Monday, August 29, 2016

Lens of Eye Guidance-Next Steps
A Stakeholder Workshop on Implementation and Research

Memorial Sloan Kettering, New York

For More Information, contact Bae P. Chu, chub@mskcc.org
# Lens of Eye Guidance-Next Steps

## A Stakeholder Workshop on Implementation and Research

**Memorial Sloan Kettering, New York**

430 E 67th St, 7:30AM – 4:00PM

<table>
<thead>
<tr>
<th>Time</th>
<th>Agenda</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:30</td>
<td>Breakfast &amp; Check In</td>
</tr>
</tbody>
</table>
| 8:00  | Welcome from Chair

  John Boice

| 8:15  | Summary of New NCRP Guidance on Lens of Eye

  Ellie Blakely

| 9:00  | Lens of Eye Dosimetry Standardization

  Chris Passmore

| 9:45  | Stakeholder Q&A Session I

  Mike Grissom/Moderator

| 10:15 | Coffee Break/Discussions                                              |
| 10:30 | Nuclear Power Plant – Assessment and Protection

  Dennis Quinn

| 11:00 | Medical Facilities – Assessment and Protection

  Lawrence Dauer

| 11:30 | International Radiation Protection Association Guidelines

  Stephen Balter

| 12:00 | Stakeholder Q&A Session II

  Mike Grissom/Moderator

| 12:30 | Box Lunch / Ongoing Discussions                                      |
| 1:00  | European Status and Radiobiology Mechanistic Review

  Elizabeth Ainsbury

| 2:15  | Lens of Eye Research and Study Needs

  Gayle Woloschak

| 3:00  | Stakeholder Q&A Session III

  Mike Grissom/Moderator

| 3:30  | Workshop Summary and Actions

  John Boice

| 4:00  | Workshop Concludes                                                   |
Lens of Eye Guidance-Next Steps
A Stakeholder Workshop on Implementation and Research
Memorial Sloan Kettering, New York
430 E 67th St, 7:30AM – 4:00PM

Welcome

John D. Boice, Jr.
National Council on Radiation Protection and Measurements
Vanderbilt University School of Medicine

John.Boice@ncrponline.org
Lens of Eye Guidance – Next Steps
Workshop on Guidance and Implementation

- Agenda
- Welcome
- Goals

Agenda - Speakers Today
New NCRP Guidance – Ellie Blakely
Lens of Eye Dosimetry – Chris Passmore
Nuclear Power Plant – Dennis Quinn
Medical Facilities – Larry Dauer
IRPA Guidelines – Steve Balter
Europe, Radiobiology, Mechanisms – Liz Ainsbury
Research & Study Needs – Gayle Woloschak
Q&A Moderator – Mike Grissom
NCRP – A Council of 100 Radiation Professionals

1929: U.S. Advisory Committee on X-Ray and Radium Protection

1946: U.S. National Committee on Radiation Protection

1964: National Council on Radiation Protection and Measurements chartered by Congress (Public Law 88-376)
Where Are the Radiation Professionals (WARP)?

Synopsis of NCRP Statement No. 12
January 23, 2015

Background: Since the discovery of x-rays and radioactivity in the late 1890s, sources of ionizing radiation have been employed in medicine, academia, industry, power generation, and national defense. To provide the safe and beneficial use of these sources of radiation, the United States developed a code of professionals with the requisite education and experience. Unfortunately, their numbers have diminished alarmingly, as assessed by the National Research Council and the Government Accountability Office.

Methods: To study the decline in radiation professionals and post-Council on Radiation Protection and Measurements (NCRP) special meeting in Arlington, Virginia to evaluate whether a sufficient number of participants could support the various radiation disciplines essential to this workshop included participants from government, industry, and academia.

Mortality among military participants at the 1957 PLUMBBOB nuclear weapons test series and on leukemia among participants at the SMOKY test

J. Radiol. Prot. 00 (2016) 1–16

Glyn G Caldwell¹, Matthew M Zack², Michael T Mumma³, Henry Falk⁴, Clark W Heath⁵, John E Till⁶, Heidi Chen⁷, and John D Boice⁷,⁸
Relevant NCRP Documents

- NCRP-91: Lens opacification considered nonstochastic (1987)
- NCRP-115: Cataract as late somatic effect (1993)
- NCRP-116: Lens of eye limit for deterministic effects (1993)
- NCRP-132: Limit scatter dose to lens to ~1-3 Gy (2000)
- NCRP-168: Emphasizes ALARA principle for eye (2011)
SC 1-23: Guidance on Radiation Dose Limits for the Lens of the Eye

Front row, left to right, Cindy Flannery (U.S. Nuclear Regulatory Commission), Eleanor Blakely (Lawrence Berkeley National Laboratory), and Gayle Woloschak (Northwestern University); back row, left to right, David Hoel (Medical University of South Carolina), Mike Grissom (NCRP consultant), Don Mayer (Entergy), Lawrence Dauer (Memorial Sloan Kettering Cancer Center), Eliseo Vaño (Complutense University, Madrid), and John D. Boice, Jr. (NCRP); side photos, top to bottom, Elizabeth Ainsbury (Public Health England), Joseph Dynlacht (Indiana University School of Medicine), Barbara Klein (University of Wisconsin-Madison), Raymond Thornton (Memorial Sloan Kettering Cancer Center), and Phung Tran (Electric Power Research Institute)
ICRP recommends 20 mSv/y for occupational limit (from 150 mSv) for lens of the eye – 2012 ICRP 118

NRC is/was reviewing current guidance

NCRP recommends 50 mGy/y for occupational limit (from 150 mSv) for lens of the eye

Radiologists (Interventional), Cardiologists, Industrial Radiographers can approach 20 mSv/y

GOALS – to address

What are the practical issues of implementation?
Does cost balance protection?
What are the research needs?
Should NCRP consider future activities?
Thanks!

Main Event

- New NCRP Guidance – Ellie Blakely
- Lens of Eye Dosimetry – Chris Passmore
- Nuclear Power Plant – Dennis Quinn
- Medical Facilities – Larry Dauer
- IRPA Guidelines – Steve Balter
- Europe, Radiobiology, Mechanisms – Liz Ainsbury
- Research & Study Needs – Gayle Woloschak
- Q&A Moderator – Mike Grissom
Summary of New NCRP Guidance on Lens of Eye

Eleanor A. Blakely, Ph.D.
Lawrence Berkeley National Laboratory
Noncancer Chronic and Degenerative Tissue Risks from Radiation

- Cataract
- Cardiac and vascular damage
- Gastrointestinal effects
- Neurodegeneration
- Fibrosis
- Immunological Effects
- Endocrine Effects
- Hereditary Effects
Radiation-induced cataract

- The human crystalline lens is known to be a radiosensitive tissue that responds with opacification in a delayed time course depending on the radiation type and exposure level.
- Opacification can be due to mal-folding of the crystalline proteins or due to misregulation of lens cell morphology.
- Cataracts are degenerative lesions that can progressively increase, and can be defined in different ways, such as minor lesions not affecting sight, or as major lesions affecting vision.
From the Executive Summary of NCRP Commentary #26

• “The apparent simplicity of the association between ionizing radiation exposures and the formation of lenticular opacities belies the complex underlying biological factors and mechanisms, including: genetic susceptibility; aging; molecular, cellular, and tissue responses dependent on various radiation exposure parameters.”
Cellular Organization of the Human Lens
Radiation-Induced Pre-Cataractous Cellular Changes in Human Lens

- Mitotic arrest of the germinative epithelial cells, followed by nuclear fragmentation & extrusion, and broadening of the nuclear bow with the appearance of abnormal mitoses
- Anterior cortical clefts appear & granular dots follow the line of fiber cells
- Abnormal fiber cell migration toward posterior pole of the lens
- Fiber cell swelling and interfibrillar clefts
- Appearance of multiple posterior subcapsular opacities due to the posterior displacement of abnormal epithelial cells
- PSC progresses in area as a granular white opacity
Age-Related Cataracts

- **Nuclear Cataract**
  - Causation linked to Smoking

- **Cortical Cataract**
  - Causation linked to diabetes & excess UV-B

- **Posterior Subcapsular**
  - Causation linked to steroids, diabetes, and IR

- **Supranuclear**
  - Causation linked to AD, Down’s Syndrome
Cataract Types

Normal
Cortical
Nuclear
PSC
Mixed

Beebe
Why do opacifications form in different anatomical locations in the lens?

- Antioxidants are unevenly distributed
- Water diffusion system redistributes small molecules, etc.
- Regions of the lens have diverse signaling receptors
Regional Distribution of Glutathione in Different Forms of Human Cataract

- Content of glutathione is high in the anterior lens cortex & epithelium, and in the posterior lens cortex & does not decrease with age

- Glutathione content is substantially lower in the lens nucleus and in supranuclear cataract

- The subcapsular cataract shows a rapid and pronounced progressive decrease in glutathione content

Pau et al., 1990
Radiation Cataract in Animal Models

- Cataract appearance after radiation exposure is dependent on:
  - Radiation type
  - Radiation dose
  - Radiation fractionation
  - Radiation dose-rate
  - Animal species and genetic background
  - Age and gender of animal at exposure
  - Life-span of the animal
  - Diet and presence of certain drugs
Problems with Radiation Cataract Studies in Animal Models

- Numerous cataract scoring systems have been used that cannot be easily normalized.

