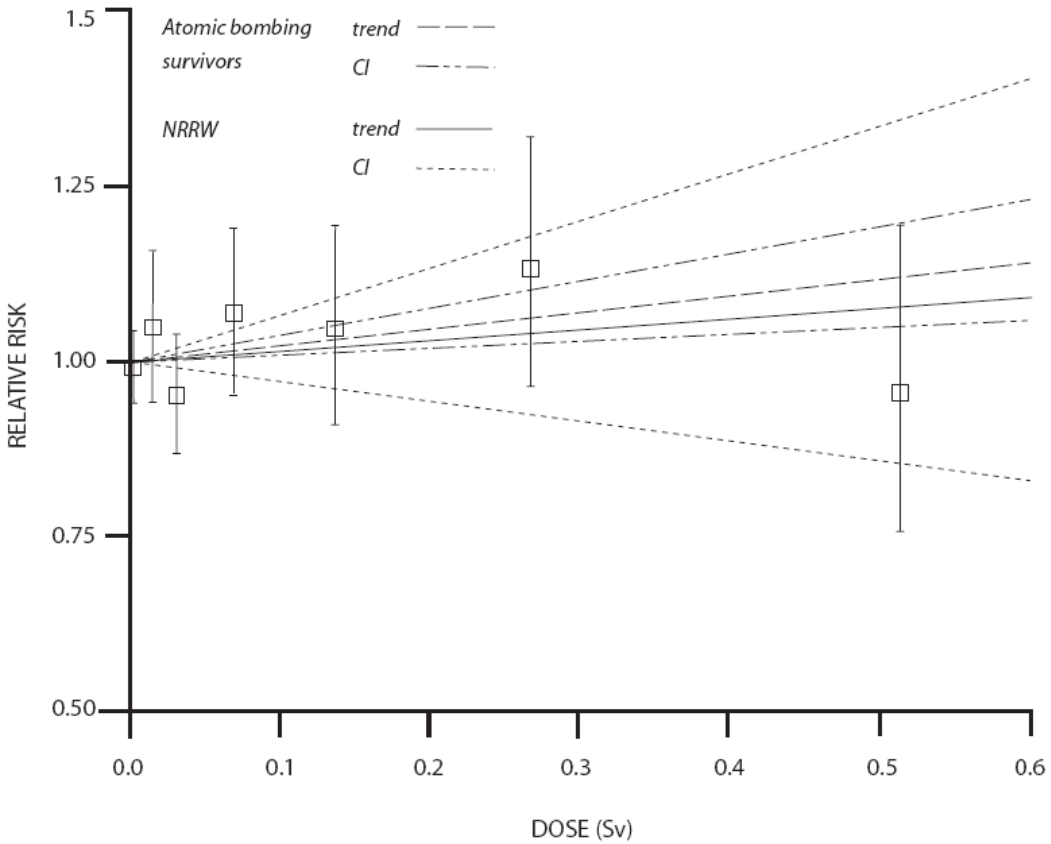
Validiteit LNT-model



Goodhead, Dudley
Health Physics. 97(5):394-406, November 2009.

