Recent Perspectives on Biological Effects of Ionizing Radiation

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WHO CARES?

Health Physicists benefit from deeper insights into the biological effects of ionizing radiation (IR) because:

- We serve workers who are routinely and chronically exposed occupationally to low levels of, and in medical settings routinely expose humans to, IR; *it’s why we do what we do*

- As members of the medical community and society, we should be well-informed about the risks as well as the benefits provided by the use of IR

- In a larger sense citizens have a right and obligation to know the relative risks faced by their society (use knowledge to fight fear and ignorance)

- [There are movements underway for changing the regulations that may impact health physics and the delivery of health care]
Is Knowledge of Radiation Bioeffects Needed?

Ratnapalan et al AJR:182, May 2004

Recommend abortion following single CT: **6% of all physicians**

Uncertain: **27%**

The biggest factor reducing physician credibility may be relatively poor knowledge of radiation risks; we cannot assess benefit/risk ratio if the denominator is not well understood [Wagner (2011)]
Two Types of Bioeffects

**Deterministic**
- Severity of effect increases with dose above a *threshold* dose
- Most effects are not endemic
- Clinical symptoms begin at about $100 \text{ rem}$ ($1 \text{ Sv}$)*
- Associated with acute (short term) high dose exposures

* See e.g. NCRP Report 138 (2001), [CDC Cutaneous Radiation Injury](https://www.cdc.gov/radiation/health-effects/index.html) web site (2013)

**Examples:**
- Epilation (hair loss)
- Erythema (skin reddening)
- Hemapoietic, GI, CNS syndrome

**Stochastic**
- *Probability* of effect increases with dose;
- Elevates incidence of effects that are already endemic (hard to detect)
- Incidence begins to increase above endemic levels in populations given acute doses of $5$ to $10 \text{ rem}$ ($0.1 \text{ Sv}$)*

* Radiation Risk in Perspective [hps.org/documents/risk_ps010-2.pdf], 2010

**Examples:**
- Cancer
- Genetic Mutations
- Developmental abnormalities (following exposure in utero)
### Acute Patient Dose Issue: Cutaneous Radiation Injury [Deterministic]

These effects are well established and demonstrated; there is no debate...

<table>
<thead>
<tr>
<th>Skin Dose (Gy)</th>
<th>Prodromal</th>
<th>Latent</th>
<th>Manifest Illness</th>
<th>3rd wave erythema</th>
<th>Recovery</th>
<th>Late Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2 CDC Grade I</td>
<td>1–2 days or not seen</td>
<td>no injury evident for 2–5 weeks</td>
<td>• 2–5 weeks, lasting 20–30 days: redness of skin, slight edema, possible increased pigmentation • 6–7 weeks, dry desquamation</td>
<td>not seen</td>
<td>complete healing expected 28–40 days after dry desquamation (3–6 months)</td>
<td>• possible slight skin atrophy • possible skin cancer decades after</td>
</tr>
<tr>
<td>&gt;15 CDC Grade II</td>
<td>6–24 hours with immediate sensation of heat lasting 1–2 days</td>
<td>no injury evident for 1–3 weeks</td>
<td>• 1–3 weeks; redness of skin, sense of heat, edema, skin may turn brown • 5–6 weeks, edema of subcutaneous tissues and blisters with moist desquamation • possible epithelialization later</td>
<td>• 10–16 weeks, injury of blood vessels, edema, and increasing pain • epilation may subside; new ulcers and necrotic changes possible</td>
<td>healing depends on size of injury and the possibility of more cycles of erythema</td>
<td>• possible skin atrophy or ulcer recurrence • possible telangiectasia (up to 10 years) • possible skin cancer decades after exposure</td>
</tr>
<tr>
<td>TJC Sentinel</td>
<td>6–24 hours with immediate sensation of heat lasting 1–2 days</td>
<td>none or less than 2 weeks</td>
<td>• 1–2 weeks: redness of skin, blisters, sense of heat, slight edema, possible increased pigmentation • followed by erosions and ulceration as well as severe pain</td>
<td>• 10–16 weeks: injury of blood vessels, edema, new ulcers, and increasing pain • possible necrosis</td>
<td>can involve ulcers that are extremely difficult to treat and that can require months to years to heal fully</td>
<td></td>
</tr>
<tr>
<td>&gt;40 CDC Grade III</td>
<td>4–24 hours, with immediate pain or tingling lasting 1–2 days</td>
<td>none or less than 2 weeks</td>
<td>• 1–4 days accompanied by blisters • early ischemia (tissue turns white, then dark blue or black with substantial pain) in most severe cases • tissue becomes necrotic within 2 weeks following exposure, accompanied by substantial pain</td>
<td>does not occur due to necrosis of skin in the affected area</td>
<td>recovery possible following amputation of severely affected areas and possible skin grafts</td>
<td>• continued plastic surgery may be required over several years • possible skin cancer decades after exposure</td>
</tr>
<tr>
<td>&gt;550 CDC Grade IV</td>
<td>occurs minutes to hours, with immediate pain or tingling, accompanied by swelling</td>
<td>none</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patient Concern [Diagnostic X-ray]:  
*Stochastic* except for extended fluoro & CT