- Difficult to extrapolate time-course of radiation-induced human cataract from animal models with diverse life spans and genetic backgrounds.
Conclusions from Particle Radiation Studies in Rodents

- Low particle fluences of HZE can cause cataract in WT strains with a high RBE (Worgul, Brenner)
- Particle dose-fractionation can enhance cataract induction (Worgul, Brenner)
- Radiation-sensitive mice (with DNA repair deficiencies) get HZE-induced cataract at lower doses and with shorter latency (Worgul, Hall, Kleiman).
- Particle-induced cataracts are gender-, hormone- and age-dependent (Dynlacht, Henderson)
- Dietary supplements reduce cataractopotential of proton- and HZE-particle radiations (Davis, Wan, Ware, Kennedy)
Radiation Cataract in Humans

• Radiation accident victims
• Patients treated with radiation for disease or medical conditions
•Occupationally-exposed radiation workers
• Atomic Bomb Survivors
Severe atomic bomb-induced cataract

- Image from woman who was 21 yrs old at time of the blast, exposed on the street 805 meters from the hypocenter with acute symptoms.

Photo courtesy of Dr. Tsugihiko Tokunaga
Individuals at risk for late effects of heavy-ion exposure

- Particle radiotherapy patients
  - Partial body high doses $> 60$ GyE exposures targeted to tumor sites but with lower doses to adjacent normal tissues usually in a 5-day per week regime over the course of several weeks

- Space travelers
  - Whole body exposures to mixed radiation types and ionization qualities totaling $<< 1$ Gy protracted over several years
Radiation Cataract in Humans Treated with RT for Cancer

- Opacification of transparent lens has been attributed to damage of the germinative epithelium resulting in a defective differentiation of lens fiber cells.
  - Clinical cataract incidence has been correlated with percent lens in the radiation field

- Review of RT case histories with lens exposure by Merriam & Focht in 60’s indicated no opacities were observed with single acute doses of less than about 2 Gy, with the lens tolerating a higher dose with increased fractionation and overall treatment time.

- There is a dose-dependent latency in the appearance of the opacity after lens exposure, with higher doses showing cataract sooner.
Dose for Cataract/Non-Cataract Cases Plotted vs. Overall Treatment Time

Merriam and Focht, 1962
PRECISION, HIGH DOSE RADIOTHERAPY: HELIUM ION TREATMENT OF UVEAL MELANOMA

WILLIAM M. SAUNDERS, PH.D., M.D.,¹,³ DEVRON H. CHAR, M.D.,² JEANNE M. QUIVEY, M.D.,¹ JOSEPH R. CASTRO, M.D.,¹,³ GEORGE T. Y. CHEN, PH.D.,³ J. MICHAEL COLLIER, PH.D.,³ AUDE CARTIGNY,³ ELEANOR A. BLAKELY, PH.D.,³ JOHN T. LYMAN, PH.D.,³ SANDRA R. ZINK, PH.D.,³ AND CORNELIUS A. TOBIAS, PH.D.³

Fig. 3. Output from Massachusetts General Hospital treatment planning program.⁷

Fig. 6: Kaplan-Meier survival curves of cataract as a function of time after therapy, with the patient population anterior segment radiation exposure. (From Meecham et al., 1993).
Radiation can cause cataract.

There is a dose-dependent latency after radiation exposure before cataract appears.

At low doses the latency is longer.

It has been assumed that not much happens during this latency period.

We are studying molecular antecedents to frank particle-induced cataract during the latency period to identify molecular markers early enough to allow biological countermeasures to be devised.
Crystallin protein super family. Post-translational modifications and the effects of development and aging.

C57BL/6J mouse
Whole lens proteome
At different ages

Hoehenwarter et al. 2006
HYPOTHESES
for mechanism of radiation cataractogenesis

• Increased genotoxic load of damage leads to cataract through a number of intermediate steps leading to altered gene expression

• Gene expression is altered without genomic changes at the level of signaling

• The effect is on protein expression directly

• There is the possibility that these three hypotheses are not mutually exclusive, and that some combination is involved
Normal Differentiation of Lens epithelial cells

Lens epithelium → Migration towards lens bow → Elongation & enucleation → Lens fiber cells

Molecular Hallmarks

- Differentiation genes
- Apoptosis sensitivity
- Cyclin-dependent kinase inhibitors CDKIs

Cyclin dependent kinases
E2F1/Rb
Underlying Mechanism of Radiation-induced Cataractogenesis

Migration towards lens bow

Elongation & enucleation

Cataractogenesis

Differentiation genes

Apoptosis sensitivity

Cyclin-dependent kinase inhibitor CDKI (p21)

Cyclin dependent kinases

E2F1/Rb
Evidence for radiation-induced premature and defective differentiation

• Morphological
  – Premature fiber cell elongation & alignment
  – Abnormal fiber cell alignment
  – Lack of complete enucleation

• Functional
  – Premature appearance of fiber cell markers including,
    • Cell adhesion molecules ($\beta$1-integrin, $\alpha$5 integrin, $\alpha$6B to $\alpha$6A isoform switching)
Radiation Cataractogenesis: A review of recent studies


Conclusions

• Etiology of cataracts is not fully known, but is likely multifactorial.

• Much of the published evidence for radiation cataract at low dose is contradictory but pointing to little or no dose threshold.

• Not clear whether a mutational mechanism or one based on lens cell function, differentiation, cell killing and/or death is operating.

Ainsbury et al., 2009
Cataract from a Chernobyl Clean-up Worker

Conclusions from Cataract Studies of Exposed Individuals from Chernobyl Accident

• Linear-quadratic dose-response models yielded mostly linear associations with weak evidence for upward curvature.

• The data do not support the ICRP 60 risk guideline assumptions of a 5-Gy threshold for “detectable opacities” from protracted, primarily low-LET, radiation exposures, but rather point to a dose-effect threshold of under 1 Gy.

• Thus, given that cataract is the dose-limiting ocular pathology in current eye risk guidelines, revision of the allowable exposure of the human visual system to ionizing radiation should be considered.

Space Radiation and Cataracts in Astronauts

F.A. Cucinotta, a F.K. Manuel, b J. Jones, a G. Iszard, b J. Murrey, c B. Djojonegro c
and M. Wear c

aNASA Johnson Space Center, bKelsey-Seybold Clinic, and cWyle Laboratories,
Houston, TX 77058
Probability of Survival Without Cataracts as a Function of Age

Low-dose group: Avg 3.6 mSv
High-dose groups: Avg. 45 mSv

Cucinotta et al., 2001
### Relative Hazard Ratios at Age 60 Comparing the High-Dose Group to the Low-Dose Group

<table>
<thead>
<tr>
<th>Cataract type</th>
<th>Lens dose from all radiation sources</th>
<th>Lens dose from space radiation only</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>1.51 (0.64, 3.59)</td>
<td>2.35 (1.01, 5.51)</td>
</tr>
<tr>
<td>Non-trace</td>
<td>2.47 (0.76, 8.01)</td>
<td>8.04 (2.51, 25.7)</td>
</tr>
<tr>
<td>Cortical or dot</td>
<td>1.64 (0.51, 5.27)</td>
<td>1.44 (0.46, 4.65)</td>
</tr>
<tr>
<td>Nuclear</td>
<td>0.83 (0.18, 3.81)</td>
<td>3.47 (0.79, 15.3)</td>
</tr>
<tr>
<td>PSC</td>
<td>1.1 (0.67, 18.1)</td>
<td>5.76 (0.97, 34.2)</td>
</tr>
<tr>
<td>PSC, Nuc or Mixed</td>
<td>1.33 (0.37, 4.83)</td>
<td>3.73 (1.05, 13.3)</td>
</tr>
</tbody>
</table>

Cucinotta et al., 2001

Chylack LT, Peterson LE, Feiveson AH, Wear ML, Manuel FK, Tung WH, Hardy DS, Marak LJ, and Cucinotta FA

Radiation Research 172, 10-20 (2009)
**Conclusions (Chylack et al., 2009)**

-Cross-sectional data for astronauts & matched ground control subjects were analyzed by fitting customized non-normal regression models to examine the effect of space radiation on nuclear, cortical and PSC opacities.

-GCR may be linked to increased PSC area and the number of PSC centers.

-Within the astronaut group, PSC size was greater in subjects with higher space radiation dose.
Conclusions (Chylack et al., 2009)

-No association was found between space radiation and nuclear cataracts.

-Cross-sectional analysis revealed a small deleterious effect of space radiation for cortical cataracts and possibly for PSC cataracts.

-These results suggest increased cataract risks at smaller radiation doses than have been reported previously.
NCRP and ICRP

Eye Dose Limit
150 mSv (yr\(^{-1}\))
Has been a long-standing Recommendation for
Occupational dose limit
ICRP Statement on Tissue Reactions
April 21, 2011

• Recent epidemiological evidence suggests that some tissue reaction effects with late manifestation may have lower threshold doses than previously considered.

• The ICRP now recommends an equivalent absorbed dose limit for the lens of the eye of 0.5 Gy in a single exposure.

