Threshold doses and circulatory disease risks

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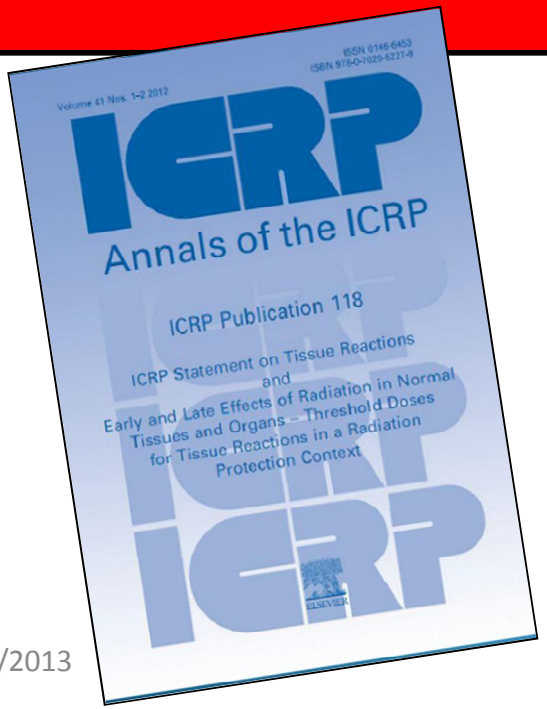
