Public Health England

UNSCEAR

UNSCEAR White Paper: Biological Mechanisms of Radiation Actions at Low Doses

Simon Bouffler

8 October 2013

Public Health England

Typical UNSCEAR reports

- Large
- Comprehensive
- Developed over several years

Public Health England

White papers

- Newer format
- Not comprehensive
- Intended to highlight major advances in rapidly developing areas
- To guide the Committee future programme of work

Public Health England

Why Biological Mechanisms?

- Conventional DNA damage / mutation paradigm important aspect of LNT justification
- UNSCEAR had a wide range of evaluations of mechanisms – some rather old
- Thematic priority for 2009-2013 – ‘Improved understanding of the effects from low dose-rate radiation exposure’
- Concern that understanding had changed

Public Health England

Earlier relevant reports

1993 –	Annex E, Mechanisms of radiation oncogenesis
1994 –	Annex B, Adaptive response to radiation in cells and organisms
2000 –	Annex F, DNA repair and mutagenesis
2000 –	Annex G, Biological effects at low radiation doses
2001 –	Annex, Hereditary effects of radiation
2006 –	Annex C, Non-targeted and delayed effects of exposure to ionizing radiation

Public Health England

Origin of White Paper

- 56th Session (July 2008): UK delegation offers to prepare a white paper reviewing -

  (i) UNSCEAR position on the mechanisms of radiation actions at low doses

  (ii) New knowledge that had become available since 2006 evaluation of non-targeted effects

Public Health England

Timeline for development

- First white paper prepared for 57th Session (August 2010) – Committee agrees to updates at appropriate intervals
- 58th Session (May 2011) – Update requested, drafted by S Bouffler reviewed by US and German delegations
- 59th Session (May 2012) issued for discussion at this session
- Noted in 2012 General Assembly report, published on UNSCEAR website late 2012

Public Health England

Low dose definition

UNSCEAR had used different values over the years

- 200 mSv or less (at 0.1 mGy / min or less) used extensively in earlier reports
- Decision / agreement for low doses to be those

  ≤ 100 mSv – consistent with ICRP and BEIR VII report

Public Health England

Judgements to 2006: Health effects of concern

- Cancer
- Heritable effects
- Mechanistic considerations may be relevant for other effects eg, circulatory disease and cataract

Public Health England

Judgements to 2006: Cancer mechanisms - I

- Main actions through induction of DNA damage in somatic cells
- Damage can be repaired but never sure to be completely error free
- Therefore smallest doses may lead to DNA sequence mutations

Public Health England

Judgements to 2006: Cancer mechanisms - II

- Cancer is multistep process
- Cancer progression subject to modulation through for example immuno-surveillance – impact uncertain
- Other potential risk modulation processes eg, adaptive responses – data inconsistent and mechanisms unclear

Public Health England

Judgements to 2006: Cancer mechanisms - III

- Non-targeted and delayed effects may be associated with radiation disease

- No evidence for NTE being causal in radiation associated disease

Public Health England

Judgements to 2006: Hereditary effects

- Radiation damage to germ cell DNA
- Repair but never certain to be error free
- Mutation induction

Public Health England

Judgements to 2006

All summarised in more detail and key quotes from relevant General Assembly reports and annexes included in an appendix

Public Health England

New areas reviewed

- Genomic instability
- Bystander and abscopal effects
- Adaptive response
- Reactive oxygen / mitochondrial function
- DNA sequence analysis
- Gene / protein expression
- Cellular interactions / tissue phenomena
- Systems biology approaches

Public Health England

Genomic instability / bystander / adaptive response

- Many publications since 2006
- Notes inter-relatedness of phenomena
- Concerns expressed on variability and reproducibility
- Possible ‘threshold’ of 0.5 Gy (low LET) for induction of transmissible instability

Public Health England

Reactive oxygen / mitochondrial function

- NTEs affected by oxygen and other radicals – possible mediators in some cases
- Differential high / low dose effects reported
- Confounding/obscuring of *in vivo* relevance by studies as ambient oxygen concentration?
- Oxygen environment can affect radiosensitivity

Public Health England

DNA sequence analysis

- Application of high throughput sequencing to cancer genome analysis – an opportunity
- Novel genome rearrangement phenomena eg, chromothripsis have been described
- A growing appreciation that epigenetic regulation through DNA methylation, histone acetylation and microRNAs can be important in cancer
- Growing awareness of differences at DNA sequence level between individuals
- Major opportunities for application to radiation effects and radiation cancer studies

Public Health England

Gene and protein expression

- Application of ‘omics technologies
- Suggestions of high / low dose differences – but lack of consistency across systems and platforms
- Application in exposure monitoring and possibly disease risk studies

Public Health England

Epigenetics

- Modulation of microRNA expression
- Modulation of methylation
- Suggested role in mediating transmissible instability in some systems
- Much to be learned and consistent pictures of effects required, particularly at low doses

Public Health England

Cellular interactions / tissue level effects

- Examples exist of modulation of cell behaviour by surrounding cells
- Possible role of irradiation in modifying the tissue environment to be more ‘permissive’ for cancer growth
- Inflammatory microenvironments may modify cancer progression
- Immuno-modulation by radiation may play a role in cancer progression, unclear if (low dose) radiation always immuno-suppressive or stimultory