• For chronic occupational exposures, the ICRP recommends an equivalent dose limit for the lens of the eye of 20 mSv in a year, averaged over defined periods of 5 years, with no single year exceeding 50 mSv.
ICRP Statement on Tissue Reactions
April 21, 2011 (continued)

• Although uncertainties remain, medical practitioners should be made aware that the absorbed dose threshold for circulatory disease may also be as low as 0.5 Gy to the heart or brain.

• The ICRP continues to recommend that optimisation of protection be applied in all exposure situations and for all categories of exposure, not only for the whole body, but also for exposures to specific tissues, particularly the lens of the eye, the heart and the cerebrovascular system.
Change in ICRP Understanding of Lens Dose Tissue Reactions (ICRP-118)

- Cataract Threshold: Old Limit ~4.5 Gy Career, New Limit ~0.5 Gy Career
- Lens Opacity Threshold: 0.5 Gy
- Yearly Limit: 0.15 Gy Career, 0.02 Gy Career

Bar chart showing absorbed dose for different thresholds and limits.
Draft recommendations

GUIDANCE ON RADIATION DOSE LIMITS FOR THE LENS OF THE EYE
Purpose

• To prepare a commentary to evaluate recent studies on the radiation dose response for development of cataracts.

• To also consider the type and severity of the cataracts, as well as dose rate.

• To provide guidance on whether existing dose limits to the lens of the eye should be changed in the US.

• To suggest research needs regarding radiation effects on and dose limits to the lens of the eye.

January 2015
NCRP Scientific Committee #1-23

Scope

• To evaluate recent cataract dose response studies.
• To evaluate differences in cataract induction by dose rate, and comment on cataract severity in context of radiation detriment.
• To discuss dose limits to protect against cataracts.
• To suggest research needs regarding radiation effects on and dose limits to the lens of the eye.
Acknowledgements

NCRP SC 1-23 Members
• Eleanor Blakely (Co-Chair)
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• Laura Atwell, Office Manager
• James Cassata, Executive Director
• David Smith, Executive Director
Addressed Four Core Questions

• Should radiation-induced cataracts be characterized as stochastic or deterministic effects?

• What effects do LET, dose rate, acute, and/or protracted dose delivery have on cataract induction and progression?

• How should detriment be evaluated for cataracts?

• Based on current evidence, should NCRP change the recommended limit for the lens of the eye?
Should radiation-induced cataracts be characterized as stochastic or deterministic effects?

Due to the incoherence of the mechanistic and epidemiologic evidence, it is not yet known if radiation cataractogenesis is strictly stochastic or deterministic in nature.

The epidemiological evidence to date indicates a threshold model, and the Committee has recommended that this model should continue to be used for radiation protection purposes at this time.
What effects do LET, dose rate, acute, and/or protracted dose delivery have on cataract induction and progression?

There is still very little evidence upon which to base an answer to this question.

The relationship between the results from animal models and risks of vision-impairing cataracts in humans is still not clear.

High-quality epidemiological and mechanistic studies are required before the question of how exposure to ionizing radiation contributes to further loss of lens clarity can be fully answered.
• How should detriment be evaluated for cataracts?

• Vision-impairing cataracts (VICs) could be considered the endpoint of greatest concern in terms of lens radiation protection.

• Cataracts certainly may affect individuals’ ability to carry out their occupations or other daily tasks (Hamada et al., 2014).
How should detriment be evaluated for cataracts?

ICRP Publication 118 (2012) noted that:

- acute doses up to about 0.1 Gy produce no functional impairment of tissues,
- detectable lens changes can be identified as low as between 0.2 and 0.5 Gy
- a nominal threshold of 0.5 Gy for acute or protracted exposure for lens tissue effects is an appropriate method for evaluating lens detriment.
How should detriment be evaluated for cataracts?

While NCRP recognizes that the mechanisms underlying the transition of minor lens opacifications to clinically significant VICs are still not well understood, it is prudent to regard eye exposures and the potential for lens tissue effects in much the same way as whole-body exposures (i.e., ensure exposures are consistent with ALARA principles), as was previously recommended by NCRP Report No. 168 (NCRP, 2010b). This includes careful justification and optimization in exposure situations including radiation doses to the lens of the eye.
• Based on current evidence, should NCRP change the recommended limit for the lens of the eye?

• Current epidemiological studies of the effect of radiation on the lens of the eye indicate it would be prudent to reduce the current recommended annual lens of the eye occupational dose limit from 150 mSv (NCRP, 1993b) down to 50 mGy, a value in harmony with the current occupational whole-body dose limit of 50 mSv (NCRP, 1993b).
Based on current evidence, should NCRP change the recommended limit for the lens of the eye? NCRP recommends changes in limits only when the science supports such change. The recommendation to lower the annual lens of the eye occupational dose limit to 50 mGy is such an example. However, NCRP recognizes that any change in limits would entail an additional cost burden, and the level of protection gained should be commensurate with the cost for implementing the change. This is particularly true for a health outcome, such as cataracts, that is generally treated with a high rate of success.
Based on current evidence, should NCRP change the recommended limit for the lens of the eye?

No new limit is recommended for public exposures to the lens of the eye, as NCRP judges that the existing annual limit of 15 mSv (NCRP, 1993b) is adequately protective, however a change to absorbed dose units of 15 mGy is recommended for consistency.
Based on current evidence, should NCRP change the recommended limit for the lens of the eye?

It should be noted that NCRP no longer recommends the use of equivalent dose for specific tissue exposures, because these quantities were developed for stochastic effects whereas the principal outcomes being addressed are specific tissue reactions (or deterministic effects) in nature. Recommended limits with regard to tissue reactions should be based on absorbed dose, as was the underlying consideration for skin dose limits (NCRP, 1989b; 1993b; 1999).
Based on current evidence, should NCRP change the recommended limit for the lens of the eye?

To apply the recommended lens limit to high-LET radiation, NCRP recommends the approach taken in NCRP Report No. 132 (2000) in which the absorbed dose is multiplied by the relative biological effectiveness of the radiation to obtain a weighted Gray (or ‘Gray equivalent’).

This may then be compared to the limit expressed
Additional Recommended Needs

• Comprehensive Evaluation of Overall Effects of Radiation on the Eye
• Dosimetry Methodology and Dose-sparing Optimization
• Additional High Quality Epidemiologic Studies
• Understanding the Mechanisms of Cataract Development
Sterols reverse protein aggregation in an eye lens paradigm, but it is not known if this is true for radiation-induced cataract

- Zhao et al., Nature 2015
- Makley et al, Science 2015
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Hp(3) Comes into Focus
Views from a Health Physicist

Christopher N. Passmore, CHP
Vice President – Dosimetry Services
Landauer, Inc.

Lens of Eye Guidance – Next Steps: A Stakeholder Workshop on Implementation and Research
August 29, 2016
History of Lens of Eye Dose Limits in US Nuclear Power

- President Eisenhower in 1960 through Federal Radiation Council (FRC60b)\(^1\)

- Whole body, head and trunk, active blood-forming organs, gonads or **lens of the eyes** are not to exceed 3 rem (0.03 Sv) in 13 consecutive weeks, and the total accumulated dose is limited to 5 rems (0.05 Sv) multiplied by the number of years beyond age 18, expressed as \(5(N-18)\), where \(N\) is the current age.

  - Total dose to lens of eye 3 rem (0.03 Sv) per quarter which also would equal a limit of 12 rem (0.12 Sv) per year.
  
  - Effectively considered part of whole body.
History of Lens of Eye Dose Limits in US Nuclear Power (cont.)

- 10CFR20 - September 1978 limits whole body, head and trunk, active blood-forming organs, gonads or **lens of the eyes** to 1.25 rem (0.0125 Sv) per quarter and 5 rem (0.05 Sv) per year.
  - Landauer starts referencing new limits in 1980 on Radiation Dosimeter Reports.

- 10CFR20 - May 1991 NRC adopted ICRP 26 recommendations and separate lens of eye limit established at 15 rem (0.15 Sv) per year.
  - 1994 Landauer starts reporting lens dose equivalent (LDE) on Radiation Dosimeter Reports.
Proposed 10CFR20 Change

• NRC proposed reduced lens of eye dose limit from 15 rem (0.15 Sv) to 5 rem (0.05 Sv) per year

• NRC recommendation not in line with ICRP 118 lens dose limit of 2 rem (0.02 Sv) per year averaged over 5 years

40 CFR 20

Federal Register / Vol. 80, No. 32 / Wednesday, March 15, 2015 / Proposed Rules

14053

FCC 1685

Nuclear Regulatory Commission

ACTION: Advance notice of proposed rulemaking; extension of comment period.

SUMMARY: On July 23, 2014, the U.S. Nuclear Regulatory Commission (NRC) published a notice of proposed rulemaking (NPR) to obtain input from members of the public on the development of a final regulatory basis. The final regulatory basis would identify protection standards that could be possible for a future application.

DATES: The comment period has been extended to June 22, 2015. Comments received after this date will not be considered if it is technically infeasible to do so, but the NRC will at least consider a notice received on or before this date.