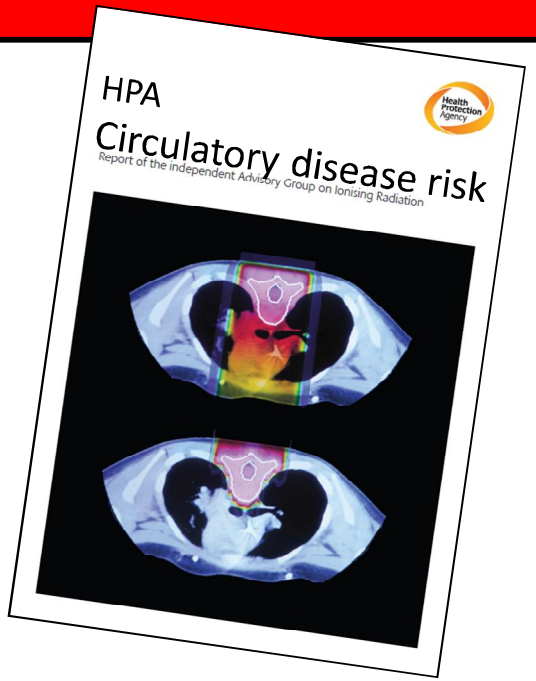
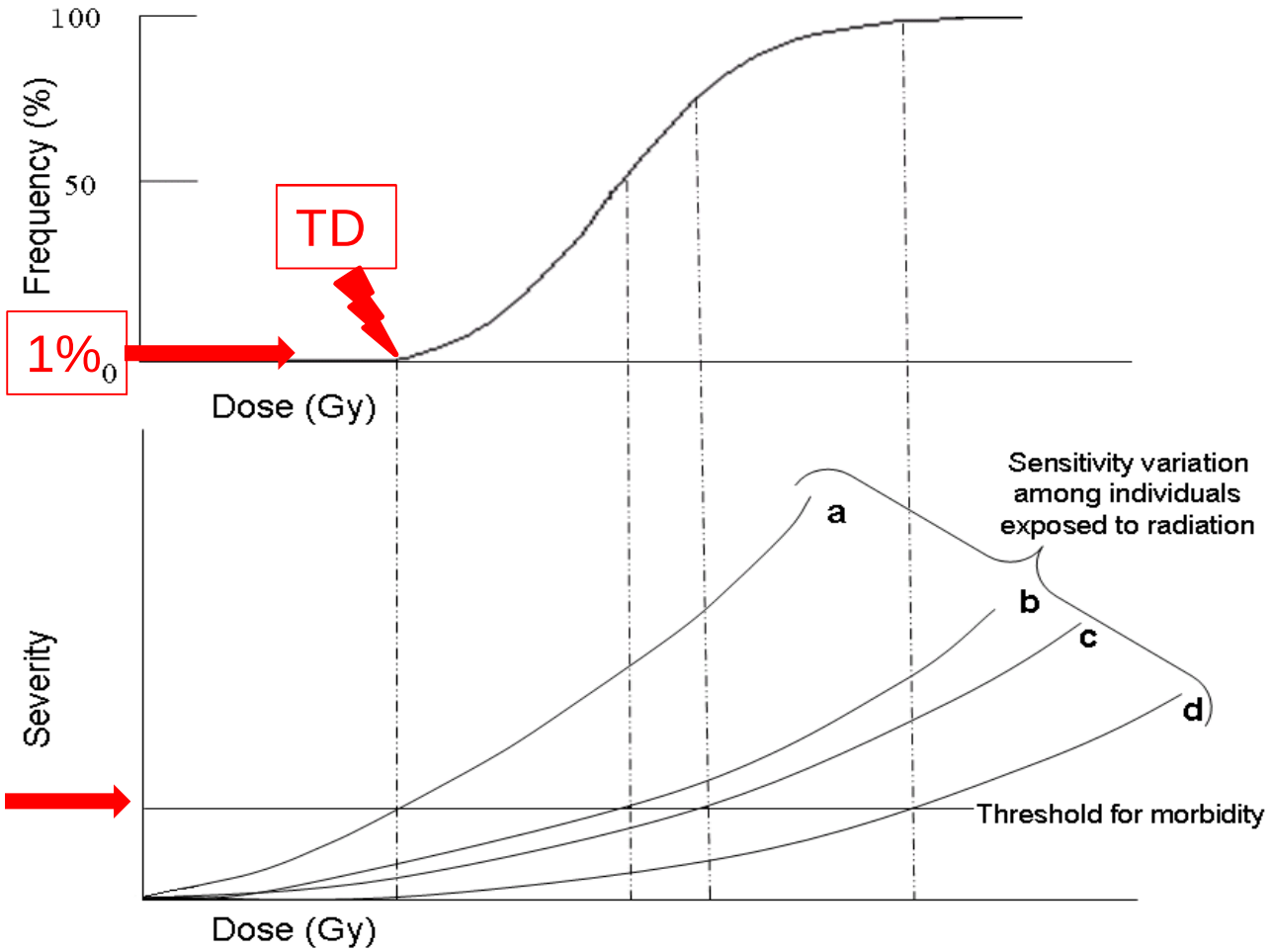
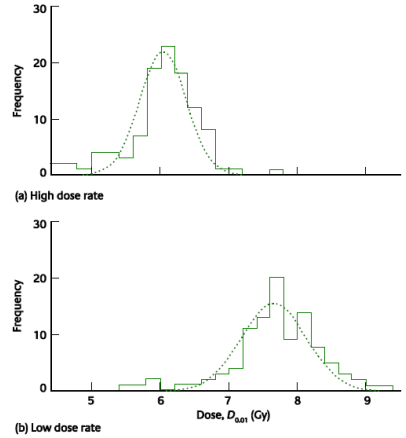
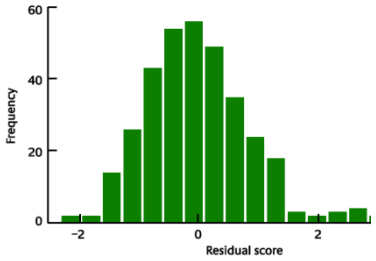