Klinische manifestaties,

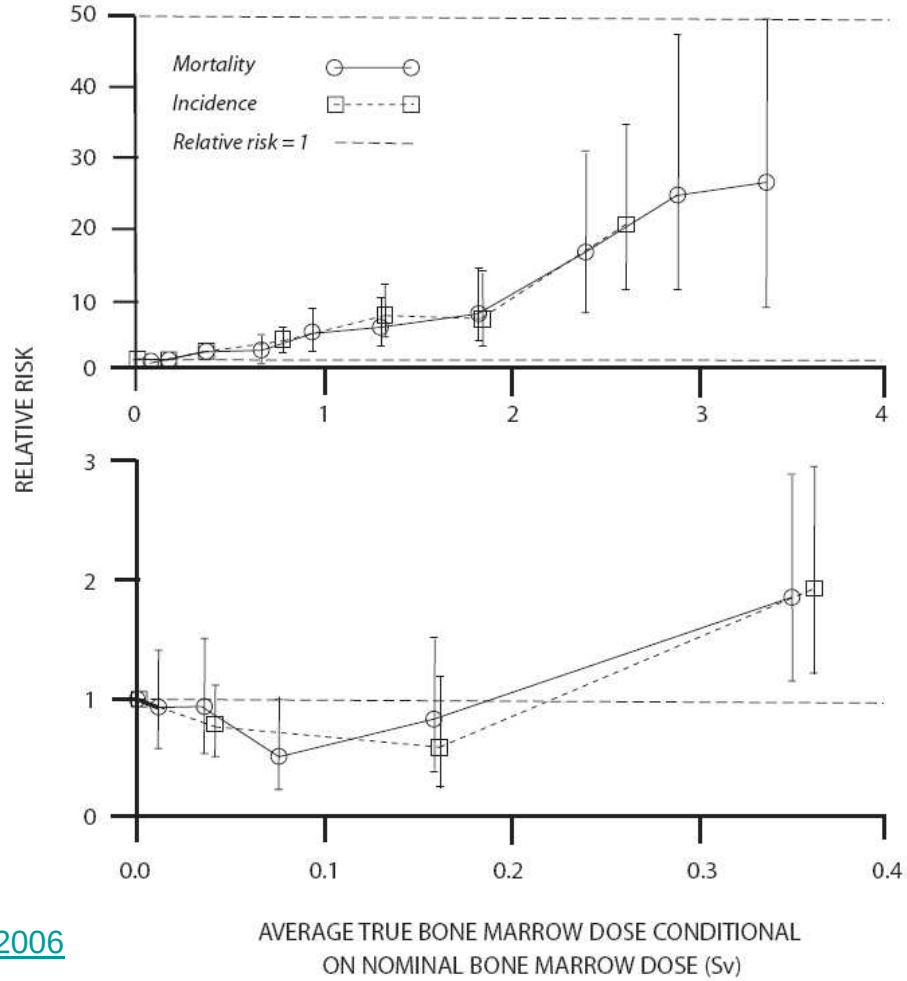
Life span study, solide tumoren



UNSCEAR, 2006

Klinische manifestaties,

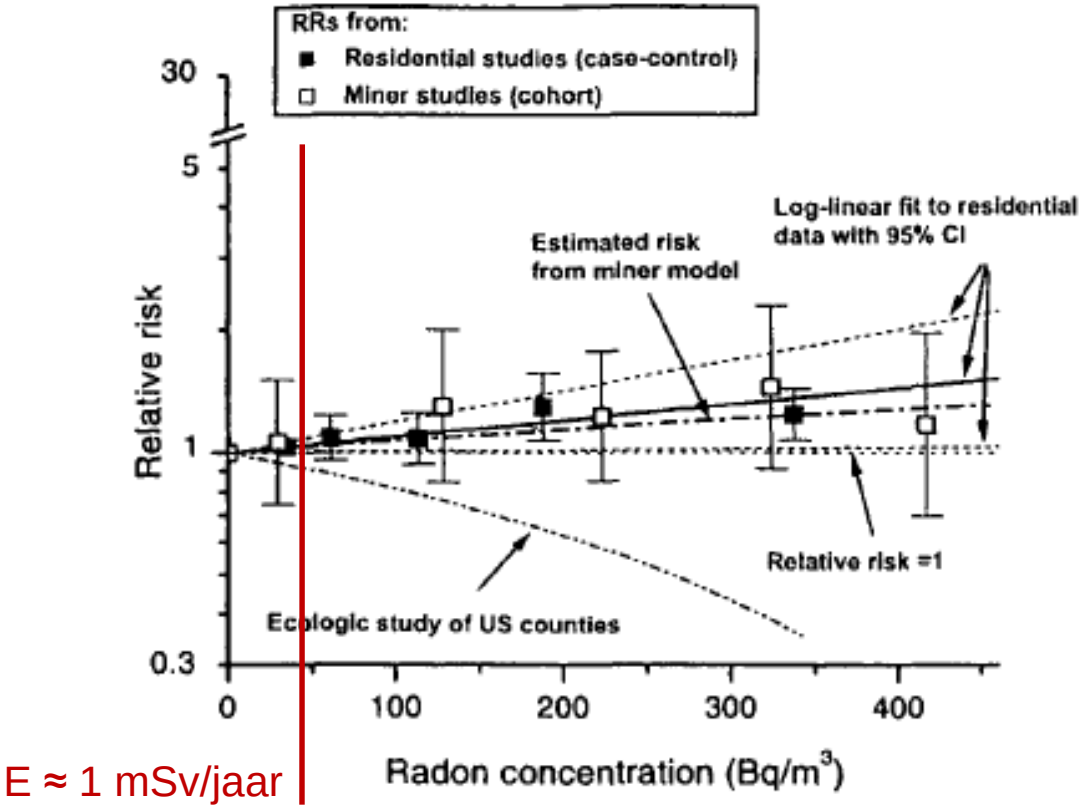
Life span studv. leukemie



UNSCEAR, 2006

Klinische manifestaties,

Longkanker t.g.v. radon



E ≈ 1 mSv/jaar

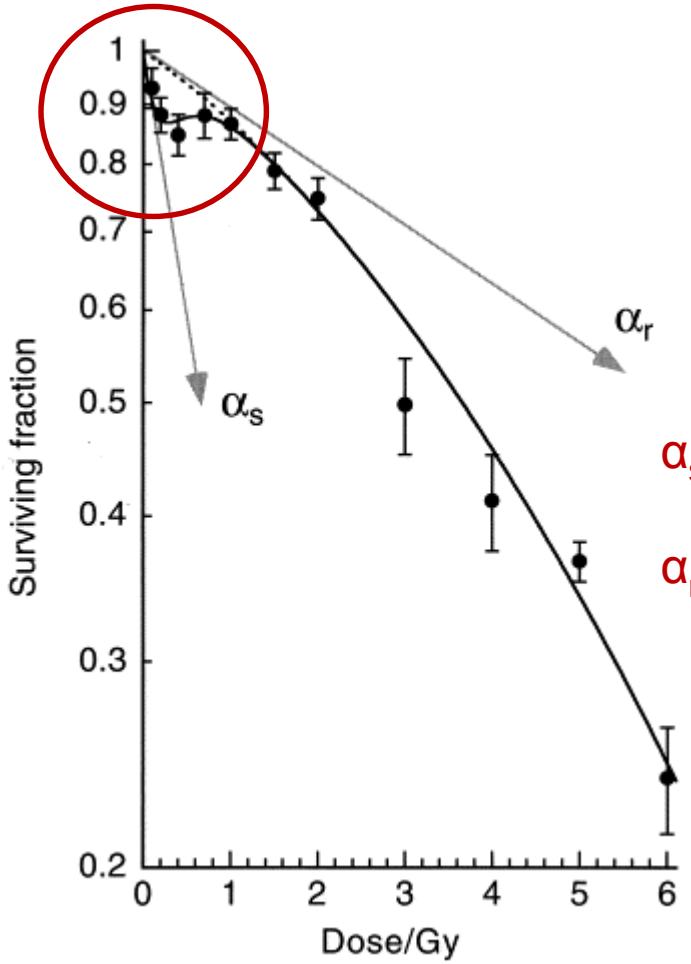
Darby et al (2001)

Samenvattend

- (geclusterde) DNA-schade is verantwoordelijk voor:
  - Mutaties
  - Celdood
  - Kankerinductie
- Moleculair sterke aanwijzingen voor LNT-model:
  - LNT dosis-effect relatie DSB's
- Klinisch geen overtuigend bewijs LNT-model:
  - Solide tumoren: LNT / LQ
  - Leukemie: drempeldosis?

verklaring?

Hyper-radiosensitiviteit

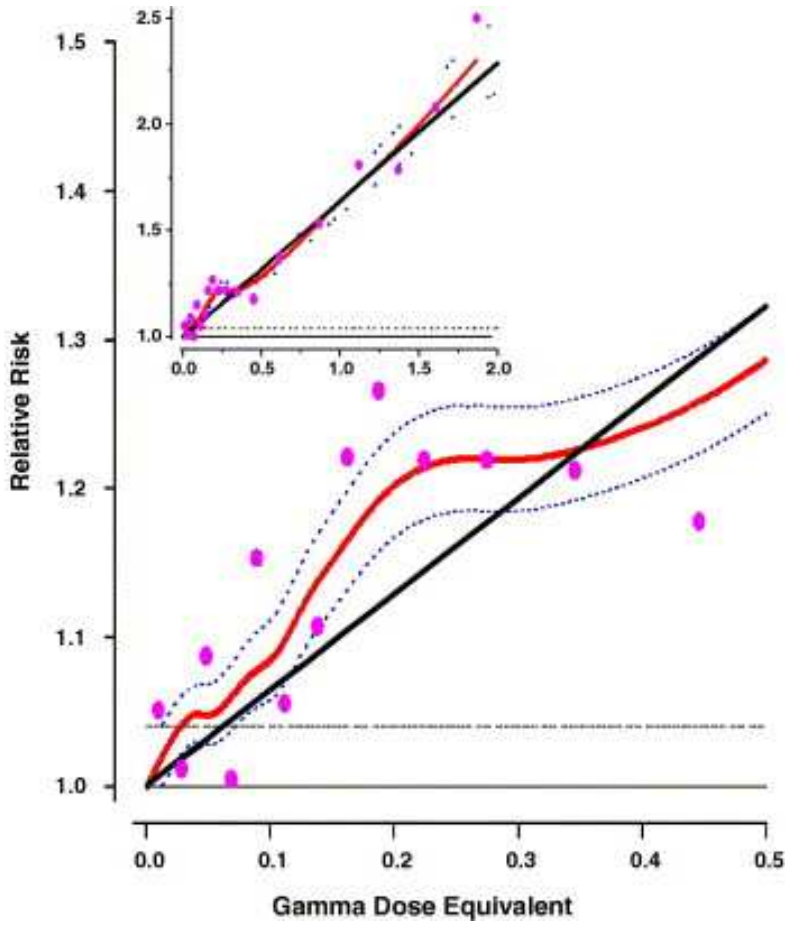


α_s → hyper-radiosensitief

α_r → geïnduceerd radioresistent

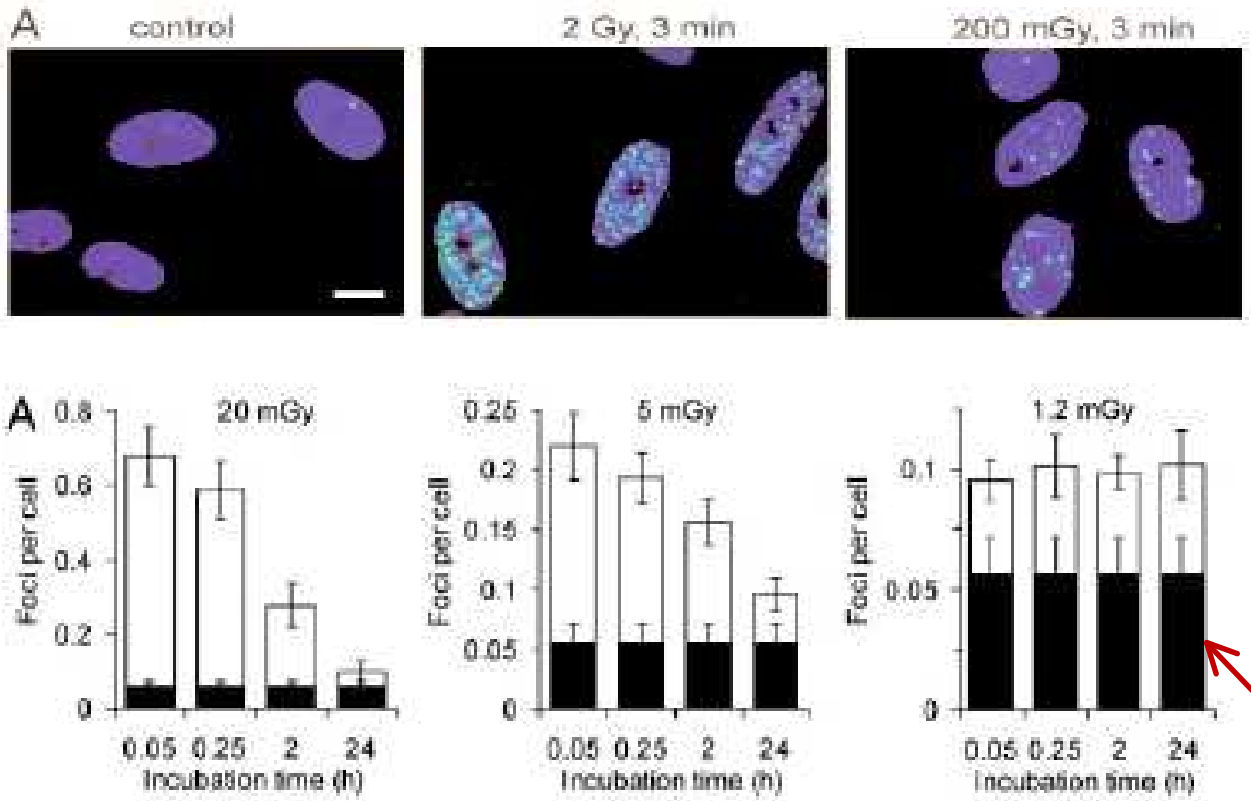
Joiner et al (2001)