ADDRESSES: You may submit comments by any of the following methods (unless this document describes a different method for submitting comments on a specific subject):

- Federal Register Web site: Go to http://www.regulations.gov and search for Docket ID NRC-2013-7279. Address questions about NRC, docket to Card...
• Occupational dose limit for shallow, lens, and deep defined in 10CFR20.1201
  – Shallow dose equivalent is defined as the personal dose equivalent at a depth of 0.07 mm in ICRU tissue and is denoted by $H_{p}(0.07)$.
  – Deep dose equivalent is defined as the personal dose equivalent at a depth of 10 mm in ICRU tissue and is denoted by $H_{p}(10)$.
  – Lens dose equivalent at the depth of 3 mm and denoted by $H_{p}(3)$

• Coefficients ($C_{k}$ factors) exists to Convert from Air Kerma to Deep and Shallow Personal Dose Equivalent but not for Lens Dose Equivalent
  – Multiplying kerma ($K_{a}$) by the conversion coefficient ($C_{k}$) yields the personal dose equivalent

• $C_{k}$ factors did not exists for lens of eye so how do you comply with 10CRF20?
10CFR20.1501
– (d) All personnel dosimeters (except for direct and indirect reading pocket ionization chambers and those dosimeters used to measure the dose to the extremities) that require processing to determine the radiation dose and that are used by licensees to comply with § 20.1201, with other applicable provisions of this chapter, or with conditions specified in a license must be processed and evaluated by a dosimetry processor—
  • (1) Holding current personnel dosimetry accreditation from the National Voluntary Laboratory Accreditation Program (NVLAP) of the National Institute of Standards and Technology; and
  • (2) Approved in this accreditation process for the type of radiation or radiations included in the NVLAP program that most closely approximates the type of radiation or radiations for which the individual wearing the dosimeter is monitored.

• National Voluntary Laboratory Accreditation Program (NVLAP) does not accredit dosimetry systems for lens dose equivalent. So how does a licensee comply?
Landauer dosimetry algorithms estimate $Hp(3)$ from $Hp(0.07)$ and $Hp(10)^2$

Using the NIST $Hp(3)$ data contained in a paper by Soares and Martin, a function was derived to allow calculation of lens-of-eye dose using shallow and deep dose values.\(^3\)

- The paper contains air kerma to dose correction factors for the three depths of interest for 21 of the photon fields
- The function can also be used to calculate the $Hp(3)$ dose directly from the $Hp(0.07)$ and $Hp(10)$ dose values

$$Hp(3) = Hp(0.07) \times \left[ 1.4 - \left( 1.04 \times e^{-\frac{Hp(10)}{Hp(0.07)}} \right) \right]$$
Landauer’s Approach to LDE before $C_k$ (cont.)

- **Photon Dose**
  - For low to medium energy photons, the 300 mg/cm$^2$ dose is calculated using this function.
  - Photons greater than 60 keV, the lens-of-eye photon dose is equivalent to $Hp(10)$

- **Beta Dose**
  - $Hp(3)$ is set equal to the calculated $Hp(0.07)$ for the weakly penetrating $^{85}$Kr
  - $Hp(3)$ approximately 45% to 50% for the more penetrating $^{90}$Sr or depleted uranium

- **Neutron Dose**
  - $Hp(3)$ is set equal to the neutron $Hp(10)$

- **Total $Hp(3)$**
  - The contribution of the photon, beta, and neutron dose are summed to arrive at the total $Hp(3)$
C_k Debate Emerges

- C_k factors dependent on phantoms
  - ORAMED project (Optimization of RAdiation protection for MEDical) for eye lens dosimetry
    - 20 cm high x 20 cm diameter cylinder
    - Water filled
    - Work started in 2008
  - PTB 2011
    - 30 cm x 30 cm x 15 cm slab
    - Water filled
    - Work started in 2012
  - PTB 2015
    - 20 cm high x 20 cm diameter cylinder
    - Water filled

- Which C_k factors to use?
  - ISO 4037-3:2016 draft has both but cylindrical phantom preferred
  - IEC 62387:2012 will be modified to adopt cylindrical phantom
  - Issues with slab phantom at large angles
Comparison of Various $C_k$ Factors for $Hp(3)$

- $C_k$ factors from IEC 62387 and NIST-Soares data are very close for NPP fields.
- Cylindrical phantom derived $C_k$ are lower
- NPP clients should experience lower $Hp(3)$ doses after moving to cylindrical phantom derived algorithms.
IEC to the Rescue

- IEC TC45/SC45B/WG14
- IEC 62387:2012 used for type testing dosimeters
- No agreed upon $Hp(3) C_k$ conversion factors internationally until IEC 62387:2012
  - Technically no agreed upon method to calculate the lens dose
  - $C_k$ factors based on Physikalisch-Technische Bundesanstalt (PTB) data
  - Dose conversion factors defined on slab phantom for $Hp(3)$ in conflict with ORAMED
  - Slab phantom is widely used and available in many calibration laboratories
- However, false start and will be changed to adopt cylindrical phantom $C_k$ for $Hp(3)$
• ISO/TC85/SC2/WG19
• Provides procedures for monitoring the dose to the skin, the extremities, and the lens of the eye.
• Provides guidance on determining when lens of eye dosimeter is needed.
• Provides guidance on the positioning of the dosimeter.
• Precursor to IAEA TechDoc 1731
• Recommends following ISO 4037 for Ck and does not take a side in the phantom debate.
• Provides easy to follow flow chart for determining if lens of eye dose monitoring is required

<table>
<thead>
<tr>
<th>Impact Factor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (Energy and angle)</td>
<td>Is the mean photon energy below about 40 keV?</td>
</tr>
<tr>
<td>If yes</td>
<td>$Hp(0.07)$ may be used for and $Hp(10)$ (see Fig. 4 in Ref. [6])</td>
</tr>
<tr>
<td>If yes</td>
<td>Is the radiation coming mainly from the front or is the person moving in the radiation field?</td>
</tr>
<tr>
<td>If yes</td>
<td>$Hp(0.07)$ may be used (see Fig. 1 in Ref. [6])</td>
</tr>
<tr>
<td>If yes</td>
<td>$Hp(0.07)$ may be used (see Fig. 1 in Ref. [6])</td>
</tr>
<tr>
<td>If yes</td>
<td>No, no lens monitoring is necessary.</td>
</tr>
<tr>
<td>B (Geometry)</td>
<td>Are low energy radiation fields present?</td>
</tr>
<tr>
<td>If yes</td>
<td>Monitoring near the eyes may be required.</td>
</tr>
<tr>
<td>If yes</td>
<td>Monitoring near the eyes may be required.</td>
</tr>
<tr>
<td>C (Protective equipment)</td>
<td>If used for the eye</td>
</tr>
<tr>
<td>If used for the head</td>
<td>Monitoring near the shielding head encloses the dose to the lens of the eye as the eye is not covered by the head shielding. Separate monitoring near the eyes is necessary.</td>
</tr>
</tbody>
</table>

• Provides guidance on when $Hp(0.07)$ and/or $Hp(10)$ can be used as a surrogate for $Hp(3)$
### TABLE 3. DOSES DUE TO PHOTON RADIATION

<table>
<thead>
<tr>
<th>Impact factor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (Energy and angle)</td>
<td>If yes: $H_p(0.07)$ may be used but not $H_p(10)$ (see Fig. 6 in Ref. [65] and Fig. 1 in Ref. [66])</td>
</tr>
<tr>
<td></td>
<td>If no: Is the radiation coming mainly from the front or is the person moving in the radiation field?</td>
</tr>
<tr>
<td></td>
<td>Are homogeneous radiation fields present?</td>
</tr>
<tr>
<td>B (Geometry)</td>
<td>If yes: Monitoring on the trunk may be used</td>
</tr>
<tr>
<td></td>
<td>Is protective equipment such as lead glasses, ceiling, table shields, and lateral suspended shields in use?</td>
</tr>
<tr>
<td>C (Protective equipment)</td>
<td>If used for the eye: Monitoring near the eyes and below the protective equipment or below an equivalent layer of material is necessary. Otherwise, appropriate correction factors to take the shielding into account should be applied.</td>
</tr>
</tbody>
</table>
Example PWR Steam Generator Jumper (nozzle dam technicians)

- Activated corrosion products Co-58 and Co-60 dominate the radiation field.  
- Photon Energy ranges from 511 keV to 1675 keV

Streaming radiation field creates non-uniform irradiation to the head.

Dosimeter on the chest and no eye protection.

IAEA TECDOC 1731 – Beta NPP

- Example PWR Steam Generator Jumper (nozzle dam technicians)
  - Activated corrosion products Co-58 and Co-60 dominate the radiation field.
  - Beta energy range from maximum beta energy ($E_{\text{max}}$) from 318 to 1491 keV
IAEA TECDOC 1731 – Photon Medical

- Example Fluoroscopy Procedure
  - Approximately 40 keV (80 kVp) photon field.

