Radiation Protection and Tissue Reactions: An ICRP Position

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ICRP Report on Tissue Reactions

Early and late effects of radiation in normal tissues and organs: threshold doses for tissue reactions and other non-cancer effects of radiation in a radiation protection context.

(In Press)

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Tissue Reactions – Deterministic Effects

For protection purposes the biological effects of radiation are separated into stochastic effects (cancer, heritable effects) and tissue reactions. The latter had previously been termed deterministic effects but were renamed as tissue reactions in the ICRP 2007 Recommendations because of the enhanced evidence that these responses could be modified after irradiation rather than being determined at the time of radiation. Such tissue reactions can occur at early or late times after irradiation. In addition, they typically exhibit a threshold dose that has been the basis for establishing recommended dose limits.
Purpose and terms of reference of the report

- Review tissue and health effects of radiation, with reference to implications for dose limits in radiation protection and for assessing health risks after accidental or therapeutic exposure

- Review literature on the non-cancer effects of radiation on normal tissues, both in the context of therapeutic doses received by cancer patients, and lower doses sustained during accidental or occupational exposures or during other incidents of unknown magnitude

- Update of ICRP Publication 41 (1984), including new data on cardiovascular effects and the risk of radiation-induced cataracts, and new data on modifiers of radiation responses
Tissue reactions (Deterministic effects)

- ICRP 41 (1984): *non-stochastic* injury in populations of cells
- ICRP 60 (1991): *deterministic effects*, causally determined by preceding events i.e. the dose
- ICRP 103 (2008): *tissue reactions (deterministic effects)*, subject to biological response modifiers (dose modifying factors 1.1 to 2)
- It is now clear that not all non-cancer responses are the result of cell killing and determined directly by the radiation exposure (*deterministic*) but can arise by a number of tissue responses directly and indirectly due to the radiation (*tissue reactions*)
Rapidly proliferating tissues (short turnover time) express radiation injury much earlier than slowly proliferating tissues.
Late Tissue Reactions

• In addition, there are some tissue reactions, particularly those involving the lens of the eye (e.g., cataracts) and the cardio and cerebrovascular systems (e.g., circulatory disease), that can occur at very long times after a radiation exposure but can still be related to this exposure.

• New data on these has led to some reconsiderations of the possible impact of tissue reactions on overall radiation risks.
Tissue damage (especially late effects) results from orchestrated biological responses at both cell and tissue level (not just cell killing)

Fibrosis results from excess collagen production in damaged fibroblasts rather than killing of fibroblast target cell population

Cytokine and other non-lethal signaling responses are activated by radiation during “silent period” (latency) and can modify the extent of tissue damage
Chapter 1: Introduction

• Definition and nature of tissue reactions to radiation

• General principles of radiation effects
  — Cell survival
  — Kinetics of tissue responses
  — Fractionation and protracted exposures
  — Isoeffect relationships
  — LET and RBE
  — Partial organ irradiation
  — Non-cytotoxic effects
Chapter 2: Response of organs and tissues to radiation

Haematopoietic and immune systems          Digestive system
Reproductive system                        Skin
Cardiovascular and Cerebrovascular Systems  Eye
Respiratory system                          Urinary Tract
Musculoskeletal system                     Endocrine system
Nervous system

Each section describes:

- Anatomical features
- Proliferative organisation and potential for proliferative recovery
- Types of tissue responses
- Total body irradiation and low dose responses
- Clinical data for therapeutic doses (dose/volume effects)
- Pre-clinical data and mechanisms
- Internal exposures
Threshold Doses

• Threshold doses have been set at a 1% incidence of an effect. Recent studies have shown that for circulatory disease and lens cataracts the threshold dose is very small and not significantly different for acute and protracted exposures.

• In mechanistic terms, this could be the case if doses lower than the threshold dose produced “single-hit” type damage or if different types of injury occur at high and low doses.

• The impact of these observations on risk have yet to be fully considered.
Cardio and cerebrovascular system

• New epidemiological data for circulatory disease at doses of <5 Gy
  — Japanese A-bomb survivors
  — Therapeutic Radiotherapy for non-cancer diseases
  — Occupational exposures (US radiologists & technologists, UK nuclear power workers)
  — Accidental exposures (Chernobyl, Mayak)

• New epidemiological data for circulatory disease at doses of >5 Gy
  — Hodgkin’s lymphoma survivors
  — Breast cancer survivors
  — Head & Neck cancer
  — Childhood leukemia, brain tumours
Mechanisms of Radiation-induced Cardiovascular Disease