- Extended fluoro procedures or repeated CT (and of course Rad Onc therapy) can cause radiation injuries
- Injuries may not appear until long after exposure; need follow up

Patient radiation doses from the vast majority of diagnostic X-ray procedures are well below the threshold for deterministic effects; therefore again the primary concern is **stochastic effects**

For clinical indications of an X-ray radiation injury, see the [CDC Cutaneous Radiation Injury](http://www.cdc.gov) site (2013)
Occupational Concern: Stochastic

Occupational doses are too small to cause deterministic effects

- Central Nervous System Syndrome (~5000 rad)
- Maximum survivable dose (~1000 rad); loss of GI crypt cells
- Erythema [skin reddening], epilation [hair loss] (~300 rad)

Threshold for **Deterministic** effects (~50 – 100 rad)

- Apparent acute threshold for *increased cancer risk* (10 rem)
- Annual **Occupational** limit (5 rem above background)

Annual **Background** – US (~0.2 – 0.6 rem)

Annual **Public** limit (0.1 rem above background)
Our Focus: Stochastic Effects

- Deterministic Effects are well understood, with clear thresholds and unequivocal clinical symptoms
- Except for prolonged Fluoro & CT, diagnostic patient doses will not approach levels (thresholds) required to produce deterministic effects
- Occupational doses are well below deterministic thresholds; the only possible effects are stochastic
- Most people will never experience deterministic effects

Not much else to say about deterministic effects; instead the rest of this presentation will focus on the much more relevant (for occupational, environmental, and most patient doses) topic of stochastic effects
Can’t always get a definitive answer in life; can’t prove a negative

A-bomb survivor and other studies established with certainty that high doses increase incidence of many solid cancer types and leukemia, but in lower ranges (100 – 200 mSv; 10 – 20 rem) risks become fuzzy, then unknown at low doses (10 – 20 mSv; 1 – 2 rem). Epidemiologic data contain intrinsic “noise” (variation by known and unknown factors related to genetics, lifestyle, other environmental exposures, sociodemographics, diagnostic accuracy, etc.) and so are generally too insensitive to provide compelling answers in the low dose range.¹

At doses <100 mSv (10 rem), effects, if any, are so small as to be unobservable and perhaps, therefore, unknowable²

1. Shore (2014)
2. Siegel (2012)
Uncertainty at Low Doses

Hard to see radiation-induced cancer at low doses, if it occurs at all, because:

- Variable background radiation levels make increased cancer risk almost impossible to detect at low exposure levels

- Cancer rates and mortality are relatively large and highly variable in different human populations; hard to see radiation-induced cancer

- No currently known biomarkers for radiation-induced cancer; can’t distinguish radiation-induced from non-rad induced¹

Not always enough information to draw definitive conclusions about whether there is an increased risk for developmental or reproductive abnormalities from fetal radiation exposure; sometimes the correct answer is “I don’t know”²

¹ Siegel (2012)
² Brent (2007)
Cancer relative risk estimates reported in the literature by food

*Figure reproduced from Schoenfeld et al (2013), with permission*
The A-Bomb Survivor Life Span Study (LSS) cohort (began 1956) ultimately expanded to 93,741 survivors (~54,000 within 2.5 km of epicenter + ~40,000 between 2.5 & 4 km, alive at 1950 census), plus 26,580 Hiroshima & Nagasaki residents not present at bombing. Reliable mortality data from Japanese death certificates; non-fatal tumor data less reliable and adjusted for loss of information due to migration away from Hiroshima & Nagasaki etc.

Dose estimates developed from 9 factors, including amounts & types of radiation emitted by nuclear explosion, detonation height, epicenter location, survivor location, amount & type of shielding provided by chemical explosives and intervening materials, etc.; mostly gamma rays.