Hyper-radiosensitiviteit



Pierce, D.A., Preston, D.L., 2000. Radiat. Res. 154, 178–186.

Hyper-radiosensitiviteit



Rothkamm et al (2003)

geen DNA-repair

Adaptieve respons

Adaptive Response of Human Lymphocytes to Low Concentrations of Radioactive Thymidine

Abstract. *When human lymphocytes were cultured with [^{3}H]thymidine, which acts as a source of low-level chronic radiation, and then exposed to 150 rad of x-rays at 5, 7, 9, or 11 hours before fixation, the yield of chromatid aberrations was less than the sum of the yields of aberrations induced by [^{3}H]thymidine and x-rays separately.*

Olivieri (1984)

Sindsdien:
honderden publicaties met *pro*- en *contra*-resultaten (eindpuntafhankelijk)

Adaptieve respons

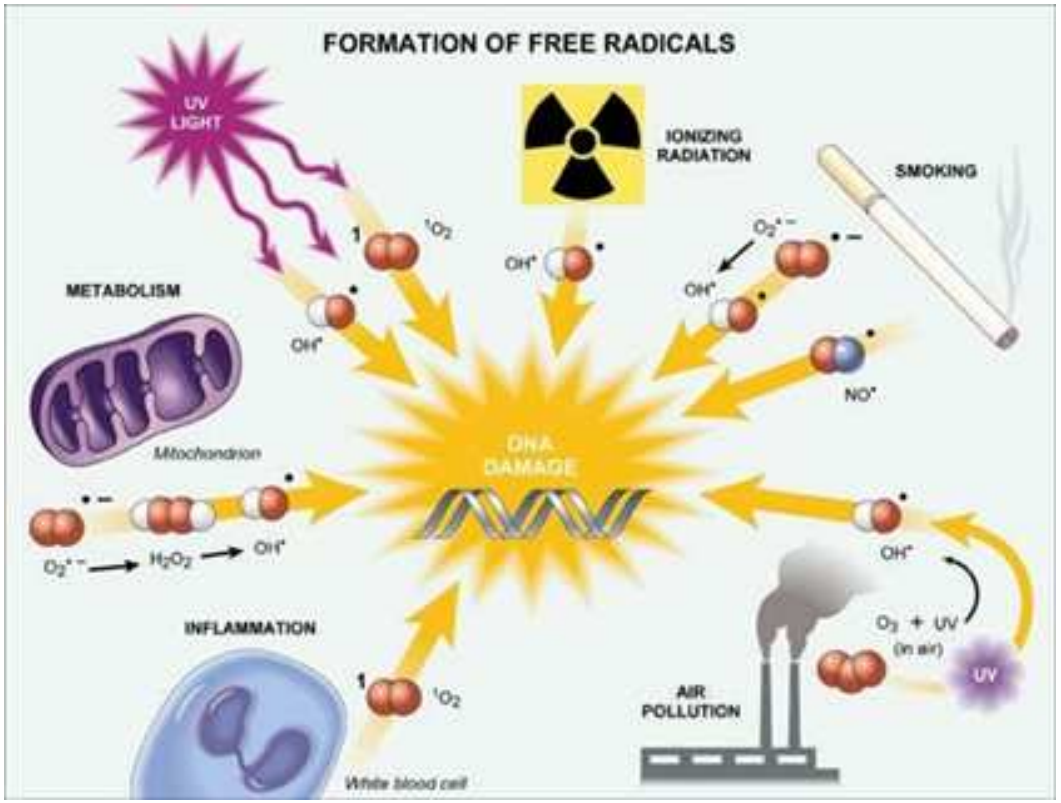
dosisafhankelijkheid

- Vooral bij dosis < 100 – 200 mGy
- Niet bij dosis > 500 mGy
- Alleen bij lage-LET straling