- There is clear evidence for an association between therapeutic doses of thoracic radiation and increased risks of cardiovascular disease.
- Inflammatory responses leading to reduced perfusion myocardial cell death and fibrosis.
- Doses above 2 Gy can also lead to atherosclerosis and the formation of unstable lesions that can result in fatal heart attack or stroke.
- Likely that other mechanisms for cardiovascular effects are operating at doses below 2 Gy.
- Understanding these is critical for the assessment of risk at low doses.
Main Conclusions

- LSS (Atomic bomb survivors) indicates ERR mortality of 0.14 per Gy (0.06-0.23) for heart diseases and 0.09 (0.01-0.17) for cerebrovascular disease
- Data for heart favour a linear relationship with no predicted threshold, for cerebrovascular effects a threshold of 0.5 Gy gives the best fit, BUT also consistent with linear-quadratic or quadratic relationships and there is considerable uncertainly below 0.5 Gy
- ERR for circulatory disease also reported for some (but not all) populations of accidental or occupational exposures, substantial heterogeneity
- ERR for heart disease and cerebrovascular disease in several irradiated cancer patient populations; effects apparent at >10y
Radiation Cataracts

- It has been assumed that radiation cataract is a deterministic effect requiring threshold doses generally greater than 2 Gy.
- This is probably the result of short follow-up periods, failure to take account of increasing latency as dose decreased, relatively few subjects with lower doses and not designed to detect early lens changes.
- Newer studies at lower doses (e.g., astronauts, medical workers, A-bomb survivors, accidentally exposed individuals, and those undergoing diagnostic or radiotherapeutic procedures) suggest dose-related lens opacification at much lower doses.
Table 4.1. Recent epidemiological studies of cataract formation where formal estimates of threshold doses were made.

<table>
<thead>
<tr>
<th>Study</th>
<th>Cataract type</th>
<th>Threshold dose</th>
<th>Confidence intervals</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>A bomb survivors (acute exposure)</td>
<td>Cortical cataracts</td>
<td>0.6 Sv</td>
<td>90%: &lt;0-1.2 Sv</td>
<td>Nakashima et al 2006</td>
</tr>
<tr>
<td></td>
<td>Posterior subcapsular opacity</td>
<td>0.7 Sv</td>
<td>90%: &lt;0-2.8 Sv</td>
<td></td>
</tr>
<tr>
<td>A bomb Survivors (acute exposure)</td>
<td>Postoperative cataracts</td>
<td>0.1 Gy</td>
<td>95%: &lt;0-0.8 Gy</td>
<td>Neriishi et al 2007</td>
</tr>
<tr>
<td>Chernobyl clean-up workers (fractionated protracted exposure)</td>
<td>Stage 1–5 cataract</td>
<td>0.50 Gy</td>
<td>95%: 0.17–0.65 Gy</td>
<td>Worgul et al 2007</td>
</tr>
<tr>
<td></td>
<td>Stage 1 cataract</td>
<td>0.34 Gy</td>
<td>95%: 0.19–0.68 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage 1 non-nuclear cataract</td>
<td>0.50 Gy</td>
<td>95%: 0.17–0.69 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage 1 superficial cortical cataract</td>
<td>0.34 Gy</td>
<td>95%: 0.18–0.51 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage 1 posterior subcapsular cataract</td>
<td>0.35 Gy</td>
<td>95%: 0.19–0.66 Gy</td>
<td></td>
</tr>
</tbody>
</table>
Radiation Cataracts (II)

• This has led to a proposed lowering of the presumptive radiation cataract threshold to 0.5 Gy and an occupational lens exposure limit of 20 mSv/yr, for acute, protracted or chronic exposure.

• Animal studies support these conclusions.

• Suggested that genotoxicity is involved in radiation cataract development.

• Clear need to better understand mechanism to establish basis for dose-response.
Other Non-cancer Effects

• Recent studies have also indicated effects at other sites from moderate/low dose exposure, e.g., respiratory and respiratory disease and CNS (in particular neuro-cognitive) damage.

• Because these are generally only observed in isolated groups or because the evidence is excessively heterogeneous, such lower dose responses have to be treated with caution.

• Continued emphasis from epidemiology and mechanistic studies is clearly indicated.
Main conclusions

• New data from both animal models and exposed human populations show that lens opacities occur at doses of <1 Gy
• Data from Japanese LSS showed best estimates of a 0.1 Gy threshold (<0-0.8) and 0.7 (Sv) (<0-2.8)
• Data from Chernobyl survivors showed best estimates of thresholds 0.3-0.5 Gy (CI 0.17-0.69)
• Animal data for lens opacities consistent with linear, no threshold dose response
• Lower thresholds arise from:
  — More sophisticated methods of scoring damage
  — Longer follow up (incidence increases with latency)
  — More data in low dose region
The present report has produced some changes to indicate threshold doses for tissue reactions, compared to those stated in ICRP 103 (ICRP, 2008).