<table>
<thead>
<tr>
<th>Est. Dose (Gy)</th>
<th>No. Persons</th>
<th>Cancer Deaths</th>
<th>Est. excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.005</td>
<td>37,458</td>
<td>3,833</td>
<td>0</td>
</tr>
<tr>
<td>0.005 – 0.20</td>
<td>37,382</td>
<td>3,945</td>
<td>83</td>
</tr>
<tr>
<td>0.20 – 1.0</td>
<td>9,631</td>
<td>1,201</td>
<td>206</td>
</tr>
<tr>
<td>&gt;1.0</td>
<td>2,101</td>
<td>356</td>
<td>151</td>
</tr>
</tbody>
</table>

Land (2011)
LSS/RERF Epidemiology Data

Estimated excess cancer risk per Gy and 95% CI.  
Adapted from Ozawa et al (2012)
Among the confounders noted: transfer of risk estimates between dissimilar populations, e.g. U.S. stomach cancer rates an order of magnitude lower than in Japan; available data in US radiogenic stomach cancer insufficient to resolve this difference definitively\(^1\). LSS demonstrates that ionizing radiation is a weak carcinogen; of \(\sim94,000\) A-bomb survivors followed 60 years after exposure, only about 1% developed cancer (848 excess) or leukemia (94 excess) attributable to radiation; no increase seen in those exposed to acute doses of \(\leq150\) mSv (15 rem)\(^2\).

1. Land (2011)
2. Siegel (2012)
Epidemiology Example: Breast Cancer

Massachusetts TB patients receiving avg 0.79 Gy (79 rad; ~88 chest X-rays) in 1920s – 1954 showed excess breast cancer, especially in women treated prior to age 30, but no increase in leukemia

Breast cancer data pooled from A-bomb survivors, MA TB patients, and women treated for partial mastitis: age at exposure greatest risk modifier:

- highest excess breast cancer incidence for women exposed at <20, little risk observed in women exposed at >45;
- no increase in lung cancer, leukemia or heart disease observed, illustrating that different tissues respond differently;
- no increase in subsequent breast cancer in women following radiation treatment for breast cancer, especially those treated at age >45 (some risk for those treated prior to menopause); long latency period between treatment and appearance of excess breast cancer

Boice (2010)
Stochastic Effects: What’s Known

Radiation therapy practitioners know and routinely apply well documented facts that dose and dose rate effect patient outcome. By general consensus cancer risk increases after acute doses >100-200 mGy (>10 – 20 rem); there are questions about the dose response at low (~<100 mGy; <10 rem) and very low (<10 mGy; <1 rem) doses. At those doses, cell and tissue response is non-linear, while energy deposition is linear.

Despite 100 years of looking, there’s a lack of evidence of adverse effects at nuclear medicine and diagnostic imaging low doses.

Studies of workers chronically exposed to low levels have shown no adverse biological effects.

1. Siegel (2012)
2. Averbeck (2009)
Epidemiology of Radiocarcinogenesis

Some types of cancer do **not** appear to be linked to radiation exposure:

- chronic lymphocytic leukemia
- pancreatic cancer
- prostate cancer
- cervical cancer
- testicular cancer
- uterine cancer
- non-Hodgkin lymphoma
- Hodgkin lymphoma
- multiple myloma

Human studies show increases only after very high (e.g. radiation therapy) doses for cancer of the:

- small intestine
- rectum
- uterus
- kidney

Boice (2010)
**What is a Model?**

**model n.** 1. A standard or example for imitation or comparison. 2. A representation, generally in miniature, to show the construction or appearance of something. 10. A simplified representation of a system or phenomenon...

*Webster’s Dictionary*

“All models are wrong. Some models are useful”

G. Box (1979)
Modeling Stochastic Effects: How Low Do They Go?

- Well established for $> \sim 100$ mSv (10 rem) acute
- Inconclusive for $< 100$ mSv (10 rem) acute
- Scientific Consensus Bodies seeking to resolve the low dose question:
  - International Commission on Radiation Protection [ICRP]
  - National Council on Radiation Protection [NCRP]
- ICRP & NCRP: uncertainty acknowledged, but the "linear no threshold" [LNT] model most appropriately addresses low dose question
- U.S. Regulations are based on NCRP & ICRP guidance; hence LNT (the assumption that any additional radiation dose adds risk) is the “law of the land”

Various models proposed by the scientific community to characterize risk at low doses
Birth of the Linear No Threshold (LNT) Model

June 1956: a Genetics Panel of the U.S. National Academy of Sciences issued a report recommending a LNT model for assessing risks to the genome from ionizing radiation (BEIR I, 1956), replacing the threshold-based model then widely accepted.

The Genetics Panel failed to provide any scientific support for this recommendation, and refused to do so when later challenged by other leading scientists.