typen

1. Voorkomen en repareren DNA-schade
2. Elimineren beschadigde cellen (apoptose, immuunsysteem)

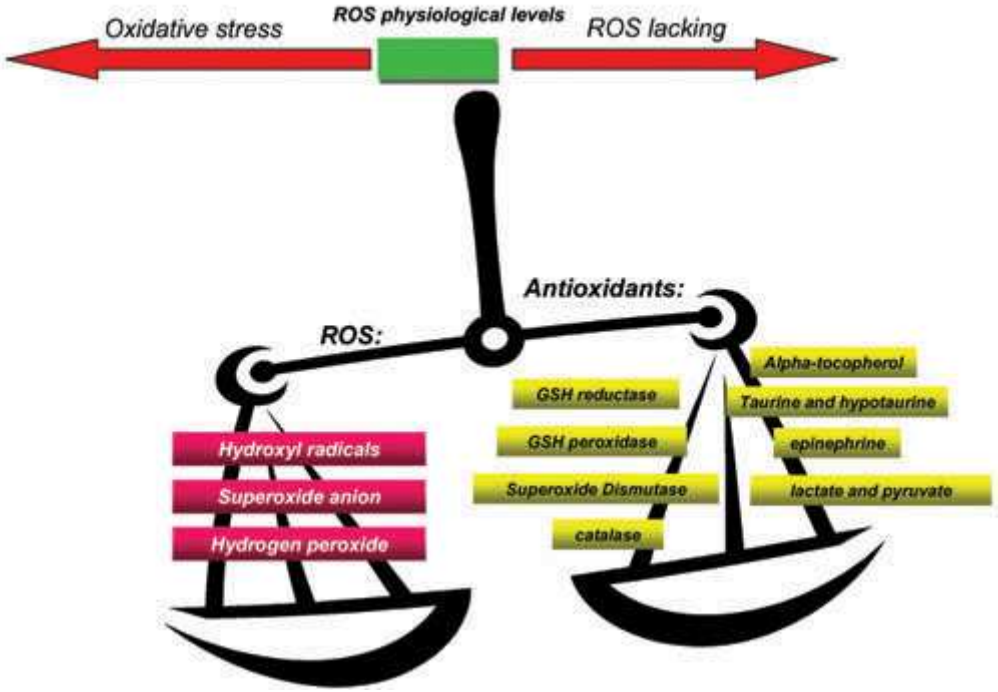
Adaptieve respons
oxidatieve stress



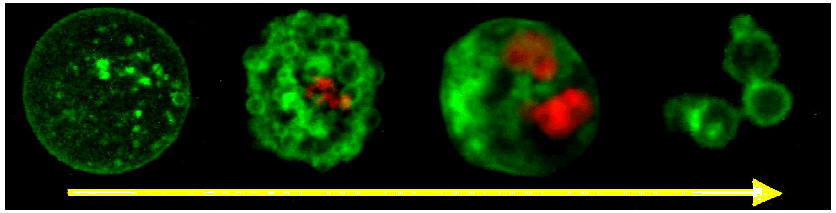
Normaal: > 10.000 hits per cel per dag

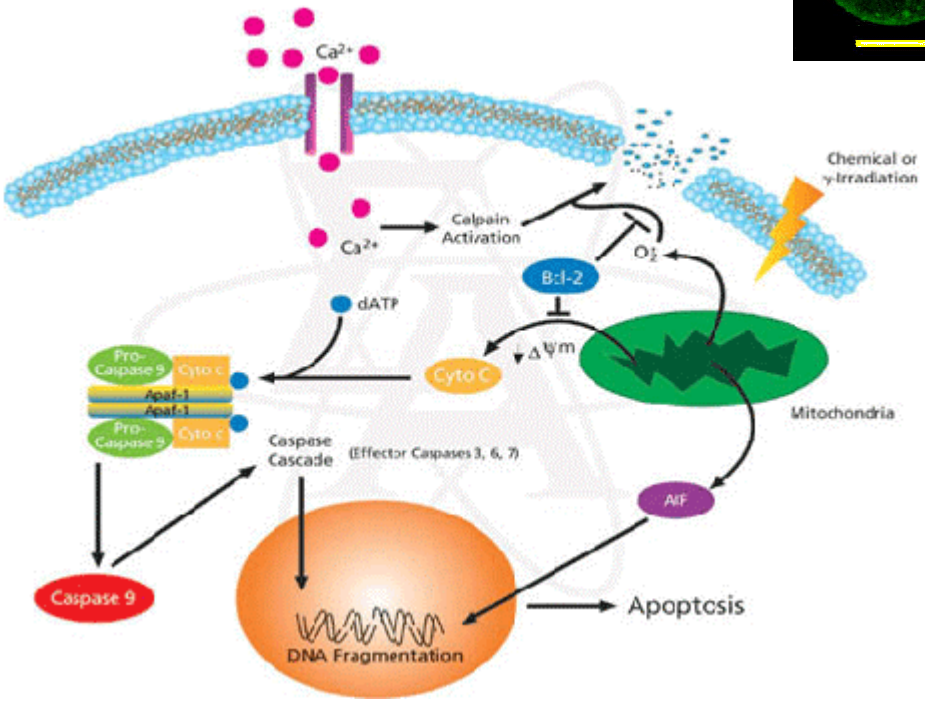
Adaptieve respons
voorkomen DNA-schade

- Upregulatie endogene radicaalvangers (antioxidanten)



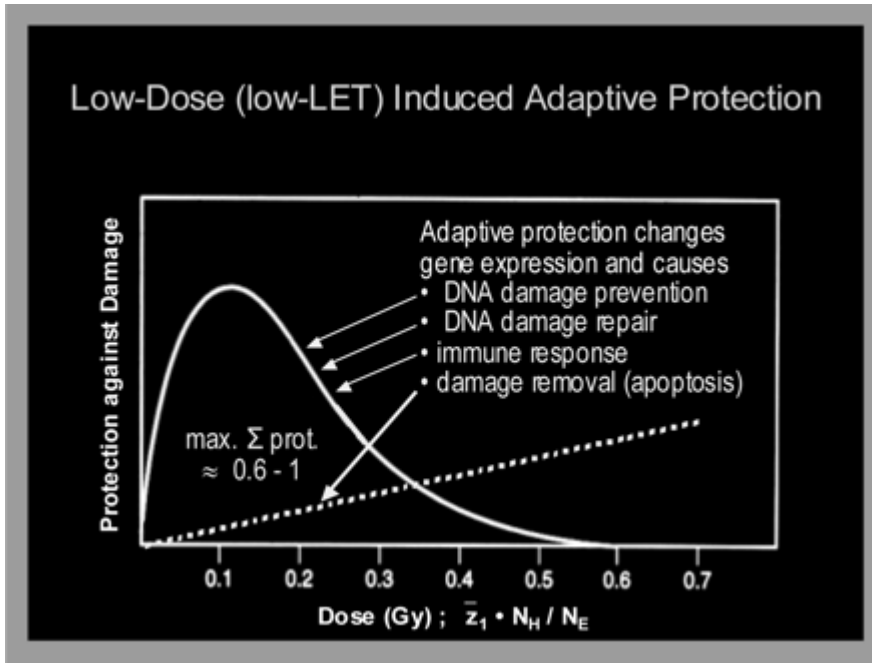
Adaptieve respons
apoptose

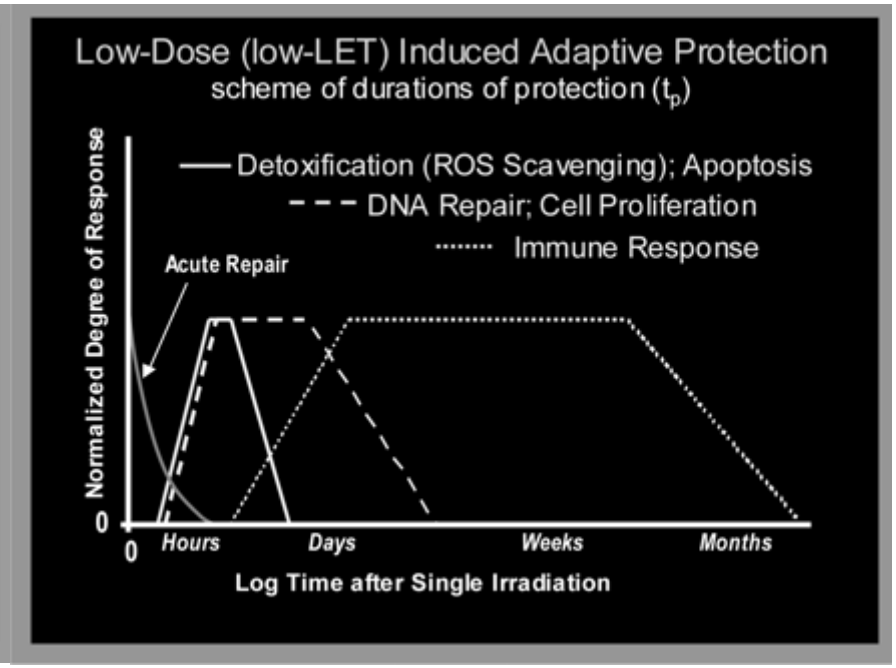




DNA-fragmenten: ca. 185 bp

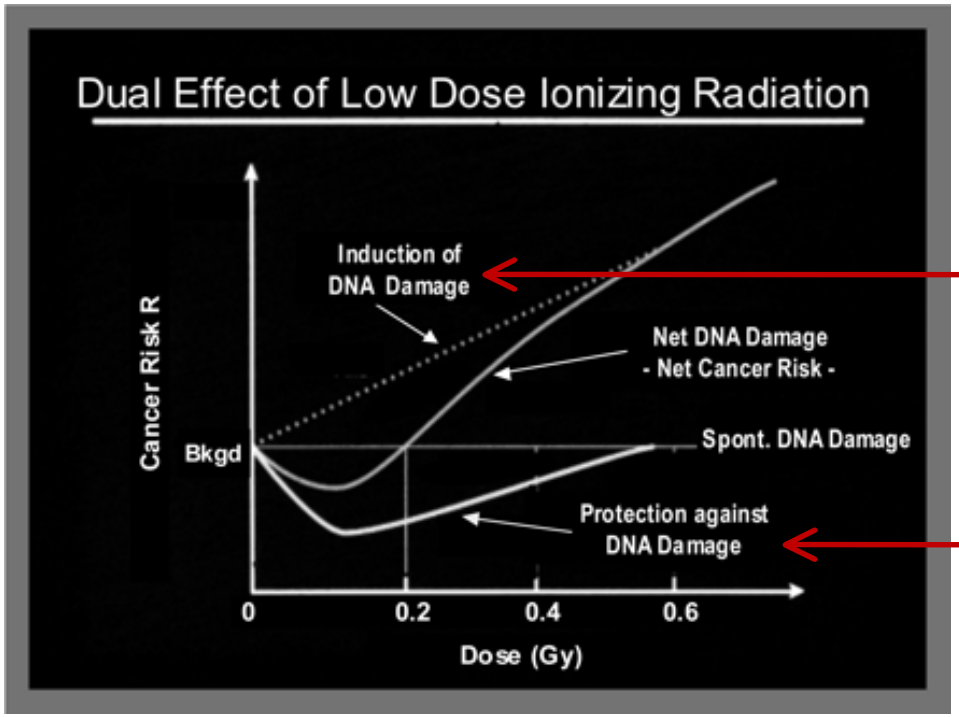
Adaptieve respons





Feinendegen (2005)