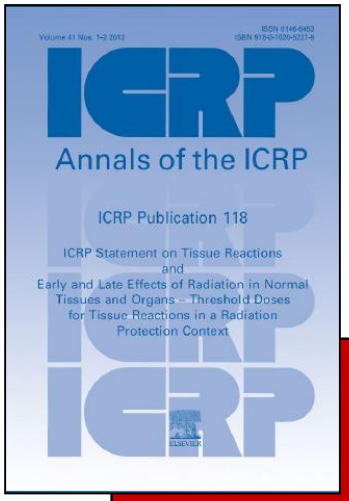
Threshold Dose (TD)







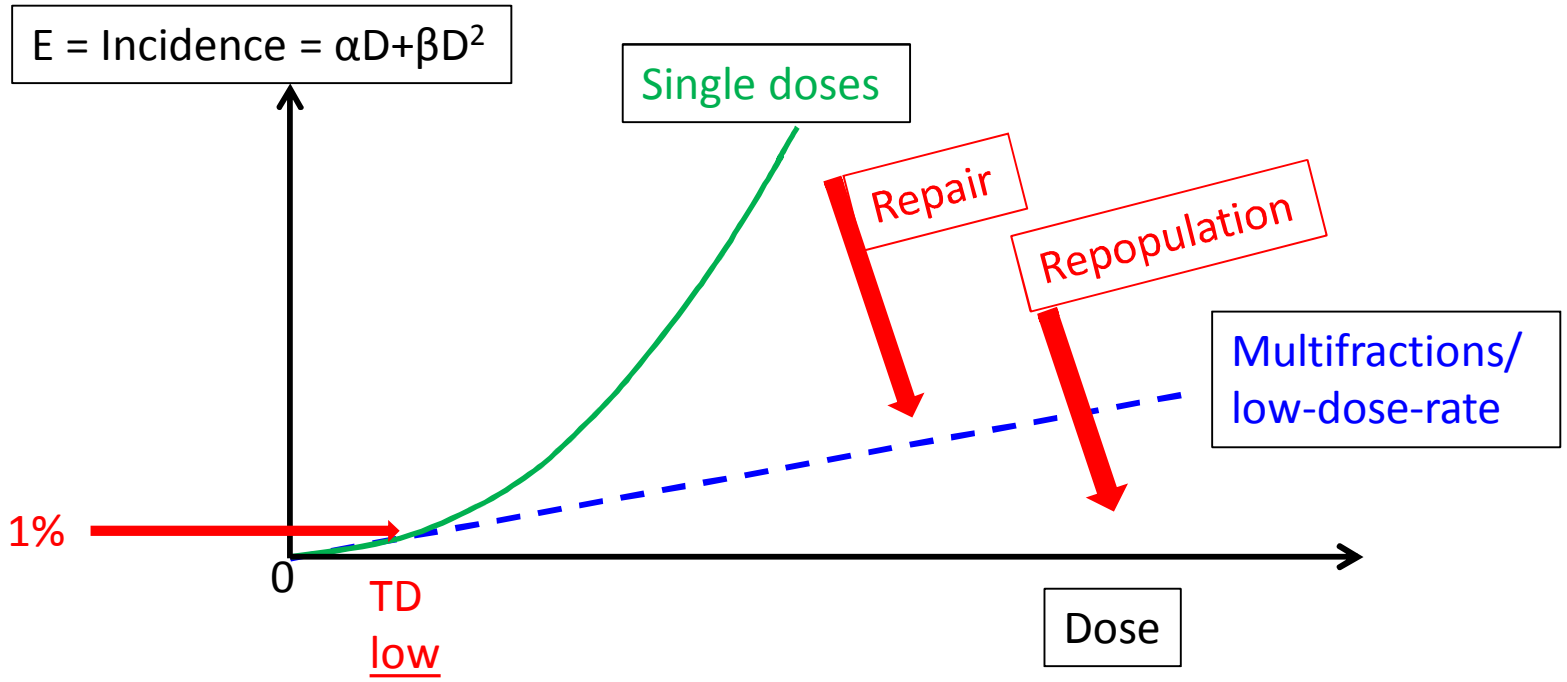
ICRP 41 (1984), 60 (1991), 103 (2007),118 (2012)