#### TABLE 3. DOSES DUE TO PHOTON RADIATION

<table>
<thead>
<tr>
<th>Impact factor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Energy and angle)</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Is the mean photon energy below about 40 keV?</td>
</tr>
<tr>
<td>If yes</td>
<td>If yes, $H_{p}(0.07)$ may be used but not $H_{p}(10)$ (see Fig. 6 in Ref. [65] and Fig. 1 in Ref. [66]).</td>
</tr>
<tr>
<td>If no</td>
<td>Is the radiation coming mainly from the front or is the person moving in the radiation field?</td>
</tr>
<tr>
<td>If yes</td>
<td>If yes, $H_{p}(0.07)$ or $H_{p}(10)$ may be used (see Fig. 1 in Ref. [66])</td>
</tr>
<tr>
<td>If no</td>
<td>If no, $H_{p}(0.07)$ may be used but not $H_{p}(10)$ (see Fig. 1 in Ref. [66]).</td>
</tr>
<tr>
<td>(Geometry)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Are homogeneous radiation fields present?</td>
</tr>
<tr>
<td>If yes</td>
<td>Monitoring on the trunk may be used.</td>
</tr>
<tr>
<td>If no</td>
<td>Monitoring near the eyes is necessary.</td>
</tr>
<tr>
<td>(Protective equipment)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Is protective equipment such as lead glasses, ceiling, table shields, and lateral suspended shields in use?</td>
</tr>
<tr>
<td>If yes</td>
<td>If used for the eye, monitoring near the eyes and below the protective equipment or below an equivalent layer of material is necessary. Otherwise, appropriate correction factors to take the shielding into account should be applied.</td>
</tr>
<tr>
<td>If no</td>
<td>If used for the trunk (e.g., a lead apron), monitoring below the shielding underestimates the dose to the lens of the eye if the eye is not covered by the trunk shielding. Separate monitoring near the eyes is necessary.</td>
</tr>
</tbody>
</table>
InLight LDR Model 2 Dosimeter Data in Nuclear Power Plant (NPP) Environment

• 26,000 InLight LDR Model 2 dosimeter results from NPP environment were studied
  – No beta response observed 100% photon only readings

• Dosimeters can be used as crude spectrometer and energy can be estimated based on the ratio of response of Element 3(Al) : Element 4 (Cu) = R34
  – R34 falls between 1.020 to 1.023, 95% of the time which indicates photons greater than 250 keV

• A lens of eye dose algorithm using cylindrical Ck factors instead of the LDR approach would not have much impact in NPP radiation environments (1% to 5%)
  – Main dose component are photons above 250 keV
  – If beta field is suspected the lens of eye tends to be protected by respiratory protection
  – Non-uniform fields encountered multiple dosimeters deployed
  – Work controlled by Radiological Work Permit (RWP) and working conditions well known
ISO and IAEA Method for Assigning $Hp(3)$

• ISO and IAEA recommend using $Hp(0.07)$ and/or $Hp(10)$ as a surrogate for $Hp(3)$ in certain environments
  – Radiation source mainly from the front of the worker recommends $Hp(0.07)$ or $Hp(10)$
    • Results in a 0.05% higher dose if $Hp(10)$ used instead of the LDR $Hp(3)$.
    • Results in -1.5% lower dose if $Hp(0.07)$ is used instead of LDR $Hp(3)$.
  – Radiation in multiple directions to the worker $Hp(10)$ should be used
    • Results in a 0.05% higher dose than the Landauer $Hp(3)$ calculation.
VISION Lens Dosimeter

- Measures $Hp(3)$ close to the eye
- Mounts on safety glasses
- Meets IEC 62387 verified by 3$^{rd}$ party
  - Irradiations conducted at Laboratoire National Henri Becquerel (LNHB)
- LiF TLD but working on Al$_2$O$_3$:C OSL version

$Hp(3) = 1.008 \times \frac{(R - BL)}{(CF \times SF)} - BG$

R = Reader output in counts,
BL = counts obtained from process Blank TLD dosimeters,
CF = Calibration Factor of reader in Counts/mrem,
SF = Sensitivity Factor for chip determined at the time of analysis
BG = Ambient Background Radiation
References


4. ORAMED: Optimization of Radiation Protection of Medical Staff, F. Vanhavere, 2011


6. NUREG/CR-1595, Radiological Assessment of Steam Generator Removal and Replacement: Update and Revision Table 2, December 1980

7. IAEA - New Dose Limits for the Lens of the Eye Implications and Implementation, E. Vano, *Practical issues for implementing the dose limit to the lens of the eye (medical)*, October 2012

8. IRPA 13, Nuclear Power Plant Data Analysis for InLight LDR Model 2 Dosimeter, C. Passmore

9. Type Test of the Lens of Eye Dosemeter of Landauer, LNHB 2015/37
Lens of the Eye Considerations for Nuclear Power Plants

Dennis Quinn, CHP
DAQ, Inc.

Presentation at NCRP/GNYCHPS Workshop
New York, NY
August 29, 2016
Outline

• Is there a problem with lens dose now?

• Situations that could cause a problem:
  • High Energy Beta and Electrons
  • Non-Uniform Radiation Fields
  • Effective Dose Equivalent Calculations

• How to prepare for the likely lens dose limit reduction.
Is there a lens dose problem now?

Limits are not restrictive:

- Whole Body Dose Limit: 50 mSv/yr
- Lens Dose Limit: 150 mSv/yr

Lens dose would need to be 3 times the whole body or Effective Dose Equivalent (EDE) limit in order to be restrictive.

Answer: No problem now.
What could cause a problem?

• High Energy Beta Fields
• Non-Uniform Radiation Fields
  • Dose gradient from above
  • Work behind a shadow shield
How high is high energy beta?

The beta must have a range of > the lens depth of 300 mg/cm\(^2\).

Typical power plant nuclides of Co-58, Co-60, Cs-134, Cs-137, Xe-133 have low to medium energy betas that cannot penetrate to the lens.
Beta Range for common Power Plant Radionuclides

Range (mg/cm²)

- Cs-134
- Cs-137
- Co-60
- Xe-133
- Co-58

300 mg/cm²
High Energy Beta at Power Plants

Although not often encountered, the following are examples of radionuclides have energies above 0.8 MeV, and they can reach the lens.

- Sr/Y-90: 2.3 MeV (failed fuel)
- Cs-138: 2.9 MeV (noble gas daughter)
- Rb-88: 5.3 MeV (noble gas daughter)
- N-16: 10.4 MeV (primary coolant activation)
Possible location of high energy beta radiation
Non-Uniform Fields

Credit for sketch: NextEra Energy, Seabrook Station
Non-Uniform Fields
Example of Worker in Mixed Beta-Gamma Non-Uniform Radiation Field
Inside containment under power could have high energy Rubidium-88
**Effective Dose Equivalent – External (EDEX)**

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Weighting Factor</th>
<th>Dose (mrem)</th>
<th>Weighted Dose (mrem)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head (and Lens)</td>
<td>0.10</td>
<td>400</td>
<td>40</td>
</tr>
<tr>
<td>Thorax</td>
<td>0.38</td>
<td>200</td>
<td>76</td>
</tr>
<tr>
<td>Abdomen</td>
<td>0.50</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>Right arm</td>
<td>0.005</td>
<td>200</td>
<td>1.0</td>
</tr>
<tr>
<td>Left arm</td>
<td>0.005</td>
<td>200</td>
<td>1.0</td>
</tr>
<tr>
<td>Right thigh</td>
<td>0.005</td>
<td>100</td>
<td>0.5</td>
</tr>
<tr>
<td>Left thigh</td>
<td>0.005</td>
<td>100</td>
<td>0.5</td>
</tr>
<tr>
<td>All (EDE)</td>
<td>1.00</td>
<td></td>
<td>169</td>
</tr>
</tbody>
</table>
Assuming Limit is reduced to 50 mSv per year for lens

Any increase above Whole Body dose is important and must be evaluated.

- Conditions that would cause higher dose to lens:
  - High beta energies.
  - Dose gradient from above or shadow shielding of the body.

- Radiation instrumentation should be able to estimate dose to the lens.

- Dosimetry must be appropriate.
Dose Rate Measurements

• Need to determine lens dose rate prior to entry to consider lens protection and proper dosimetry.
• In some cases, air scattered electrons could be present that will add to the beta dose.
• Most instruments used for dose rate surveys (ion chambers) estimate deep dose (10 mm depth) and shallow dose (0.07 mm depth).
• Some instruments are available that measure dose at 300 mg/cm².
Dose Rate Measurements at 300 mg/cm²

Canberra Babyline - 81
Rotem Ram - Ion

There may be other instruments that can measure at 300 mg/cm², and this is not an endorsement of these products.
Personnel Dosimetry

• Need a dosimeter correctly placed to monitor the lens or be conservative in the dose estimation.
• Dosimeter must be able to monitor beta dose at high energy, and the dose algorithm should be understood.
• NVLAP does not currently test lens dose, but that is expected to change.
• Need a multi-element dosimeter in order to estimated the dose at 300 mg/cm².
• Size of dosimeter is important, especially if placing the dosimeter near the eyes.
Personnel Protection

If high energy beta and electrons are present, then protection should be considered. Safety glasses with side shields are effective, and are standard equipment at some power plants. Other facial coverings such as bubble hoods and respirators will have some protection.
## Personnel Protection Examples

<table>
<thead>
<tr>
<th>Item</th>
<th>Density Thickness (mg/cm²)</th>
<th>Maximum beta energy shielded (MeV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0 (+300)</td>
<td>0.78</td>
</tr>
<tr>
<td>Glove Bag</td>
<td>45 (+300)</td>
<td>0.87</td>
</tr>
<tr>
<td>Face Shield</td>
<td>132 (+300)</td>
<td>1.04</td>
</tr>
<tr>
<td>Safety Glasses (with side shields)</td>
<td>280 (+300)</td>
<td>1.32</td>
</tr>
<tr>
<td>MSA Ultraview Resp. Lens</td>
<td>308 (+300)</td>
<td>1.37</td>
</tr>
</tbody>
</table>
What should be done?