Adaptieve respons



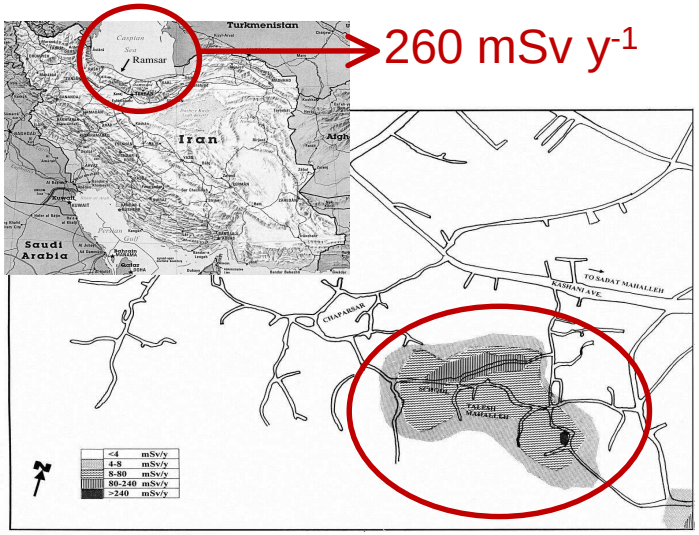
Moleculair effect

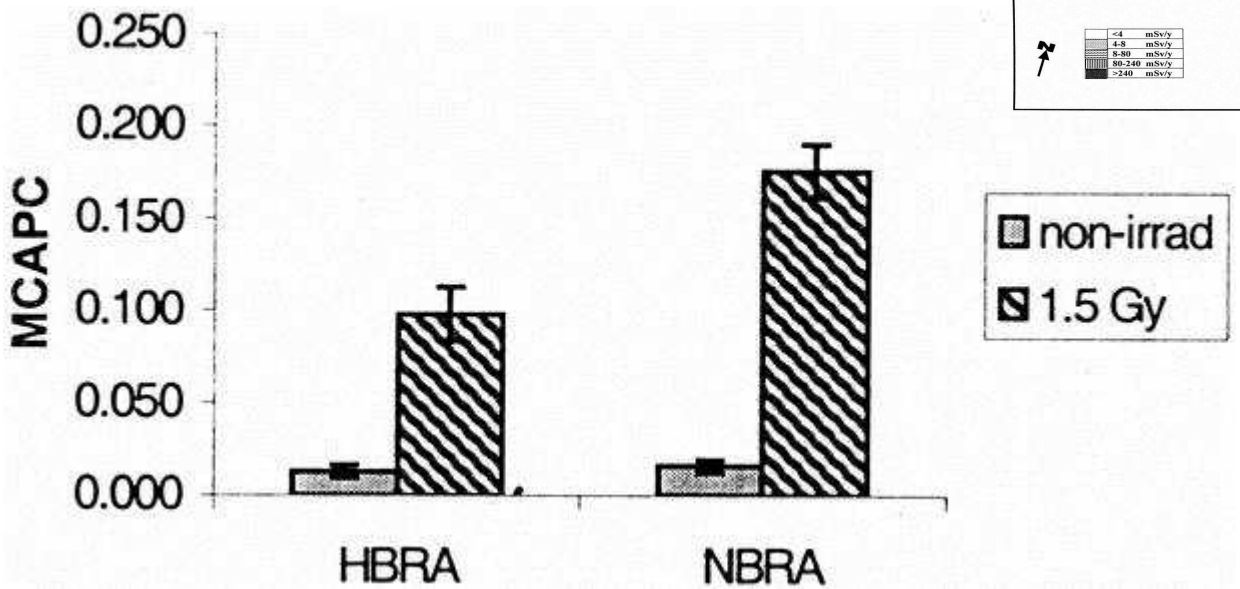
Cellulair effect

Feinendegen (2005)

Overcompensatie mechanismen = ‘radiation hormesis’

Adaptieve respons
bij hoge achtergrondstraling



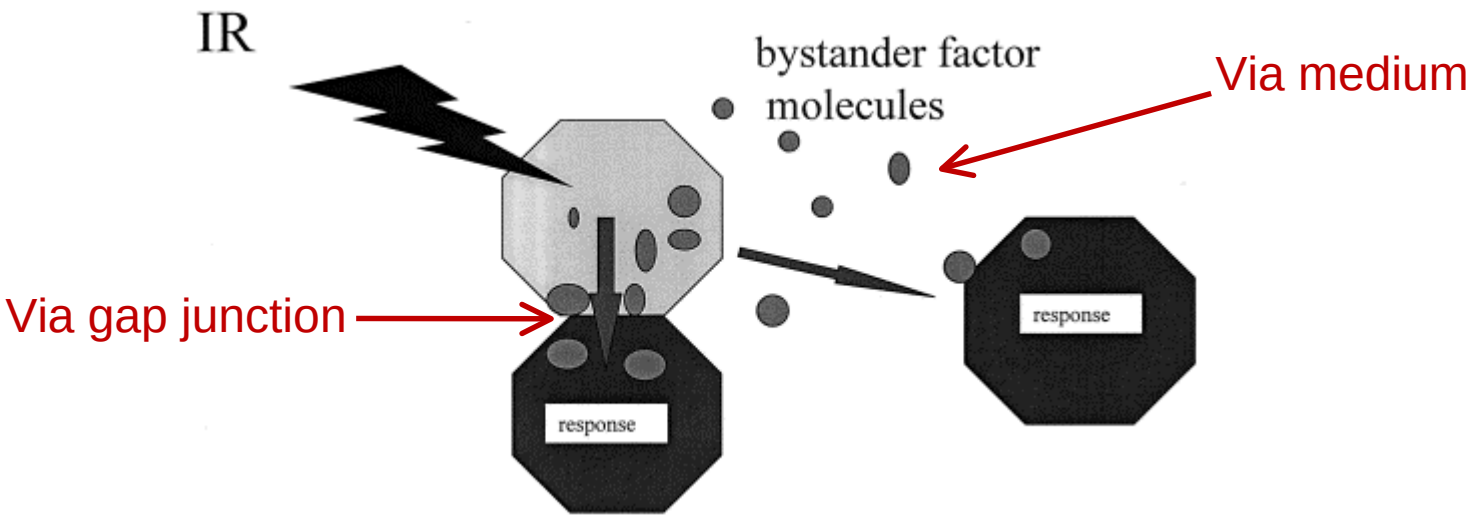


Ghiassi-nejad (2002)