• *First*, the threshold dose for radiation-induced eye cataracts is now considered to be around 0.5 Gy for both acute and fractionated exposures, in line with various recent epidemiological studies.

• *Second*, circulatory disease has been recognised as an important late effect of radiation exposure, both for mortality and morbidity. An approximate threshold dose of 0.5 Gy has been proposed for acute, and fractionated/protracted exposures, although the data to support this are rather uncertain.
• *Third*, the threshold dose values for chronic exposures depend on the exposure duration and the follow-up period after exposure. Differences between these time variables among different studies makes the values more uncertain. The values quoted for both the lens and the circulatory system assume the same incidence of injury irrespective of the acute or chronic nature of the exposure over a working life, with more than 10 years follow-up.
• *Fourth*, much more information has become available regarding the effect of biological response modifiers in mitigating the tissue reactions, which has the effect of modifying threshold doses. These modifications are agent, tissue and schedule specific, and they are likely to have increasing impact in the future, concomitant with increases in scientific and medical knowledge.
As a general conclusion, the ICRP judges on the basis of existing evidence, that acute doses up to around 100 mGy produce no functional impairment of tissues. This includes the lens of the eye regarding the risk of cataract, with the caveat that for this tissue the use of a threshold model remains uncertain.

Hence for most applications of ICRP recommendations in occupational or public situations, the stochastic risks of induced cancer and heritable effects remain the principal risks to consider. At higher doses the risk of tissue reactions (deterministic effects) becomes increasingly important, in particular regarding accidents and medical exposures.
Modulating Factors and Risk Assessment

- Summary risk estimates provide the overall average lifetime excess risk of cancer and non-cancer (where possible) for a general population and for a working population and are designed for a practical system of protection.
- These estimates are averages for a range of factors that can modify risk – race, sex, age-at-exposure, attained age and time-since exposure.
- Beyond these intrinsic characteristics of the risk estimate, there are a number of lifestyle factors and inherent characteristics that can modify risk.
- These can include smoking, alcohol and drug use, diet and obesity and certain genetic conditions.
- The discussion revolves around how to incorporate specific modifying factors into the risk assessment process.
Genetic Predisposition and Risk Assessment

• Need to understand the role of genetic susceptibility in overall cancer risk.

• The need for radiation protection is to provide protection to the population as a whole and this might be done by establishing how much of the risk is accountable for by susceptible subgroups.

• Such information would be necessary for transfer of risk among populations, for example.

• A possible longer-term approach is perhaps to sum all potentially deleterious variants for cancer risk and develop a susceptibility score for specific tumors. This can then be built into risk estimates.
Journal of Radiological Protection has just issued a volume on the International Expert Symposium in Fukushima: Radiation and Health Risks. Articles are free to read at:

http://iopscience.iop.org/0952-4746/32/1
Extra Slides
Radon, Smoking and Lung Cancer

• A good example of how a modulating factor can impact risk assessment is provide by the induction of lung cancer by radon in smokers and non-smokers.

• A major concern relates to the calculation of radon exposure limits that do not differentiate between smokers and non-smokers.

• Need to revisit the issue especially now that new data are becoming available.
Table 4.2 Summary of results of many of the studies of radiation-induced lens changes.