ICRP Publication 118 (2012): "Nominal" threshold doses

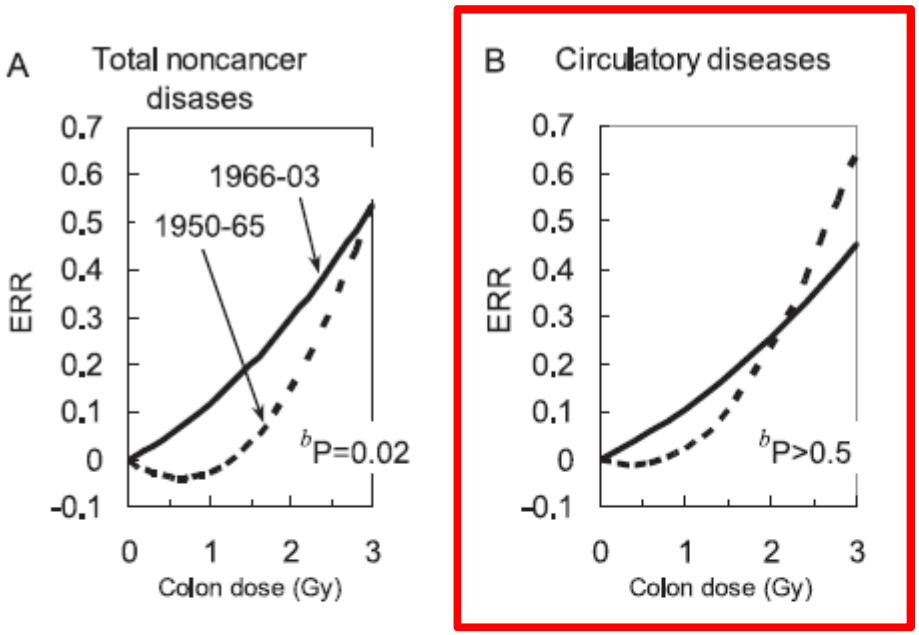
Effect	Time to develop effect	Acute exposure Gy	Fractionated or chronic exposure Gy
Skin erythema Skin burns Late atrophy	1-4 weeks 2-3 weeks >1 year	<3-6 5-10 10	30 35 40
Lens cataract (visual impairment)	>20 years	~0.5	~0.5
Cardiovascular disease	**>10-15 years**	**~0.5**	**~0.5**

Multi-fractionated doses or low-dose-rate



Why would the Threshold Dose be independent of Fractionation/ Dose-rate?

- **Greater statistical uncertainties below 0.5 Gy**
- **Response at low doses due to irrepairable and persistent radiation lesions**
- **<u>Different target cell populations at risk for low doses versus higher doses?</u>**



20y

21-58y follow-up

Circulatory Disease Mortality of Atomic Bomb Survivors 1950–2003

Ozasa et al. Radiat. Res. 177, 229 (2012)

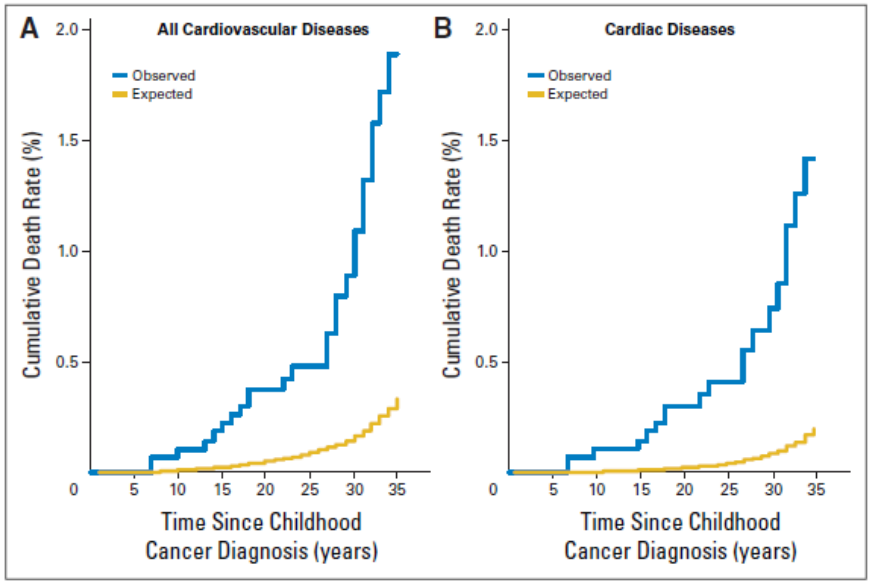
Systematic Review and Meta-analysis of Circulatory Disease from Exposure to Low-Level Ionizing Radiation and Estimates of Potential Population Mortality Risks