Samenvattend

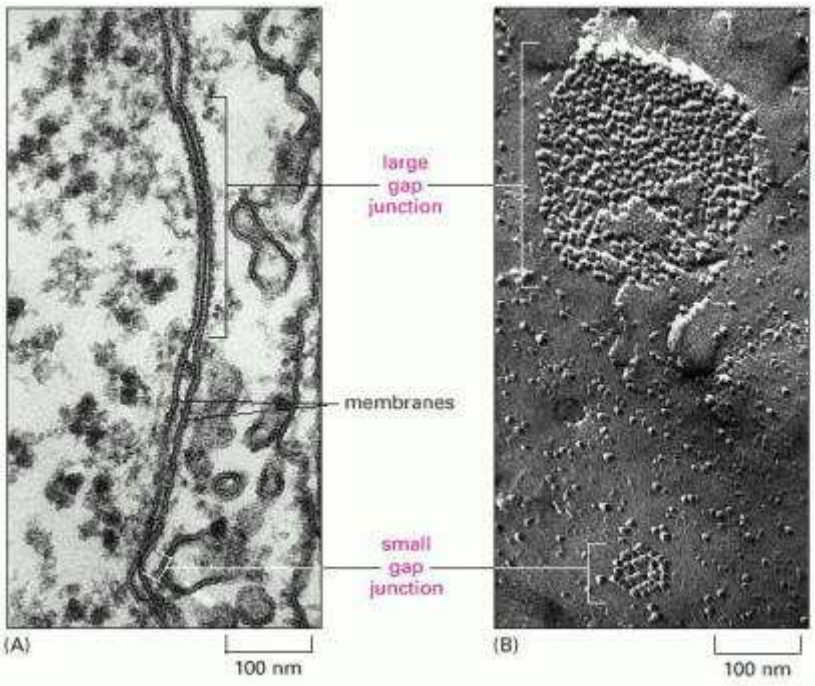
- AR is te vergelijken met een biologische stress-respons:
  - Oxidatieve stress reactie
  - Apoptose
  - Overcompensatie (hormesis)
- AR behelst een scala aan verdedigingstypen:
  - Moleculair
  - Cellulair
- AR kan een drempeldosis en hormesis verklaren
- Onderliggende mechanismen van AR zijn niet goed bekend

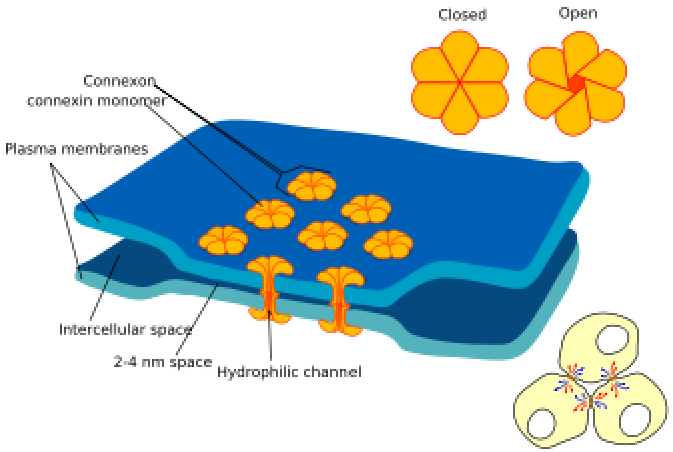
‘Bystander’ effect



Mothersill et al (2004)

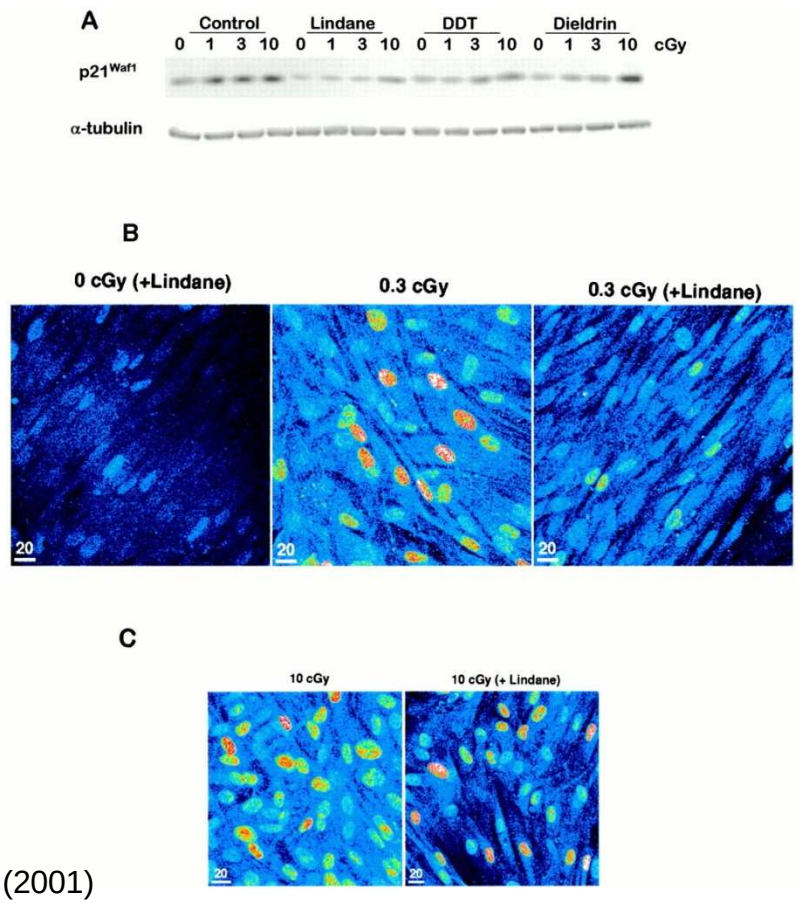
Gap junction





‘Bystander’ effect

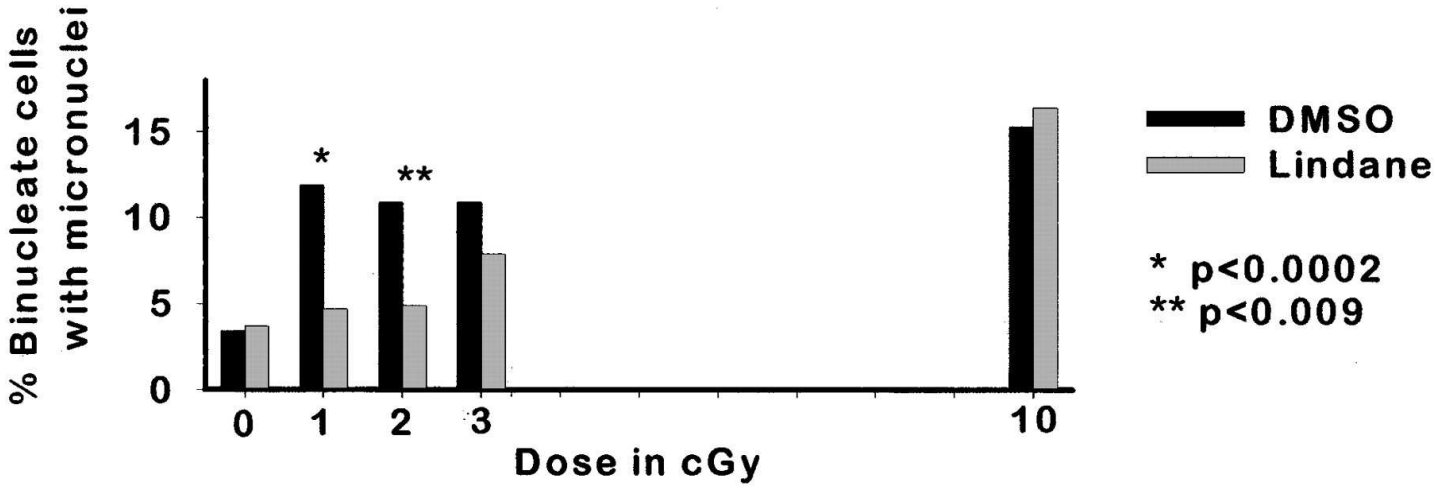
via gap junction



Azzam et al (2001)