1. Evaluate existing dosimetry and know how it responds to high energy beta.
2. Consider new dosimetry commercially available.
3. Stay tuned for NVLAP actions on lens dosimetry.
4. Determine what plant areas or situations (e.g., damaged fuel) will be important for lens dose:
   - Evaluate nuclide mixes in each plant area or situation.
   - Consider measurement of lens dose rate directly.
5. Evaluate safety glasses and other protective equipment.
6. Train RP staff so they understand what’s coming.
Lens of Eye Radiation Protection
Medical Considerations

LAWRENCE T. DAUER

NCRP & GNYCHPS Workshop

Memorial Sloan Kettering Cancer Center
Lens of Eye Radiation Protection

Medical Considerations

- PATIENT IMPLICATIONS
- OCCUPATIONAL IMPLICATIONS
- NEEDS AND OPPORTUNITIES
Lens of Eye Radiation Protection
Medical Considerations

PATIENT IMPLICATIONS/OPPORTUNITIES
Rising Use of Radiation in Medicine

- **Annual E per capita for Med Procedures:**
  - United States: 0.5 mSv (1980) to 3.0 mSv (2006)
  - Worldwide: 0.3 mSv (1980) to 0.6 mSv (2007)

- **United States (2006):**
  - 337 M Diagnostic/Interventional Radiology
  - 18 M Nuclear Medicine

- **Worldwide (2006):**
  - 3.6 B Total
  - 3.1 B Diagnostic/Interventional Radiology
  - 0.5 B Dental
  - 37 M Nuclear Medicine

Mettler et al, Radiology, 2009, 253
Computed Tomography Usage

- Was growing ~10%/y
- Up to ~80 M/y in U.S.
- ~10% in children
- Perhaps slowing some...
- ED CT usage continues to increase. (Larson 2011).
  - Growing ~16%/y
  - Double every 4.7 y

U.S. CT Usage Est. (Millions)
RT Dose for Cataract / Non-Cataract Cases vs. Overall Treatment Time

Merriam & Focht
1962
## Radiation Therapy – Cataract Epidemiology

<table>
<thead>
<tr>
<th>Early studies specifically associated with RT (1950s)</th>
<th>Recent studies – lower thresholds for posterior lens changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>~ 2-8 Gy threshold</td>
<td>0.2-0.8 Gy (Tinea capitis) Albert (‘68)</td>
</tr>
<tr>
<td>o 0-84 y age</td>
<td>0.1-0.4 Gy (Skin hemangioma) Wilde and Sjostrand (‘97), Hall (‘99).</td>
</tr>
<tr>
<td>o 1-40 y followup</td>
<td>Uncertainties, but still lower than before.</td>
</tr>
<tr>
<td>o 0.2-69Gy Lens doses</td>
<td>See NCRP SC 1-23.</td>
</tr>
<tr>
<td>o Small case series</td>
<td></td>
</tr>
<tr>
<td>o Cogan and Dreisler (‘53)</td>
<td></td>
</tr>
<tr>
<td>o Merrriam and Focht (‘57)</td>
<td></td>
</tr>
<tr>
<td>o Qvist and Zachau (‘59)</td>
<td></td>
</tr>
</tbody>
</table>
# Comparing Some Potential RT Complications

<table>
<thead>
<tr>
<th>Detriment/Effect</th>
<th>Tissue</th>
<th>Gy (Acute to Fractionated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of Eyelashes</td>
<td>Eyelid</td>
<td>10 to &gt;20</td>
</tr>
<tr>
<td>Acute Conjunctivitis</td>
<td>Conjunctiv a</td>
<td>27 to &gt;30</td>
</tr>
<tr>
<td>Chronic Conjunctivitis</td>
<td>Conjunctiv a</td>
<td>50</td>
</tr>
<tr>
<td>Ocular Dryness</td>
<td>Lacrimal</td>
<td>&gt;30 to &gt;50 (1+ y latency)</td>
</tr>
<tr>
<td>Ulceration</td>
<td>Cornea</td>
<td>20 to &gt;60</td>
</tr>
<tr>
<td>Irisitis</td>
<td>Iris</td>
<td>20 to &gt;70</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>Retina</td>
<td>30 to &gt;70</td>
</tr>
<tr>
<td>Cataract</td>
<td>Lens</td>
<td>~0.5 - 2 (10+ y latency)</td>
</tr>
</tbody>
</table>
RT Optimization Possible?

- Tradeoff between high tumor dose and clinically acceptable organs at risk dose.
- Threshold doses for tissue reactions can be reached in some patients during RT (including lens).
- Most treatment planning systems do not accurately account for such low doses (especially out of field).
- Doses to RT patients from associated imaging procedures are not generally accounted for.
- While local control is paramount, RT plans and processes should be examined with care.

## Patient Potential for >0.5 Gy to Lens of Eye

- Radiation Therapy
  - External Beam
  - Brachytherapy
- Neuroradiology Interventional Procedures
- Repeated Brain Perfusion CT
  - 81-348 mGy (Zhang2012)
  - 124 mGy (Perisinakis2013)
- Repeated Head CT
- Repeated Dental Cone Beam CT?

- Optimization strategies should attempt to minimize the possibility of exceeding 0.5 Gy for lens of eye in patients, both for individual high-dose exposures and multiple moderate dose exposures (repeated head CT or interventional procedures)
  - (Vano, Miller, Dauer 2015)
Lens Dose – CT Optimization Strategies

(Nikupaavo et al 2015, AJR)

(Kudomi et al 2014, ECR)

(Prins et al 2011, Oral Surg)
## Lens Dose - CT Optimization Strategies

<table>
<thead>
<tr>
<th>CT</th>
<th>Dose</th>
<th>Image Noise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bismuth Shield</td>
<td>&lt;10-40%</td>
<td>&gt;20-30%</td>
</tr>
<tr>
<td>Organ Based TCM</td>
<td>&lt;25-50%</td>
<td>&gt;20-30%</td>
</tr>
<tr>
<td>Gantry Tilt Angle 10-12 degrees</td>
<td>&lt;75-85%</td>
<td>&lt;~25%</td>
</tr>
<tr>
<td>6-7.5 degrees</td>
<td>&lt;7-20%</td>
<td>~</td>
</tr>
<tr>
<td>(shorter range &lt;DLP overall)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Dental Cone Beam CT

<table>
<thead>
<tr>
<th>Dose</th>
<th>Image Noise</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; Field of View</td>
<td>&lt;~25%</td>
</tr>
<tr>
<td>Patient Lead Glasses</td>
<td>~ take care positioning</td>
</tr>
</tbody>
</table>
Lens of Eye Radiation Protection

Medical Considerations

OCCUPATIONAL IMPLICATIONS
• ~760 person-Sv worldwide in 1994.
• ~3540 person-Sv worldwide in 2002.
• **Physicians, technicians, nurses** and others involved constitute the largest single group of workers occupationally exposed to man-made sources of radiation.
• More than 80% of CT techs and general radiographers do not have measurable exposure.
• **IR/IC FGI MDs are the most exposed in medicine.**
NCRP-160 (2009)

- Medical staff exposures contributed the most (39%) to the U.S. occupational exposures.
- ~2.5 Million monitored workers.
- ~0.75 Million received measured doses.
- ~550 Person-Sv.
- Average E = 0.75 mSv.
- Data from ~2006.