Mark P. Little,[1] Tamara V. Azizova,[2] Dimitry Bazyka,[3] Simon D. Bouffler,[4] Elisabeth Cardis,[5] Sergey Chekin,[6] Vadim V. Chumak,[3] Francis A. Cucinotta,[7] Florent de Vathaire,[8] Per Hall,[9] John D. Harrison,[4] Guido Hildebrandt,[10,11] Victor Ivanov,[6] Valeriy V. Kashcheev,[6] Sergiy V. Klymenko,[3] Michaela Kreuzer,[12] Olivier Laurent,[13] Kotaro Ozasa,[14] Thierry Schneider,[15] Soile Tapio,[16] Andrew M. Taylor,[17] Ioanna Tzoulaki,[18] Wendy L. Vandoolaeghe,[18] Richard Wakeford,[19] Lydia B. Zablotska,[20] Wei Zhang,[4] and Steven E. Lipshultz[21]

- Doses <0.5 Gy or <10 mGy/day
- 10 studies: Medical, occupational, atomic bomb survivors; assumed LNT, 5 years latency then constant ERR
- Excess population risks for all circulatory diseases combined = 2.5-8.5 % per Sv
- Versus cancer risk = 4.2-5.6 % per Sv

Environ Health Perspec. 120, 1504 (2012)

Cardiovascular mortality after radiotherapy for childhood cancer



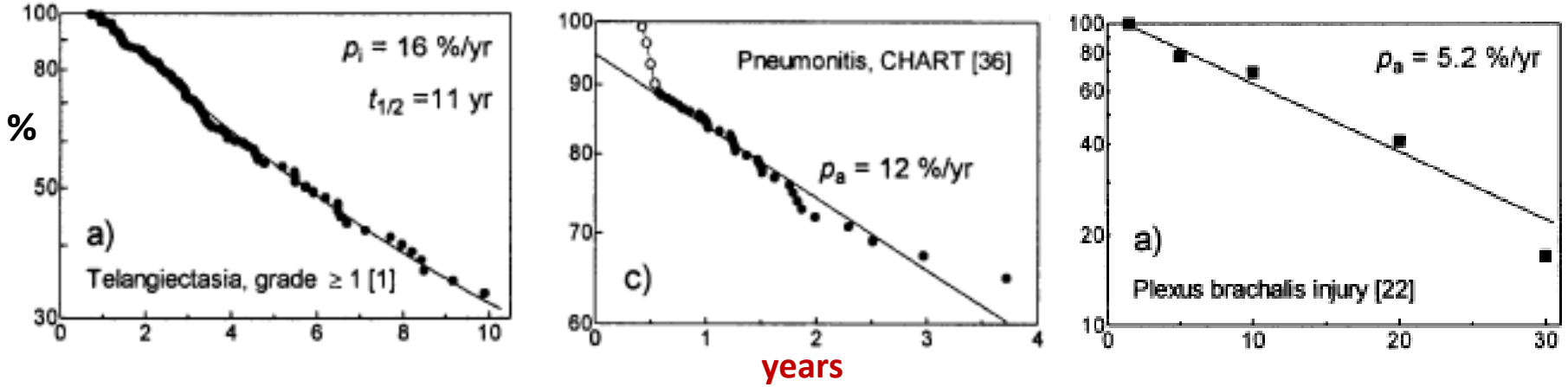
Mean heart dose Gy	No. of patients	RR (95% CI)
<1	1243	3 (0.3-28)
1-5	508	2.5 (0.2-42)
5-15	421	12.5 (1.4-116)
>15	541	25 (3-210)

Assuming LNT, Excess Relative Risk at 1 Gy ~ 60 %

Tukenova et al. 2010. J Clin Oncol. 28, 1308

"Quantification of late complications after radiation therapy"