‘Bystander’ effect

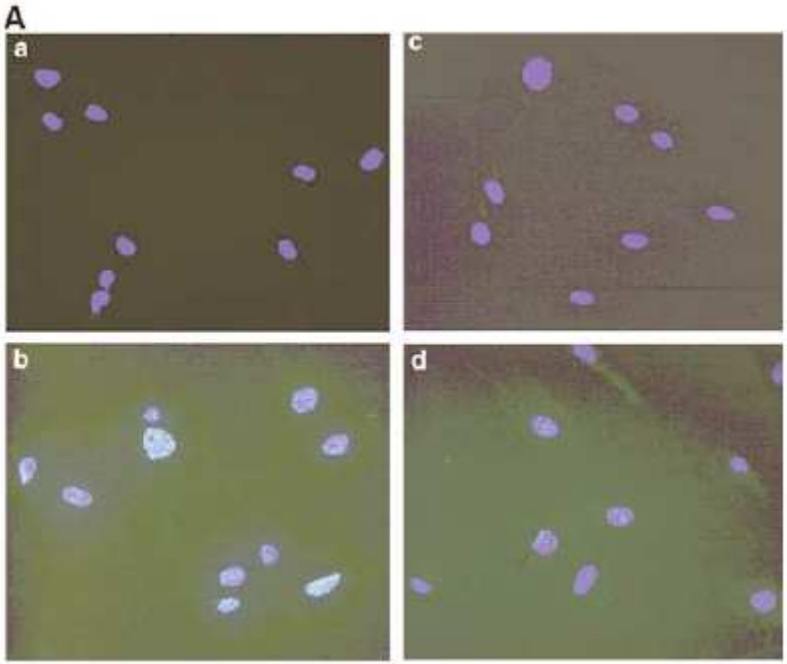
via gap junction



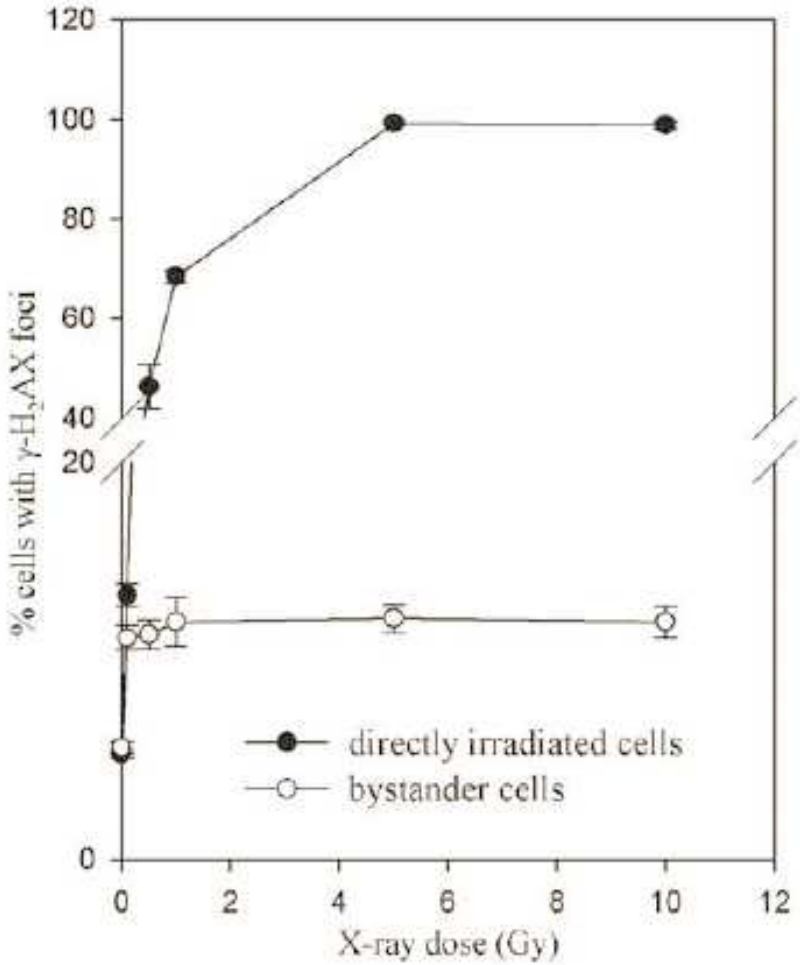
Azzam et al (2001)

‘Bystander’ effect

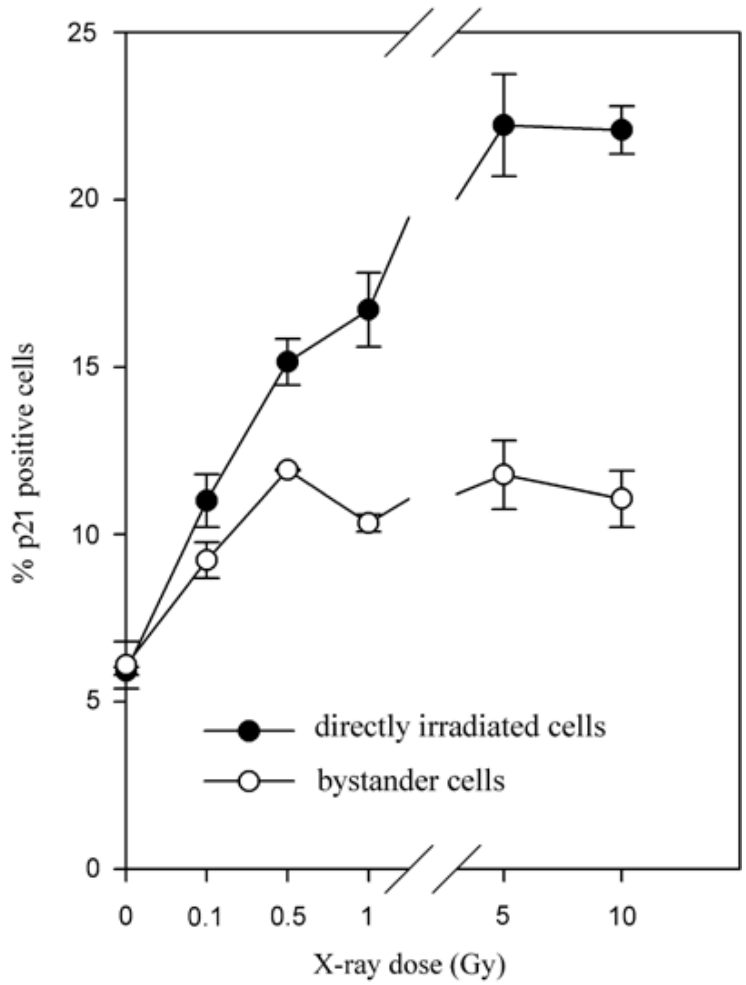
via medium transfer



Yang et al (2005)



‘Bystander’ effect
via medium transfer



Yang et al (2005)