- Hospital, 384
- Other Med, 125
- Veterinary, 13
- VA, 10
- Dental, 11
- Med School, 7
Expanding Use of Radioactive Materials

- Diagnostic Imaging/IR/IC
- PET Imaging
  - Scans and Rad Onc Sims
- Multimodality
  - PET/CT
  - PET/MRI
- Nuclear Medicine
  - Tracers
  - Stress Tests
  - Scan
- Localization
  - Sentinel Node
  - Rad Seed Localization
Measurable Unprotected LDE (mSv/y)
2011 MSKCC

Bins (mSv/y)
<table>
<thead>
<tr>
<th>Exposed Medical Staff</th>
<th>Avg</th>
<th>Min</th>
<th>25%</th>
<th>50%</th>
<th>75%</th>
<th>95%</th>
<th>99%</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR/FGI MD no Pb glasses</td>
<td>11.1</td>
<td>0.1</td>
<td>0.5</td>
<td>7.0</td>
<td>19.3</td>
<td>32.5</td>
<td>35.7</td>
<td>36.5</td>
</tr>
<tr>
<td>Radiopharmacist</td>
<td>4.7</td>
<td>0.1</td>
<td>4.3</td>
<td>5.0</td>
<td>6.4</td>
<td>8.0</td>
<td>8.5</td>
<td>8.6</td>
</tr>
<tr>
<td>IR/ FGI Tech-Nurse no Pb</td>
<td>2.5</td>
<td>0.1</td>
<td>0.4</td>
<td>1.1</td>
<td>1.9</td>
<td>12.0</td>
<td>19.1</td>
<td>19.3</td>
</tr>
<tr>
<td>NM Tech-Nurse</td>
<td>2.4</td>
<td>0.1</td>
<td>0.3</td>
<td>0.9</td>
<td>2.8</td>
<td>9.8</td>
<td>15.5</td>
<td>19.0</td>
</tr>
<tr>
<td>Hospital Average **</td>
<td>2.1</td>
<td>0.1</td>
<td>0.2</td>
<td>0.5</td>
<td>2.0</td>
<td>8.5</td>
<td>19.6</td>
<td>36.5</td>
</tr>
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<td>NM MD</td>
<td>1.9</td>
<td>0.1</td>
<td>0.5</td>
<td>1.4</td>
<td>2.6</td>
<td>6.2</td>
<td>7.2</td>
<td>7.6</td>
</tr>
<tr>
<td>Research Radiochem</td>
<td>1.9</td>
<td>0.1</td>
<td>0.1</td>
<td>0.6</td>
<td>3.3</td>
<td>6.3</td>
<td>7.8</td>
<td>8.2</td>
</tr>
<tr>
<td>Commercial Radiopharm</td>
<td>1.6</td>
<td>0.1</td>
<td>0.1</td>
<td>0.3</td>
<td>1.3</td>
<td>7.1</td>
<td>23.5</td>
<td>70.2</td>
</tr>
<tr>
<td>Health Physics – Rad Safety</td>
<td>1.1</td>
<td>0.1</td>
<td>0.5</td>
<td>1.0</td>
<td>1.9</td>
<td>2.2</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Inpatient Nurse</td>
<td>0.4</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
<td>0.4</td>
<td>0.9</td>
<td>1.8</td>
<td>2.2</td>
</tr>
</tbody>
</table>
IR/IC FGI Lens Doses Vary by Procedure

<table>
<thead>
<tr>
<th>Procedure</th>
<th>~~mSv/Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embolization</td>
<td>0.8</td>
</tr>
<tr>
<td>Cardiology</td>
<td>0.5</td>
</tr>
<tr>
<td>ERCP</td>
<td>0.5</td>
</tr>
<tr>
<td>Biliary Stent/Drain</td>
<td>0.3</td>
</tr>
<tr>
<td>Vertebroplasty</td>
<td>0.1</td>
</tr>
<tr>
<td>TIPS</td>
<td>0.03</td>
</tr>
<tr>
<td>Cerebral Angio</td>
<td>0.02</td>
</tr>
</tbody>
</table>

- Training
- Methodology
- Complexity
- Patient Factors
- Equipment
- Lens Dose correlates with Patient Dose

~4-7 μGy Lens /Gy cm²
FGI IR/IC Protection Controls (NCRP-168)

- **Engineering**
  - Equipment
  - Structural Shielding
  - Equipment Shielding
- **Safe Work Practices**
  - SOPs
  - 10 Commandments/Pearls
- **Administrative**
  - Training/Credentialing
  - Expectations
- **PPE**
  (aprons/collar/glasses, etc.)
Operator Training / Credentialing

- Equipment design and shielding help... **BUT**
- Training and Credentialing needs improvement.
- Europe leads in operator training.
- Only ~27 states enacted legislation regarding radiation education for FGI operators
Lens of Eye Radiation Protection
Medical Considerations
Important to Perform a Monitoring Assessment

Assessment Categories:
- Exposure Scenario
- Type of Radiation Field
- Energy and Angle
- Geometry
- Homogeneity
- Protective Equipment
- Mixed Radiation Fields

(UCSF, 2016)
# How to Monitor Lens Dose?

<table>
<thead>
<tr>
<th>Radiation Field</th>
<th>$H_p(0.07)/H_{\text{lens}}$</th>
<th>$H_p(3)/H_{\text{lens}}$</th>
<th>$H_p(10)/H_{\text{lens}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photons &lt; 30 keV</td>
<td>0.9 – 5</td>
<td>0.6 – 1</td>
<td>0.01 – 0.9</td>
</tr>
<tr>
<td>Photons &gt; 30 keV</td>
<td>0.8 – 1.1</td>
<td>1 – 1.2</td>
<td>0.9 – 1.2</td>
</tr>
<tr>
<td>Electrons</td>
<td>1-500</td>
<td>~1</td>
<td>&lt;&lt;1 – 1.2</td>
</tr>
<tr>
<td>Adequate?</td>
<td>Perhaps for photon radiation</td>
<td>OK for Photons. Necessary for Beta</td>
<td>Not for low E photons or beta.</td>
</tr>
</tbody>
</table>

R. Behrens and G. Dietze
Phys Med Bio 56 (2011) 511
Practical Lens Dosimeter Choices – Starts with actually wearing them!

- **DDE dosimeters** (Whole Body) $H_p(10)$:
  - On trunk or waist far from eyes.
  - Underestimate at low photon energies (too thick)
  - Under lead apron if in use.

- **SDE dosimeters** (Extremity) $H_p(0.07)$:
  - Must be worn facing the beam/scatter
  - Worn near eye (note NCRP-168 factor of ~1 at collar)
  - OK for photons, overestimates for high energy beta (too thin)

- **LDE dosimeters** (Eye) $H_p(3)$ – exist?:
  - Must be worn facing the beam/scatter
  - Only type OK for both photons and high energy beta.
# How to Monitor?

## Table 3. Doses Due to Photon Radiation

<table>
<thead>
<tr>
<th>Impact factor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (Energy and angle)</td>
<td>Is the mean photon energy below about 40 keV?</td>
</tr>
<tr>
<td></td>
<td>If yes ↓</td>
</tr>
<tr>
<td></td>
<td>$H_p(0.07)$ may be used but not $H_p(10)$ (see Fig. 6 in Ref. [65] and Fig. 1 in Ref. [66])</td>
</tr>
<tr>
<td></td>
<td>If no ↓</td>
</tr>
<tr>
<td></td>
<td>Is the radiation coming mainly from the front or is the person moving in the radiation field?</td>
</tr>
<tr>
<td></td>
<td>If yes ↓</td>
</tr>
<tr>
<td></td>
<td>$H_p(0.07)$ or $H_p(10)$ may be used (see Fig. 1 in Ref. [66])</td>
</tr>
<tr>
<td></td>
<td>If no ↓</td>
</tr>
<tr>
<td></td>
<td>$H_p(0.07)$ may be used but not $H_p(10)$ (see Fig. 1 in Ref. [66])</td>
</tr>
</tbody>
</table>

## Table 4. Doses Due to Beta Radiation

<table>
<thead>
<tr>
<th>Impact factor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (Energy and angle)</td>
<td>Is the maximum beta energy above about 0.7 MeV?</td>
</tr>
<tr>
<td></td>
<td>If no ↓</td>
</tr>
<tr>
<td></td>
<td>No monitoring due to beta radiation is necessary as it does not penetrate to the lens of the eye.</td>
</tr>
<tr>
<td></td>
<td>If yes ↓</td>
</tr>
<tr>
<td></td>
<td>Monitoring is necessary as described in lines B and C.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B (Geometry)</th>
<th>Is homogeneous radiation fields present?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>If yes ↓</td>
</tr>
<tr>
<td></td>
<td>Monitoring on the trunk may be used.</td>
</tr>
<tr>
<td></td>
<td>If no ↓</td>
</tr>
<tr>
<td></td>
<td>Monitoring near the eyes is necessary.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C (Protective equipment)</th>
<th>Is protective equipment such as shields and glasses that are thick enough to absorb the beta radiation in use?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>If used for the eye ↓</td>
</tr>
<tr>
<td></td>
<td>Consider ‘photon radiation’ as the beta radiation is completely absorbed in the shielding; however, bremsstrahlung has to be taken into account — the contributions from both that produced outside and that produced inside the shielding.</td>
</tr>
<tr>
<td></td>
<td>If not used ↓</td>
</tr>
<tr>
<td></td>
<td>$H_p(3)$ is the only appropriate quantity.</td>
</tr>
</tbody>
</table>
How to Monitor Lens Dose?