Public Health England

Systems Biology

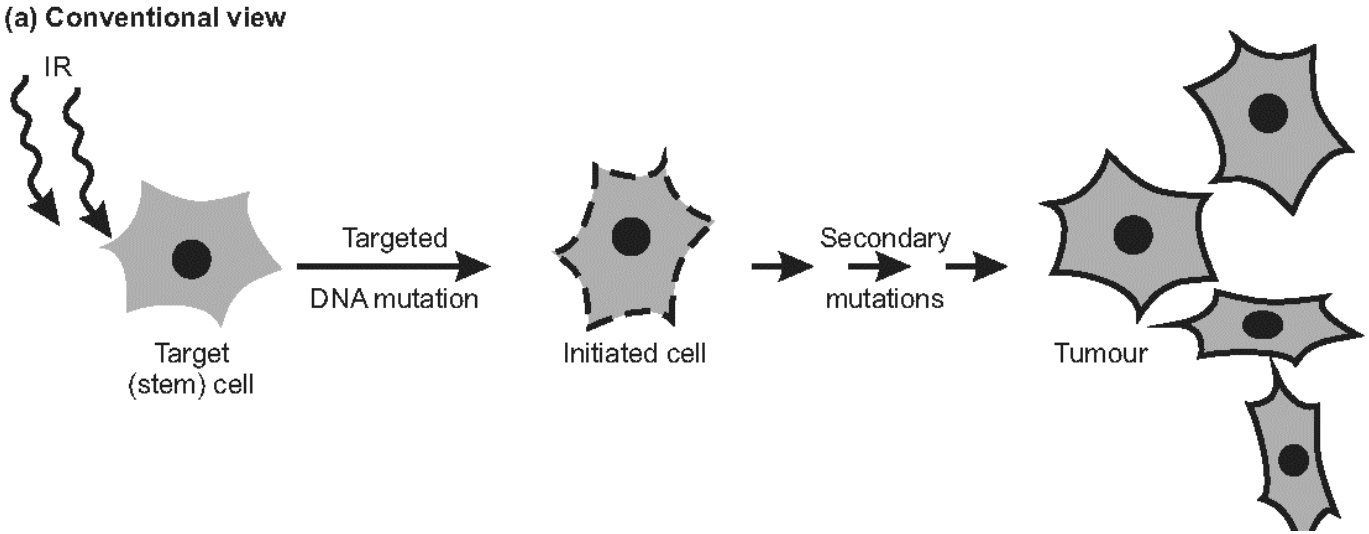
- Will play a role in integrating the many phenomena described

- Systems level descriptions of radiation carcinogenesis will take considerable time to develop