The LNT model was quickly generalized to include cancer risk and later adopted by the E.P.A. for carcinogenic risk assessment.

The requirement to minimize this hypothetical cancer risk led to the ALARA radiation protection policy now included in the regulations.

1. Cuttler (2016)
Organizations Supporting (and opposing) the LNT Model

The ICRP recommends the use of the LNT hypothesis for the development of radiation controls. NCRP position: no alternative is more plausible than LNT, but other models cannot be excluded.

The BEIR [Biological Effects of Ionizing Radiation] VII report (2006) states that a single acute 100 mGy (10 rad) low LET radiation dose might increase lifetime cancer risk in U.S. populations from 42% to 43%, and that the LNT (or linear quadratic for leukemia) model is “not inconsistent” with all observed data.

The French Academy of Science “doubts the validity of using LNT for carcinogenic risk of low doses (<100 mSv; 10 rem) and even more for very low doses (<10 mSv; 1 rem); LNT should not be used for risk assessment.”¹

¹ Siegel (2012)

“A comprehensive review of available biological and biophysical data supports a “linear-no-threshold” (LNT) risk model—that the risk of cancer proceeds in a linear fashion at lower doses without a threshold and that the smallest dose has the potential to cause a small increase in risk to humans.”

Basis of the LNT Model

Stochastic risk estimates for low doses are based on observed effects at high doses and high dose rates, especially A-bomb survivors\(^1\).

Public health data does not show effects at low doses & dose rates (<100 mSv, 10 rem); instead models “guess” at risk from lower doses\(^1\).

Research shows biological mechanisms at low doses and dose rates are different; to account for this, ICRP introduced a simplistic dose & dose rate effectiveness factor (DDREF) of 2 but assumed LNT for protracted or fractionated doses (i.e. divide risk estimate by 2) to arrive at simplistic cancer induction risk factors such as “5% per Sv”, which still likely overestimate low dose effects\(^1,2\).

LNT’s appeal: generates “estimated risk” for any radiation dose, even at levels where no risk is known to exist (i.e. creates the illusion of a quantitative risk assessment and certainty)\(^1\).

1. Siegel (2012)
2. Raabe (2010)
LNT Performance on Predicting Radiocarcinogenesis at Low Doses

At low doses LNT fails as a predictor of excess cancer in populations:

- A-bomb survivor (LSS) data (acute doses) do not in any way predict observed carcinogenesis associated with protracted (chronic) doses.

- LNT fails to predict observed effects or lack thereof for protracted exposure to IR; e.g. no observed excess lung cancer from cumulative dose of 1 Sv (100 rem), where LNT predicts ~1.6 relative risk.

- LNT predicts significant excess cancer after 1986 Chernobyl event, but no apparent effect of this widespread protracted exposure was observed, except for elevated thyroid disease incidence associated with very high acute doses from short-lived I-131 in milk.

- Raabe (2010)
Dr. Toohey on LNT

- It’s not great science; the osteosarcoma incidence in radium dial workers rejects it at 98% confidence level.

- We do not know the risk (if any) at doses below 100 mSv when received at low dose rates

- It is one way of doing risk-benefit analysis (“the standard canard of corporate shills”)

- However, most importantly, it is public policy, and it will not be changed by scientific arguments, because public policy is not based on science

Toohey RE (2016)
Proper Use of the LNT Model

LNT cannot be used for *estimating risk* and should only be used for *risk management* if conservatism is justified; the idea that no level of radiation exposure is “safe” generates significant public fear that’s nearly impossible to manage in case of a major radiological event\(^1\).

LNT should not be used to dispense radiation-related medical advice to concerned patients or members of the public, or as a predictive model of radiation injury in populations or individuals exposed to low doses\(^1\).

Applying effective doses to populations of patients and deriving some risk factor based on a healthy population biases communication and sends misdirected benefit/risk message, which can have detrimental consequences if they cause patients to refuse necessary medical tests\(^2\).

1. Siegel (2012):
2. Wagner (2011)
Animal studies show modifying agents (e.g. diet, hormones, promoting or suppressing chemicals) can have as large an effect as radiation characteristics on carcinogenesis.