<table>
<thead>
<tr>
<th>Author</th>
<th>No.</th>
<th>Age at exposure (years)</th>
<th>FU time (years)</th>
<th>Dose range or average (Gy)*</th>
<th>Fractions</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatments</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cogan et al., 1953</td>
<td>40</td>
<td>15-70</td>
<td>7 (1-14)</td>
<td>0.23-24</td>
<td>1 to n</td>
<td>5 cats None &lt; 5 Gy</td>
<td>Small case series, short FU</td>
</tr>
<tr>
<td>Merriam et al., 1957</td>
<td>100</td>
<td>0.9-84</td>
<td>5-9</td>
<td>0.25-69</td>
<td>1 to n</td>
<td>All cats &gt; 2 Gy or fractions &gt; 5 Gy</td>
<td>Clinical series, n=33 at &lt; 200 r, short FU</td>
</tr>
<tr>
<td>Qvist et al, 1959</td>
<td>56</td>
<td>Infants</td>
<td>&gt;20-40</td>
<td>&gt;1</td>
<td>1-15</td>
<td>4 cats at &gt;6.9 Gy</td>
<td>Small study</td>
</tr>
<tr>
<td>Albert et al., 1968</td>
<td>234</td>
<td>8 (1-14)</td>
<td>10</td>
<td>0.5</td>
<td>5 (over a few minutes)</td>
<td>13 opacities</td>
<td>Small study</td>
</tr>
<tr>
<td>Wilde and Sjostrand, 1997</td>
<td>20</td>
<td>0.2-1</td>
<td>30-46</td>
<td>1-11 Ra-226</td>
<td>1 (1.5-3 h)</td>
<td>Opacities vs. dose</td>
<td>Small study</td>
</tr>
<tr>
<td>Hall et al., 1999</td>
<td>484</td>
<td>0.4 (0-1.3)</td>
<td>46</td>
<td>0.4 (0.8-4) Ra-226</td>
<td>2 (1-14)</td>
<td>Cats vs. dose</td>
<td>Cortical not nuclear vs. dose</td>
</tr>
<tr>
<td><strong>A-bomb survivors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cogan et al., 1950</td>
<td>1,000</td>
<td>All</td>
<td>4</td>
<td>NA</td>
<td>1</td>
<td>Some opacities</td>
<td>Screening study</td>
</tr>
<tr>
<td>Choshi 1983</td>
<td>2,385</td>
<td>All</td>
<td>33-35</td>
<td>&gt;1</td>
<td>1</td>
<td>Increased opacities</td>
<td>No dose-response estimated</td>
</tr>
<tr>
<td>Otake 1996</td>
<td>~2,000</td>
<td>All</td>
<td>18-19</td>
<td>NA</td>
<td>1</td>
<td>Various opacities / cataracts</td>
<td>Screening study</td>
</tr>
<tr>
<td>Nakashima et al., 2006</td>
<td>&gt;700</td>
<td>~8.8</td>
<td>55-57</td>
<td>0.52 (0-&gt;2) Sv</td>
<td>1</td>
<td>Threshold 0.6-0.7 Sv</td>
<td>Increased opacities</td>
</tr>
<tr>
<td>Neriishi et al., 2007</td>
<td>3,761</td>
<td>0-&gt;20</td>
<td>55-57</td>
<td>0-&gt;3</td>
<td>1</td>
<td>Threshold 0.1 (0-0.8) Gy</td>
<td>12.7% cataract surgery</td>
</tr>
<tr>
<td><strong>Accidents, residents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day et al., 1995</td>
<td>991</td>
<td>0-12</td>
<td>5-7</td>
<td>0.030 Sv</td>
<td>Protracted</td>
<td>Some opacities</td>
<td>residents</td>
</tr>
<tr>
<td>Nadejima et al., 2002</td>
<td>41</td>
<td>~35</td>
<td>14</td>
<td>0.2, 3.2</td>
<td>Protracted</td>
<td>Cats at 3.2 Gy</td>
<td>Small study</td>
</tr>
<tr>
<td>Worgul et al., 2007</td>
<td>8,607</td>
<td>Adults</td>
<td>12-14</td>
<td>0-1</td>
<td>Protracted</td>
<td>Opacities</td>
<td>clean-up workers</td>
</tr>
<tr>
<td>Hsieh et al., 2010</td>
<td>73</td>
<td>&lt;20</td>
<td>4.7</td>
<td>~0.200 Sv</td>
<td>~7 y</td>
<td>Some opacities</td>
<td>Residential exposure</td>
</tr>
<tr>
<td><strong>Workers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Junk et al., 2004</td>
<td>59</td>
<td>NA</td>
<td>5-36</td>
<td>NA</td>
<td>5-36 y</td>
<td>Cats at long times</td>
<td>Chronic exposure</td>
</tr>
<tr>
<td>Shang et al., 2007</td>
<td>584</td>
<td>20-57</td>
<td>0.3-35</td>
<td>NA</td>
<td>0.4-35 y</td>
<td>Opacities at long times</td>
<td>Chronic exposure</td>
</tr>
<tr>
<td>Chodick et al., 2008</td>
<td>35,705</td>
<td>Workers</td>
<td>~19</td>
<td>0.005-0.06</td>
<td>6-13 y</td>
<td>Cats at higher dose</td>
<td>RT’s self reporting</td>
</tr>
<tr>
<td>Kleiman et al., 2009</td>
<td>78</td>
<td>IC workers</td>
<td>1-40</td>
<td>NA</td>
<td>Chronic</td>
<td>Some opacities</td>
<td>Doses unknown</td>
</tr>
</tbody>
</table>

No = number of subjects. n = number (many) fractions. FU = follow-up time. cats = cataracts. RT = Radiologic Technologists. IC = Interventional Cardiologists.

Constructed by J Hendry from information courtesy of Dr. R.E. Shore, RERF, Hiroshima, Japan.