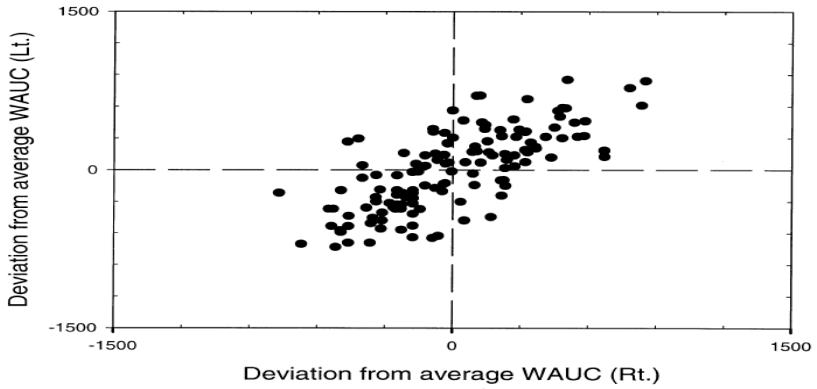
"The annual rate of the incidence of complications per patient at risk remains about constant with time after treatment (i.e. ~exponential kinetics). This implies that a *random process* might be involved in the occurrence of late radiation sequelae."
Jung et al. Radiother. Oncol. 61, 233 (2001)



"*Patient-related* versus *stochastic* components of variability for skin telangiectasia in paired bilateral radiotherapy fields"

"For a given fractionation schedule, *patient-related* factors explain 81–90% of the patient-to-patient variation in telangiectasia level seen after radiotherapy. The remaining 10–19% are explained by *stochastic* effects."

Safwat, Bentzen, Turesson, Hendry. Int J Rad Onc Biol Phys 52, 198 (2002)



Left field

Right field

Conclusions: cardiovascular damage after irradiation

- Doses < 1 Gy inhibit inflammatory cell adhesion to endothelium and inhibit development atherosclerosis (inhibition Esel, stimulated release TGFβ)
- Doses > 2 Gy induce inflammatory and thrombotic changes (activated chemokine signaling between leukocytes/EC, activated ROS)

- **Large arteries:** > 2 Gy initiates development atherosclerosis and predispose to inflammatory, unstable plaque
- **Heart:** >2 Gy causes capillary loss and damage, leading to perfusion defects, myocardial cell death and fibrosis

- Increased risks of circulatory disease after low dose TBI may be secondary to increased cholesterol levels and renal damage (proteinuria, hypertension)

Fiona Stewart (2012)

ApoE-/- mice: 5x cholesterol, predisposition to atherosclerosis

- **14 Gy, or 20 x 2 Gy** in 4 weeks, accelerated atherosclerosis with an inflammatory thrombotic plaque phenotype (Hoving *et al.* 2008).
- Doses of **0.025-0.5 Gy**, at an early or late stage of disease, impacted variously on the development of atherosclerosis (Mitchel *et al.* 2011).
- Cardiac exposure to **0.2 Gy** induces significant physiological, histopathological, cellular and molecular heart alterations, with mild functional impairment and an early pro-inflammatory polarization of macrophages (Monceau, Doerr *et al.* 2013).

HPA Report on Circulatory Disease Risk

- *"Conclusions:* Were the involvement of a stochastic process to be demonstrated convincingly, it would have significant implications with respect to radiation risk coefficients. However, atherosclerotic disease is a multifunctional disorder and all aspects of its biology need to be considered in relation to causal factors.
- **We do not consider that the available evidence justifies consideration of a stochastic component as being established, although it remains as a possibility.**
- Clearly, further work is needed to establish whether or not radiation can induce transformation of SMC to a plaque-type phenotype, whether this induction is a stochastic process, and whether it plays a significant role in atherogenic development. Similarly, more information is required on the lower range dose–response for the processes implicated in atherosclerotic disease such as inflammation, thrombosis and fibrosis."

HPA UK. RCE-16 (2010)

Euratom FP7: PROCARDIO project