Cancer promoters:
- croton oil
- hormones (e.g. estrogen & thyroid)
- saline instilled in the lungs with Po-210
- repeated bleedings of rats subjected to X-rays developed leukemia
- microbial environment (less cancer in germ-free mice)
- dietary restrictions
- diet
- exposure to turpentine (considered classic cancer promoting agent)

Cancer suppressors:
- vitamins & related compounds
- protease inhibitors
- hormones
- arachidonic acid metabolism modifiers
- protein kinase C inhibitors
- certain drugs (e.g. Valium, aspirin)
- numerous agents that interact with free radicals (e.g. anti-oxidants)

Kennedy (2009)
Carcinogenesis: Other Factors

Recently popular combination cancer prevention studies suggest that no single agent can completely prevent cancer, but seem to suggest that combining anti-oxidant activity and protease inhibitors can prevent radiocarcinogenesis.

Data show a strong correlation between ingesting soybean products & fresh vegetables and a reduced incidence of breast, colon & prostate cancer:

- these are major cancers in the western world but significantly less prevalent in the Pacific basin
- the offspring of Asians migrating to the US develop these cancers at about the same rate as the US population, suggesting that diet rather than hereditary factors are most important

Kennedy (2009)
Actual radiation effects directly observed in research animals show:

1) Cancer risk for protracted or fractionated ionizing radiation exposure is a non-linear function of lifetime average dose rate to the affected tissues and exhibits a virtual threshold at low average dose rates.

2) Cumulative dose is neither an accurate or appropriate measure of cancer induction risk for protracted or fractionated exposure except for describing the virtual threshold for various exposures.

3) Cancer promotion as seen in LSS is for brief high dose and dose rate exposures; cannot be used to estimate cancer induction risk from protracted or fractionated ionizing radiation exposures over long periods and low dose rates.

- Raabe (2010)
Environmental (Background) Radiation

Natural background radiation levels vary widely between different geographic areas; **how does background radiation impact cancer?**

Possible impact tested globally in high background radiation areas, e.g. in Ramsar, Iran, ~130 mSv/y (13 rem/y), no excess cancer observed; indeed there appears to be an inverse relationship\(^1\).

NRC: Although radiation may cause cancers at high doses and dose rates, currently there are no data to establish unequivocally the occurrence of cancer following exposure to low doses and dose rates – below about 1,000 mrem (10 mSv). Those living in areas having high levels of background radiation – above 1,000 mrem (10 mSv) per year – such as Denver have shown no adverse biological effects\(^2\).

1. Siegel (2012)
Insights from Microdosimetry

Given inherent uncertainty associated with epidemiological studies, researchers turned to microdosimetry to see low level bioeffects.

Cell level microdosimetry molecular biology studies indicate that while energy deposition and resulting prompt damage appear linearly proportional to dose, the biological response at the gene, cell & tissue levels are not linear; cells respond to low dose, low dose rate IR either through repair or cell suicide (apoptosis)\(^1\)

IR is not a very effective carcinogen because cell-killing is more probable than carcinogenic effects, which is quite different from some chemical carcinogens; implies a new model for low dose response of cells: not all are damaged, and those that are heavily damaged can be eliminated without effecting whole cell populations or tissue integrity\(^2\)

\(^1\) Ulsh (2010)
\(^2\) Averbeck (2009)
What Microdosimetry says about LNT

LNT is based on a “target” cellular model that implies biological effects are directly proportional to energy deposition; microdosimetry studies don’t support LNT at low DDR. The DDREF introduced to improve fit to data demonstrates ICRP acknowledges LNT is not strictly correct; if high & low doses produce quantitatively distinct responses in cancer endpoints, it becomes implausible to assume cancer dose response remains linear from background to acute lethality\(^1\)

Formerly, when we did not know much about cellular mechanisms, LNT was a practical approach to deal with uncertainties; now we have cell-level data reducing uncertainty, and while there’s more that’s still not known, we have seen that at low doses, dose response is non-linear\(^2\)

1 Ulsh (2010)
2 Averbeck (2009)
Exposure In Utero: What’s Known

Neurobehavioral/Teratogenic Effects and Malformations:

The minimum threshold for neurobehavioral effects is about ~0.2 Gy (20 rad) at the most sensitive stage (midgestation, 8–15 weeks); higher doses can cause microcephaly & mental retardation; from week 15 on much higher doses are needed to produce mental retardation.

Teratogenic effects are primarily threshold, with no observable effects below about 0.1 Gy (10 rad).

During organogenesis (8-15 weeks) ~1 Gy (100 rad) can produce a high incidence of malformations.

Animal studies indicate that (for low LET radiation like X-rays) fractionated dose is much less efficient at producing in utero effects than single acute exposure providing the same total dose.