‘Bystander’ effect

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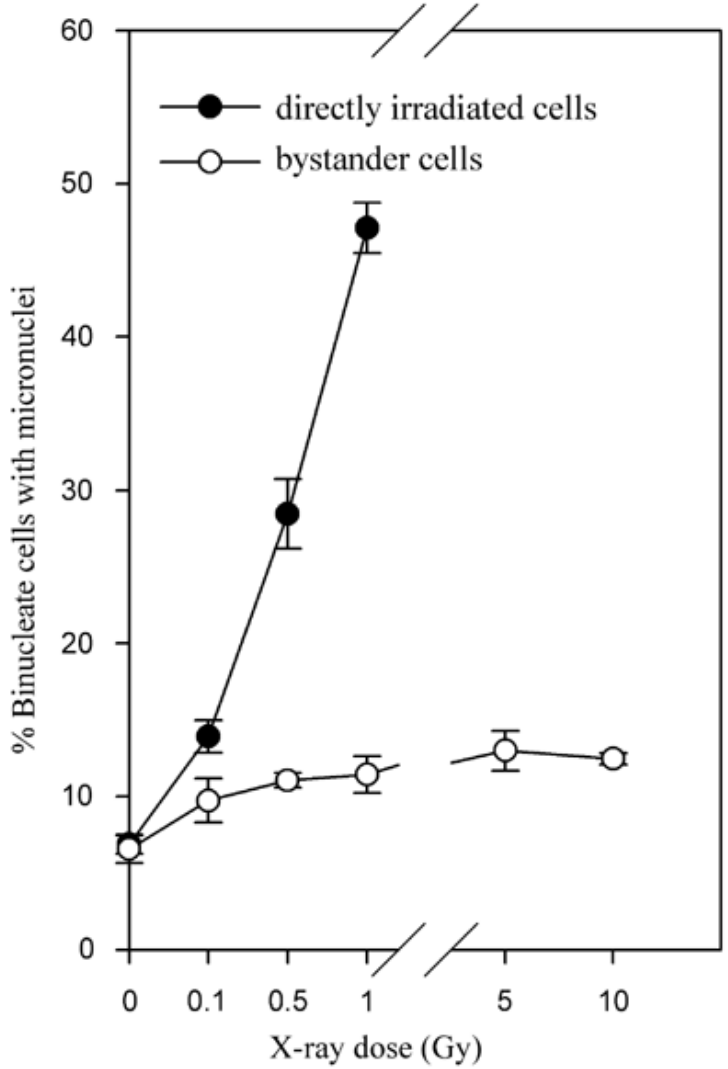
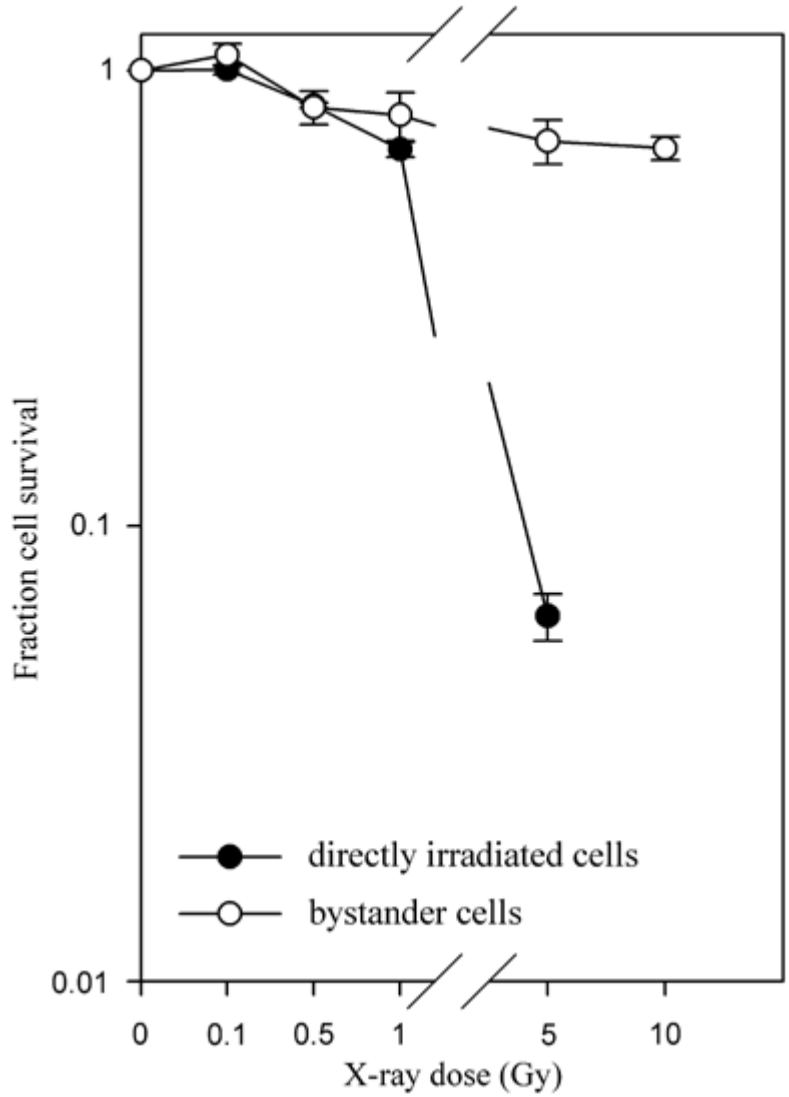


Yang et al (2005)

‘Bystander’ effect

via medium transfer

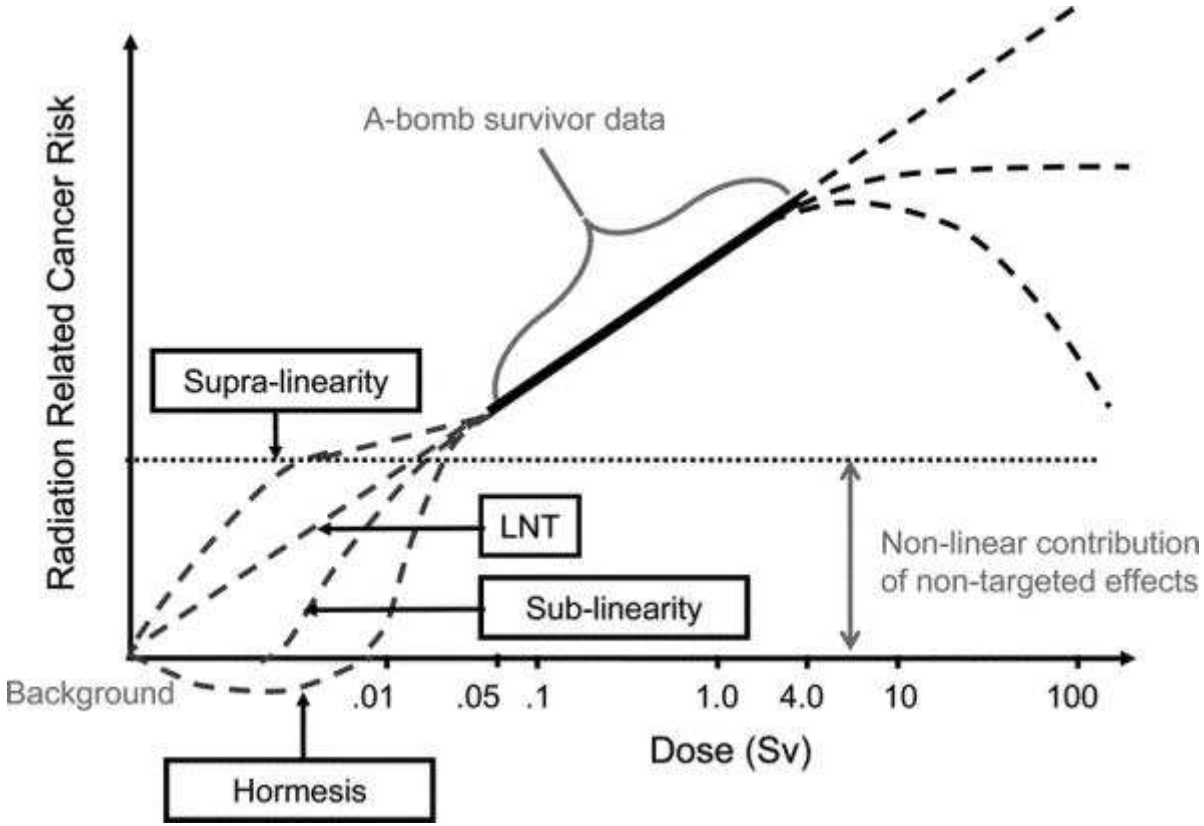


Yang et al (2005)

Samenvattend

- ByE zijn beschreven voor zowel hoge- als lage-LET straling
- Stralingseffecten kunnen worden doorgegeven aan niet-bestraalde cellen via:
  - Gap junctions
  - Laagmoleculaire signaalmoleculen
- ByE kunnen afwijkingen van het lineaire model verklaren
- ByE kunnen divers van aard zijn
  - Mutaties
  - Chromosoom aberraties
  - Celdood

Samenvattend



Morgan, William; Sowa, Marianne
Health Physics. 97(5):426-432, November 2009.

Overwegingen

- LNT-model is NIET veilig genoeg:
  - Hyper-radiosensitiviteit bij zeer lage dosis
  - ‘Bystander’ effect → weefselreactie
- LNT-model is TE veilig:
  - Adaptieve respons → drempeldosis
  - ‘Radiation hormesis’ → risicoverlaging

Kortom

- Nog te weinig bekend van onderliggende mechanismen en samenhang van adaptieve respons, ‘bystander’ effect (en genomische instabiliteit) → meer onderzoek
- Aanpassing van LNT-model op termijn valt niet uit te sluiten
- ICRP: Voorlopig houden we nog vast aan LNT-model

Dank voor uw aandacht !