



Public Health
England

BEIR VIII Planning Meeting

Recent reviews and novel data - low dose radiobiology

Simon Bouffler
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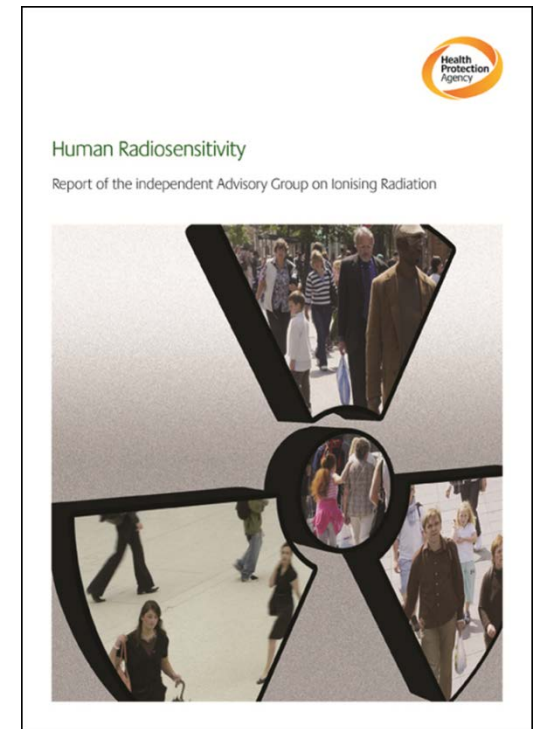
Outline

- Advisory Group on Ionising Radiation activities – human radiosensitivity, transgenerational effects
- UNSCEAR White Paper, 2012
- Newer cellular and genetic studies
- Epigenetic effects – potential importance
- Relevant European projects and activities
- Current PHE studies



AGIR Human Radiosensitivity (2013)

- Clear evidence for variation in sensitivity to cancer and tissue damage
- Genetic and lifestyle factors affect individual sensitivity as well as age and gender
- No reliable predictive tests of inherited susceptibility
- Genetic basis not well understood



https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/333058/RCE-21_v2_for_website.pdf



AGIR Transgenerational Effects (2013)

- Animal and cellular studies at > 1 Gy indicate transgenerational effects, especially when males exposed
- No human data indicate effects on health
- Effects may be limited to short times post exposure

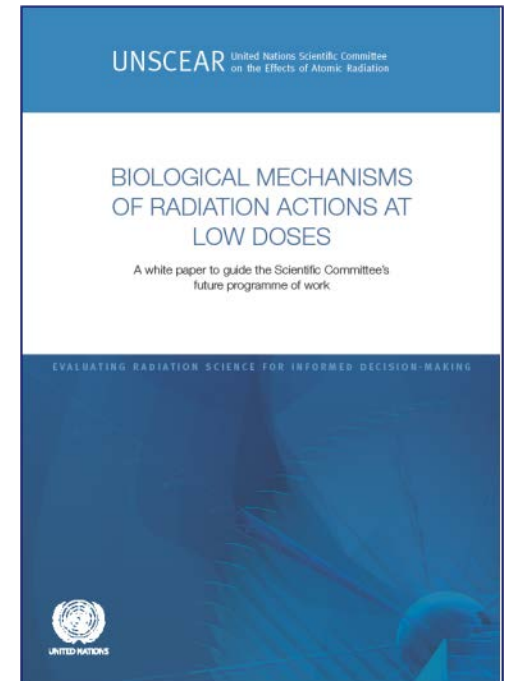
http://webarchive.nationalarchives.gov.uk/20140722091854/http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317139141166

See also *Little et al (2013) Mutat Res 753:50-67*



UNSCEAR White Paper (2012)

- Reviewed post 2006 data on genomic instability bystander and abscopal effects, adaptive response, ROS/mitochondrial effects, DNA sequencing, Gene and protein expression, tissue level phenomena
- On non-targeted effects concluded – many more data, results mixed in outcome, little coherence. No indication of causal association of non-targeted effects with radiogenic disease



http://www.unscear.org/docs/reports/Biological_mechanisms_WP_12-57831.pdf



DNA repair genes as risk modifiers

- NHEJ and HR DSB repair gene deficiencies modulate radiation cancer risk in animal studies (*Degg et al, 2003; Haines et al, 2010*)
- Repair gene deficiencies also modulate cataract risk in animal models (*Kleiman et al, 2007; Worgul et al, 2005*)

Strengthened case for early DNA damage being of fundamental importance in radiation cancer, and perhaps cataract



Cellular studies – DNA damage and repair

- Linearity of DSB / foci formation questioned (*eg, Neumaier et al 2012; Beels et al 2009, 2010*)
- Incomplete repair of foci following low doses (*eg, Rothkamm and Lobrich 2003; Grudzenski et al 2010*)
- G2/M checkpoint has activation threshold of 10-20 DSB (*Lobrich and Jeggo 2007*)
- Intercellular induction of apoptosis (*Bauer 2007*)

What is the fate of cells with residual damage?