Brent (2007)
Cancer and Leukemia:

Historically some epidemiological studies suggested increased leukemia in persons exposed to low doses (0.1 – 0.02 Gy) in utero, but those studies had recognized flaws; none of the 86 A-bomb survivors exposed in utero developed leukemia, despite significantly higher doses than the patient cohort in the studies.¹ No cohort study has shown significant increase in leukemia or childhood cancers following in utero exposures, including A-bomb survivors exposed in utero (except in “self-reported” studies that are suspect).²

2. Boice (2010)
Radiation Exposure In Utero

Ramifications for Medical Exposure

Numerous studies indicate no radiation effects on the fetus from irradiation of the parent that does not expose the fetus, except for doses high enough to produce radiation sickness, where general decline in health impacts pregnancy.

The risks of the vast majority of diagnostic radiological procedures do not represent significant reproductive or developmental risks and do not warrant the interruption of wanted pregnancies. Therapeutic procedures do present potential developmental risks; however each case has to be evaluated because frequently the risks are not increased.

Evaluations of allegations of radiation-induced malformations necessitate detailed analysis and cannot be performed superficially.

Brent (2007)
What about Cataracts?

Three main locations for cataract (lens opacity) formation:

- **Cortical** [peripheral (outside) edge]; commonly found in diabetic patients, also associated with UV.

- **Nuclear** [central (nuclear) portion]: most common type of age-related cataract, caused by yellowing and hardening of the lens.

- **Posterior Subcapsular (PSC)** [back surface of the lens]: associated generally (but not exclusively) with ionizing radiation.

Confounding Risk Factors: age, diabetes mellitus, corticosteroid use, smoking, UV (including sun) exposure.
Radiation Induced Cataracts: An Emerging Issue

- Well-established correlation (to PSC lens changes) seen in staff involved in interventional procedures [ICRP 85; Chodick et al (RT), 1998; Vano et al (interventional cardiologists), 2010]; current debate is over dose required (threshold), not the effect.

- Historically assumed threshold of ~5 Sv (500 rem) for fractionated, and ~2 Sv (200 rem) for acute, exposure [ICRP 60 (1990), ICRP 85 (2000) & ICRP 103 (2007)];

- Current US regulatory lens of the eye occupational limit is 150 mSv (15 rem) per year based in old ICRP guidance, i.e. 4.5 Sv (450 rem) over a 30 year career.

- Recent studies (e.g. Chernobyl, aviators/astronauts, interventional radiologists) prompted ICRP to propose a 0.5 Sv (50 rem) cumulative threshold [ICRP 118 (2012)], implying 0.5 Sv (50 rem) produces 1% increase in incidence of disease (also evidence of increased cardiovascular disease); there is some dissent…

- ICRP (2011) now recommends 20 mSv/year (2 rem/y) annual limit averaged over 5 years, with no single year exceeding 50 mSv (5 rem); also suggesting cataract formation may be stochastic with no threshold rather than deterministic [LNT!!!]
Radiogenic Cataract Epidemiology

Recent (2007, 2012) A-bomb survivor studies indicate 32% excess of cataracts requiring surgical removal per Gy (100 rad), with an apparent threshold at about 0.5 Gy (50 rad); also recent studies of interventional cardiologists and associated nurses/technicians receiving largest cumulative doses suggest an occupational radiation-related cataract risk (these epidemiological studies were difficult to conduct, have potential sample selection biases, small sample sizes, and very uncertain dosimetry).¹

35,705 US radiologic technologists aged 24-44 tracked nearly 20 years (1983 – 2004) using two follow up questionnaires; self-reported data indicated those in the highest dose category (mean 60 mGy; 6 rad) had ~18% higher incidence of cataracts than those in lowest dose category (mean 5 mGy; 0.5 rad) after correcting for self-reported known risk factors (e.g. cigarette smoking, diabetes, etc.).²

1. Shore (2014)
2. Chodick (2008)
What’s the “Background” Incidence of Cataracts?

2010 U.S. Prevalence Rates for Cataract by Age and Race

NIH/National Eye Institute – Cataracts https://nei.nih.gov/eyedata/cataract
ICRP/IAEA Case for Assuming Lower Threshold for Cataracts

In a February 4, 2016 webinar, ICRP representatives cited epidemiological evidence and presented the following “hard data”:

2010 IAEA 8 country study: Detailed ophthalmological exam of 22 controls and 44 interventional cardiologists with estimated total cumulative doses of 0.5 to >3 Sv (50 – 300 rem) showed higher incidence (51% vs 9% for controls) of posterior lens changes “characteristic of ionizing radiation exposure” in the exposed group

- Stated strength: based on actual clinical observation of lens
- Acknowledged weaknesses: small sample size; “very rough” estimation of doses (subject’s doses were based on recollection of case load, recalled compliance rates with using shielding eyewear and overhead shields, etc.; not actual measured dosimetry)