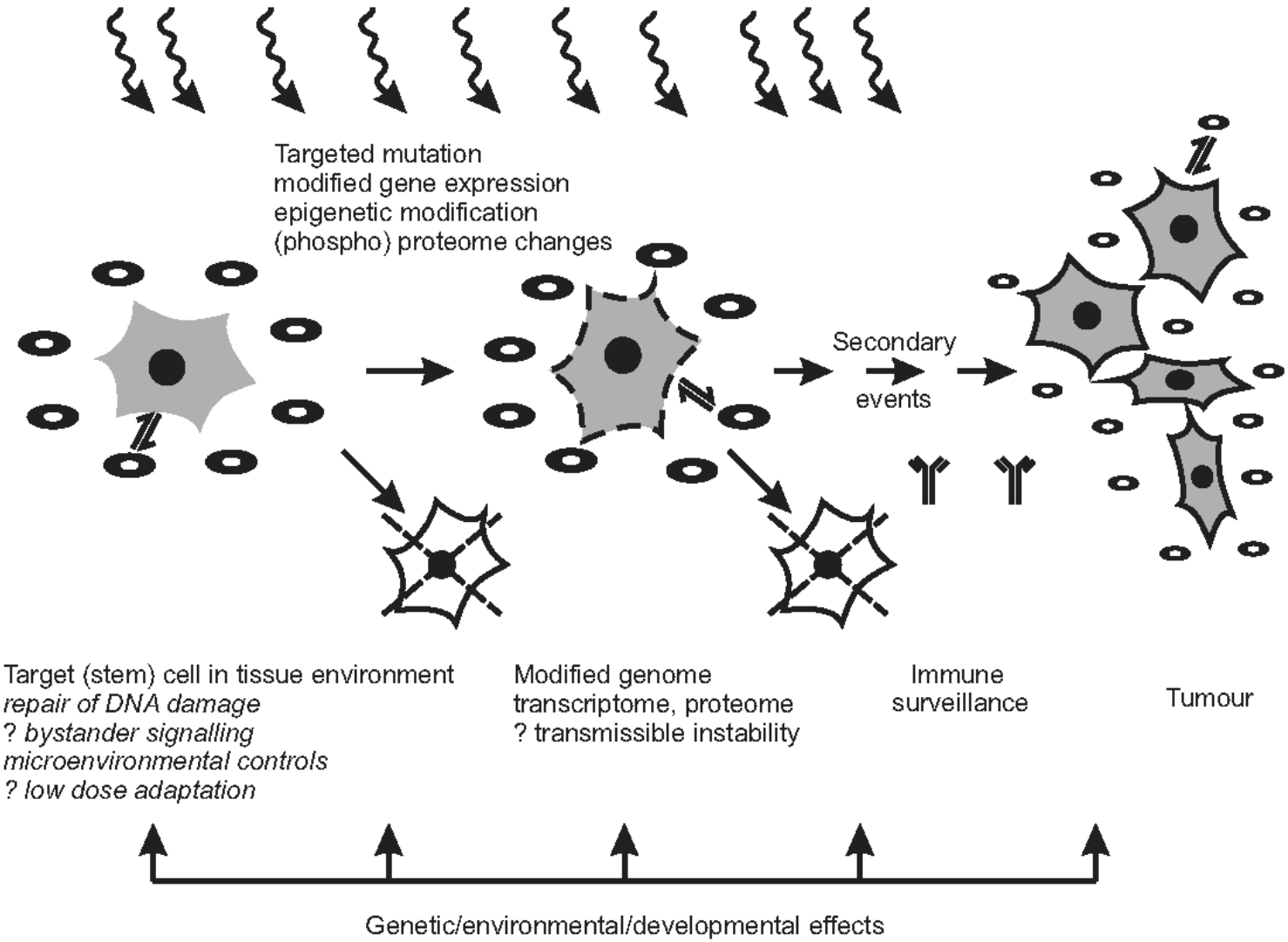
Public Health England

Conclusions

- More NTE data available, mechanistic understanding improving, but many studies remain observational.
- Differential gene/protein expression observed – but how consistent are studies?
- Lack of evidence for causal association of NTE and radiation disease
- Systems framework can guide integration of mechanistic data


(a) Conventional view
IR
Target
(stem) cell
Targeted
DNA mutation
Initiated cell
Secondary
mutations
Tumour

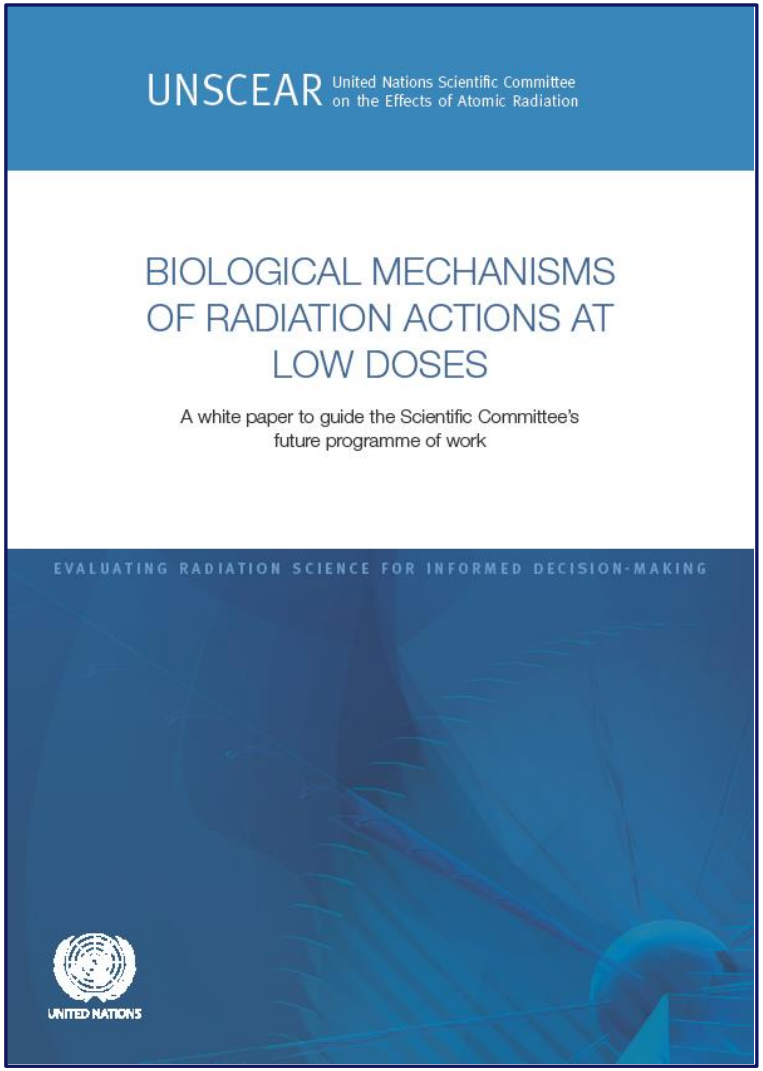
(b) Systems view



Public Health England

Recommendations

- UNSCEAR agreed to encourage research into mechanistic understanding that can contribute to understanding of disease risk
- To consider developing further biologically based risk models and systems level framework to integrate mechanistic data into risk assessment
- To review the field in 3-4 years



Thanks for your attention

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