Cellular studies – gene mutation

- Reduction in mutation frequency below spontaneous by 0.2 Gy in *Drosophila* larvae (*Koana et al 2012*)
- Linear dose-response 50-500 mGy for large deletions (*Boei et al 2012*)
- Dose-rate dependency of λ bacteriophage transgene mutation in mouse spleen and liver (*Okudaira et al 2010*)
- Germ cell mouse mutation retrospective analyses (*Russell and Hunsicker, 2012*)

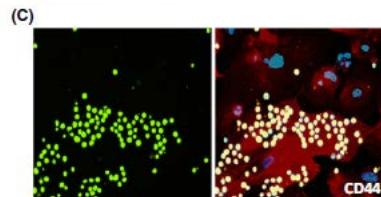
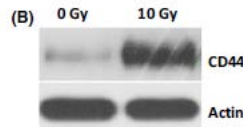
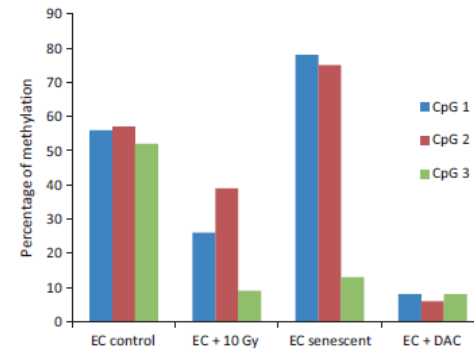
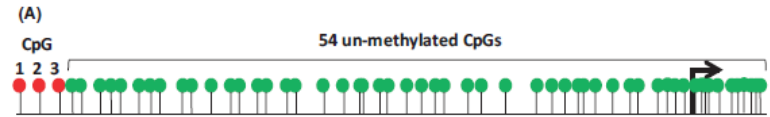
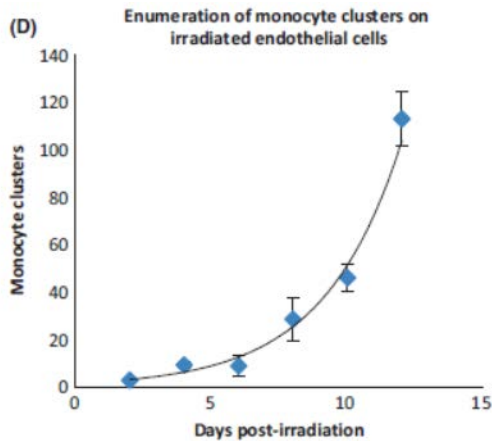
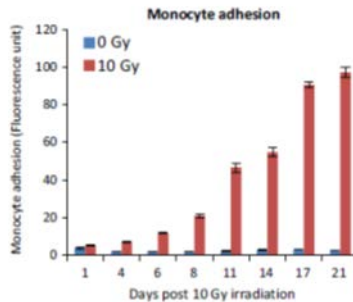
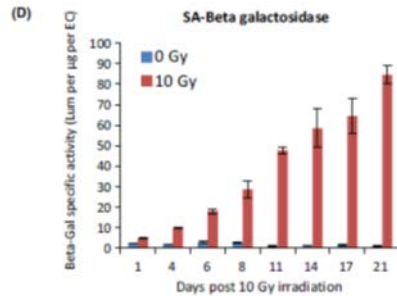
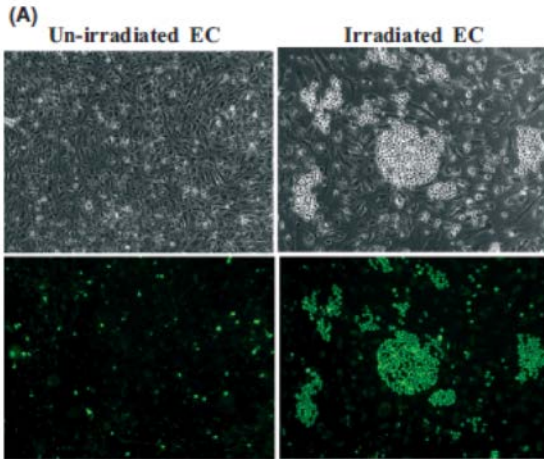


Cellular studies – chromosomal aberrations

- *In vivo* studies in mice examining dose-rate dependence of translocation and dicentric / ring formation (*Tanaka et al 2009, 2013*)
- Linear dose-dependence of micronucleus formation 0-100 mGy *in vitro* (*Boei et al 2012*) and 10-100 mGy *in vivo* (*Manning et al 2014*)



Epigenetic effects of radiation on endothelial cells



Lowe & Raj (2014)
Ageing Cell 13:900-910



EU funded activities - I

Networks:

DoReMi, OPERRA, CONCERT

Aims:

Bringing together relevant researchers with interests in RP

Drive towards integration of epidemiology and experimental approaches



EU funded activities - II

Specific projects:

- Circulatory diseases (*Procardio, Cerebrad*)
- Effects – stem cells (*RISK-IR*)
- Micro/non-coding RNAs (*Dark-Risk*)
- Epidemiology eg, CT, Mayak etc (*EpiCT, SOLO, SEMI-NUC*)
- Integration (*EpiRadBio*)



Current PHE activities

- Epidemiology – NRRW and collaboration on INWORKS
- Cancer mechanisms – models to link early events to disease
- Non-cancer mechanisms – atherosclerotic disease and cataract
- Epigenetic effects



Summary

- Are there data posing a significant challenge to BEIR VII conclusions?

No

- What studies could impact on low dose risk estimation?
 - *better linkage of early changes to disease*
 - *identification of epigenetically regulated targets in radiogenic disease and associated radiation response*
 - *unexpected differences in response of target (stem / progenitor) cells*
 - *greater understanding of immuno-modulation and micro-environmental control effects*