ICRP Webinar: “Is cataract a real risk to those working in interventional suites”. February 4, 2016
IAEA Cataract Study: https://rpop.iaea.org/rpop/rpop/content/news/relid-cataract-study.htm
ICRP Conclusions on Cataracts

Changes during the past two decades in the ICRP’s understanding of radiation-induced cataracts are based on:

1. Published reports of excess cataracts in personnel working in interventional radiology suites

2. IAEA “controlled study” documented cataracts/lens opacities in staff working in interventional suites

Therefore the ICRP has reduced their previously assumed threshold dose for inducing cataracts \textit{not a concern for aphakic people}

Although cataracts are age-dependent and largely treatable, there are risks of cataract surgery, and radiation-induced cataracts should be 100% preventable

ICRP Conclusion: \textit{More research is needed}...

ICRP Webinar: “Is cataract a real risk to those working in interventional suites”. February 4, 2016
Cataract visual exams, categorization, and severity scoring have advanced in recent decades, as have radiation dosimetry accuracy and ophthalmological instrumentation. However most epidemiological evidence for radiation-induced cataracts was not obtained with these new quantitative tools. Understanding of lens biology has expanded but relies heavily on rodent models; not clearly extrapolated to humans. Due to these limitations, it is not yet possible to quantitatively estimate a specific threshold for detectable opacity of vision-impairing cataracts from either acute or chronic exposure. NCRP plans to determine by **mid-2016** whether there’s sufficient evidence to support changing the current 150 mSv/y LDE limit. 

Dauer et al (2016)
For much more NCRP on Cataracts

See:

NCRP/NY Chapter HPS “Lens of eye guidance – next steps; a stakeholder workshop on implementation and research.”

August 29, 2016 – Memorial Sloan Kettering, New York


- Including:
  - Summary of New NCRP Guidance on Lens of Eye
  - Lens of Eye Dosimetry Standardization
  - IRPA Guidelines
  - European Status and Radiobiology Mechanistic Review
  - etc.
Genetic Effects

Studies of 80,000 offspring of A-bomb survivors evaluated every conceivable measure of genetic disease or hereditary effect, including malformations, chromosomal abnormalities or translocations, stillbirths, neonatal deaths, cancer, and others - no evidence for any statistically significant effect was observed; hence doubling dose is estimated to be ~2 Gy (200 rad).

Epidemiology has not revealed heritable effects in humans, so risk estimates for radiation protection purposes are based on mouse data.

Boice (2010)
The US regulatory system is based on ensuring *no deterministic effects* occur in occupationally exposed populations, and *stochastic risks* are kept to levels comparable to the accidental death risk in “safe” industries; regulatory dose limits were derived based on:

- 50 mSv/y (5 rem/y) tends toward average doses <10 mSv (1 rem/y)
- <10 mSv/y (1 rem/y) keeps LNT estimated risk <0.01%, comparable to accidental death risk in “safest” industries, based on estimated $10^{-2}$/Sv assumed cancer risk; revised ICRP cancer risk of $5 \times 10^{-2}$/Sv led to ICRP’s 20 mSv/y (2 rem/y) recommendation to get same LNT-based risk

- Public limit was 10% of occupational limit (5mSv; 0.5 rem), but then was lowered to 2% (1 mSv; 0.1 rem)

The NRC accepts LNT as a conservative model for acceptable risk
Regulatory Perspective

The NRC is considering changing the 50 mSv/y (5 rem/y) “whole body” limit to 20 mSv/y (2 rem/y) based on ICRP recommendations; factors influencing the downward trend in dose limits include:

1) Geneticists *speculate* [with no data] that radiation would result in significant rises in observed genetic effects in exposed populations (seen in animal studies but never humans)

2) Changes in observed number of cancers in human populations exposed to high radiation doses (mainly Japanese A-bomb survivors)

Regulatory dose limits currently have inconsistencies: 1 mSv/y (0.1 rem/y) for the public, 5 mSv/term (0.5 rem/term) for declared pregnant workers, 50 mSv/y (5 rem/y) for undeclared pregnant workers

Radiation-related regulatory compliance costs ~$9 billion annually, for minimal risk reduction

Siegel (2012)
The NRC is considering changing the 150 mSv/y (15 rem/y) lens of the eye limit to 50 mSv/y (5 rem/y) based on ICRP recommendations:

“The NRC believes that it is appropriate, and scientifically justified, to explore in greater detail the impacts of a reduction in the dose limit for the lens of the eye to 50 mSv (5 rem). The NRC also believes that further discussion on how the prevention of cataracts (which can be corrected by a well-established surgical procedure) compares to efforts to reduce the probability of cancer (a disease posing a far greater health risk) is necessary. The approaches under consideration include

- aligning closer with the ICRP recommendations,
- adopting the ICRP recommendations, or
- retaining the current dose limit.“

NRC (2012)
Conclusions

Biological effects caused by high radiation doses, including increased cancer, are well documented and justifiably feared, but it takes large doses to large populations to detect an increase in cancer frequency.¹

Based on the historical record (A-bomb, Three Mile Island, Chernobyl), and natural background, radiation is a weak carcinogen at doses higher than most people will ever encounter in their lifetimes; radiation effects have only been observed due to high doses delivered acutely, and never due to chronic exposure to low doses.¹

Environmental factors, including diet, are known to influence carcinogenesis in animals and humans. Radiocarcinogenesis enhancing or suppressing agents can have as large an effect as radiation characteristics. Dietary factors may be the most important determinants of radiocarcinogenic risk.²

1. Siegel (2012)
2. Kennedy (2009)
More Conclusions

Fear of assumed risk at low doses renders ALARA ambiguous because of the imperative to keep doses below “safe” limits.¹

Managing intentional application of radiation to humans for medical purposes is not a matter of radiation protection, nor should ALARA be applied to medical radiation use; it’s about maximizing benefit/risk ratio.²

LNT is used for risk assessment and risk management, but only risk management is valid in the low dose region; this dichotomy is not contradictory but sends conflicting messages about risk. LNT should not be used for predicting radiation effects in exposed populations & individuals.¹

Overestimating radiation risks may be more detrimental than understanding them; may result in unnecessary traumatic evacuations, suicides, and unneeded abortions, and divert funds from real societal benefit.¹

1. Siegel (2012)  
2. Wagner (2011)
1. Based on:
   - Epidemiology (A-bomb survivors, Chernobyl, Fukushima, medically exposed cohorts, various background radiation levels)
   - Animal Studies
   - Microdosimetry Studies (cell & molecular level)

Ionizing radiation is a weak carcinogen that increases the incidence of cancer in populations exposed acutely to >10 rem, but has no apparent effect at lower doses or dose rates.

2. Ionizing radiation appears to increase the incidence of subcapsular posterior cataracts in populations exposed to >200 rem acute or >500 rem protracted/fractionated; however some new evidence hints that the threshold for cataracts may be lower (e.g. IAEA theorizes that a 50 rem dose increases incidence by 1%)
More Summary

3. LNT does not accurately predict observed carcinogenesis rates in populations exposed acutely to less than 10 rem

4. LNT should never be used for estimating the risk to populations or individuals exposed to < 10 rem acutely

5. Other risk factors (e.g. diet, exposure to other agents) seem to have a much larger effect on carcinogenesis than ionizing radiation at dose levels experienced by the vast majority of people

6. We rightly worry about deterministic effects and must remain diligent to prevent them when feasible, and to support providing treatment when appropriate (i.e. a skin burn due to a life-saving interventional procedure does NOT represent an overexposure)

7. Seek credible information to inform optimal decisions and counter baseless fear
Residents promptly followed evacuation orders, first within 2 km, then 3 km, finally 20-30 km, often with only the clothing they wore; pets & livestock were abandoned without food or water

Intensive care patients were moved, or left in hospitals, without adequate care; ≥60 patients died in during this rapid protective evacuation

Inhabitants were not allowed to return home until estimated annual doses dropped below 20 mSv (2 rem), and later 5 mSv (0.5 rem), causing tremendous stress and anxiety; led to some suicides

Avoided doses in the most effected areas ranged from 10 to 50 mSv (1 to 5 rem) during the first four months; no evidence of any avoided cancers

LNT hypothesis may be practical for setting occupational dose limits, but should be disregarded in emergency situations; here it caused fatalities

Miska (2014)
Our Choice:

Understand the Risks or Fear All Radiation

“The Three Mile Island, Chernobyl, and Fukushima Diiachi accidents produced anxiety and uncertainty about short and long-term consequences; these uncertainties were exacerbated by:

- contradictory information from scientists and government and industry authorities;
- loss of faith in experts, related to protective actions taken to minimize potential radiation exposure;
- information of uncertain validity on both formal and informal media; and
- rapid spread of rumors about birth defects, heart disease, and, especially, cancer.”

- IAEA (2015)
References


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International Commission on Radiological Protection. Statement on tissue reactions. ICRP ref 4825-3093-1464, April 21, 2011


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