Properly calibrated Hp(3) with dosimeter worn close to eye – if impractical ... consider the following:

<table>
<thead>
<tr>
<th>Hp(0.07) or Hp(10)</th>
<th>Hp(0.07)</th>
<th>Hp(3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At trunk</td>
<td>At Eyes behind glasses -</td>
<td>If beta &gt;0.7 MeV –</td>
</tr>
<tr>
<td></td>
<td>or At neck and apply CF</td>
<td>and Not shielded</td>
</tr>
</tbody>
</table>

- Radiochemistry      | Interventional Radiology  | Beta Brachytherapy             |
- Radiopharmacy        | Interventional Cardiology | Beta Radiochemistry             |
- Nuclear Medicine Staff | Interventional Tech      | Beta Radiopharmacy             |
- Researchers (> 40 keV) | Interventional Nurse     | Beta Researchers               |
- Brachytherapy general | Interventional Anesthesia |                                |
- Floor Nurses         | Implant Brachytherapy    |                                |
- General Radiology Tech |                          |                                |
- Health Physics       |                          |                                |

Lens of Eye Monitoring - Some Challenges

- Absorbed dose to the lens in \textit{mGy}.
  - Lens modeling
  - How best to monitor with available dosimeters?
- Shielding and PPE modeling
- Interventionalists (radiology/cardiology)
  - Badge location (generally outside the collar, nearer eye needed?, shield correction factor?)
- What if leaded glasses or ceiling shields are used?
  - Divide by 3+ if audited use can be verified/validated—likely a conservative estimate of actual lens dose.
ICRP External Dose Factors for Lens of Eye

- Stylized eye phantoms.
- New dose conversion coefficients.
- ICRP-116, Appendix F.
ICRP Publication 116, App. F
Voxel Eye Model
(RPI - Caracappa et al PMB 59 - 2014)
RPI Adult Male Voxel Phantom

Ultra-Fine Eye Model
Xu et al 2016 - AAPM
Lens of Eye Radiation Protection
Medical Considerations

STAFF PROTECTION
ALARA / Optimization for IR Staff

- Training, Behavior Modification & PPE
  - ~45% reduction in LDE over 3 year period.
- Protect the Patient = Protect the staff

Interventional Radiologist’s Lens Doses
Directly Correlated with Patient Kerma-Area-Product

Dauer et al, 2010, JVIR
Lieto and Jackson 2000
Optimization in IR Procedures
Reduces Lens of Eye Dose as well

- Dose > in larger patients.
- mA low as possible.
- kVp high as needed.
- Patient at max distance from x-ray tube
- Detector as close to the patient as possible.
- Don’t overuse geometric or electronic magnification.
- Remove grid on small patients if image quality not compromised.
- Always collimate down to the area of interest.
- Use PPE (shield patient, use ceiling shields, leaded eyewear).
- Keep beam on time, photospot shots, and movies to minimum.
Shielding Strategies for FGI LDE reduction

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Reduction Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaded glasses</td>
<td>3 - 10</td>
</tr>
<tr>
<td>Shielded drape</td>
<td>25</td>
</tr>
<tr>
<td>Leaded glasses + drape</td>
<td>140</td>
</tr>
<tr>
<td>Ceiling shield</td>
<td>130</td>
</tr>
<tr>
<td>Rolling shield</td>
<td>1000</td>
</tr>
</tbody>
</table>

Thornton, Dauer et al 2010 JVIR
Monte Carlo Assessment of Dose to the Lens of the Eye IR (Xu et al. 2016 [RPI/MSKCC]– AAPM meeting)
Monte Carlo Assessment of Dose to the Lens of the Eye IR (Xu et al. 2016 [RPI/MSKCC]– AAPM meeting)

Graph showing annual equivalent dose (mSv) for different angles and protection levels:
- **PA**: No Protection, Lead Glasses, Lead Mask
- **LAO45°**: No Protection, Lead Glasses, Lead Mask
- **RAO45°**: No Protection, Lead Glasses, Lead Mask
Monte Carlo Assessment of Dose to the Lens of the Eye IR (Xu et al. 2016 [RPI/MSKCC]– AAPM meeting)

![Graph showing annual equivalent dose to the eye lens for different doctor postures and eye wear.](image-url)
Several Needs and Opportunities

- Need for new, high-quality epidemiology and basic research on mechanisms of action.
  - Patients
  - Occupational Staff
- Increasing knowledge of pathogenesis, prevention and treatment of lens damage.
- Quality treatment planning in EBRT, Brachy.
- Work with ophthalmologists!
- Dosimetry – modeling + algorithms for occupational exposure scenarios?
- On-going opportunity for dose-sparing optimization (e.g. CT) and the need for more education and more accurate dose assessment for potentially exposed populations.
- Need additional information on children effects.
- Longitudinal studies.
Lens of Eye Radiation Protection
Medical Considerations

Lawrence T. Dauer, PhD, DABHP
Department of Medical Physics
Department of Radiology
Memorial Sloan-Kettering Cancer Center
dauerl@mskcc.org
International Radiation Protection Association
EYE DOSE GUIDANCE
(and EPRI Workshop)
-- SPRING 2016 --

Stephen Balter, Ph.D.
Professor of Clinical Radiology (Physics) (in Medicine)
FOR THE IRPA WORKING GROUP
HPS – NCRP Workshop, New York, August 2016
2015 IRPA survey of professionals on the new dose limit to the lens of the eye and wider issues associated with tissue reactions

Marie Claire Cantone, Merce Ginjaume, Saveta Miljanic, Colin J Martin, Keiichi Akahane, Louisa Mpete, Severino C Michelin, Cynthia M Flannery, Lawrence T Dauer, Stephen Balter
A questionnaire sent to all the IRPA ASs on April 23rd, 2015

**Topic 1  Implications for Dosimetry**

*Q1 – Q8* - implications for monitoring and assessing dose to the lens of the eye and the interpretation of the results.

**Topic 2  Implications for Methods of Protection**

*Q9 – Q12* - implications for methods (e.g., procedures or the design phase of equipment, facilities, and protective equipment) used to reduce dose to the eye, in the context of optimization of protection.

**Topic 3  Wider Implications of Implementing the Revised Limit**

*Q13 – Q18* - long term impact on working activities; - changes in Health surveillance; - more claims for compensation

**Topic 4  Legislative and other general aspects**

*Q19 – Q22* - guidelines addressing monitoring related to new limit; -consultation for legislation; -wider issue of tissue reactions, also circulatory disease
Conclusions from the survey
Direct implication in dosimetry and protection

- ASs devoted most attention to the medical area, non-uniform exposure (interventional radiology and cardiology)
  A dosimeter measuring Hp(3) close to the eye is considered the ideal method and used in pilot studies;

Because of the limited availability of Hp(3) dosimeters, Hp(0.07) and Hp(10) are predominantly used;

When use a dosimeter close to the eye → it should be on a head band¹, suggestions on the position: the side of the head, the eyebrow ridge, on the forehead, or attached into the protective glasses;

¹ Not seen as practical by medical HPs attending the IRPA eye presentation.
Conclusions from the survey
Direct implication in dosimetry and protection

- The dosimeter is **worn at the collar** outside the lead apron, but no correction factor is applied;
- **Protective systems are not always available** and used at different levels, hospital to hospital, even within the same country;

- **In nuclear installations**, shielding masks, glove-boxes and remote systems were in use before the introduction of the new dose limit, and no major changes are foreseen;

- **Regardless of the area of use**, issues emerge, beside the economic ones, about the discomfort associated with using lead glasses, since they are heavy and not being suitably fitted for individuals.
Related Activities

Radiation Induced Cataracts: Science, Policy, and Impacts Radiation Protection Workshop
Wednesday, 1 June 2015

EPRI Update:
Lens of the Eye Projects

IAEA
International Atomic Energy Agency TECDOC No. 1731

Implications for Occupational Radiation Protection of the New Dose Limit for the Lens of the Eye
The primary purpose of IRPA is to provide a medium whereby those engaged in radiation protection activities in all countries may communicate more readily with each other and through this process advance radiation protection in many parts of the world. This includes relevant aspects of such branches of knowledge as science, medicine, engineering, technology and law, to provide for the protection of man and his environment from the hazards caused by radiation, and thereby to facilitate the safe use of medical, scientific, and industrial radiological practices for the benefit of mankind.

Latest News

- New Lens of Eye Area on the IRPA Website
- Update on the June 2016 IAEA Radiation Safety Standards Committee Meeting
- Just Released: IRPA Bulletin No 10 - Special IRPA14 Issue
- FS-IRPA Workshop on RP Culture in Waste Management, 14-16 Nov 2016, St Ursanne Switzerland
- IRPA President Roger Coates awarded Officer of the Order of the British Empire (OBE)
- ICRU Invites Nominations for the Gray Medal
- Check out IRPA’s New YouTube Channel
IRPA Guidance is based on 20 mSv/y

- ICRP recommendation is 20 mSv/y
- NCRP may be 50 mSv/y

![Graph showing Measurable LDE (mSv/y) - 2011 MSKCC](image)

<table>
<thead>
<tr>
<th>Exposed Medical Staff</th>
<th>Avg</th>
<th>Min</th>
<th>25%</th>
<th>50%</th>
<th>75%</th>
<th>95%</th>
<th>99%</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR/FGI MD no Pb glasses</td>
<td>11.1</td>
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<td>4.7</td>
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<td>6.4</td>
<td>8.0</td>
<td>8.5</td>
<td>8.6</td>
</tr>
<tr>
<td>IR/ FGI Tech-Nurse no Pb</td>
<td>2.5</td>
<td>0.1</td>
<td>0.4</td>
<td>1.1</td>
<td>1.9</td>
<td>12.0</td>
<td><strong>19.1</strong></td>
<td>19.3</td>
</tr>
<tr>
<td>NM Tech-Nurse</td>
<td>2.4</td>
<td>0.1</td>
<td>0.3</td>
<td>0.9</td>
<td>2.8</td>
<td>9.8</td>
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<tr>
<td>Hospital Average **</td>
<td>2.1</td>
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<td>0.5</td>
<td>2.0</td>
<td>8.5</td>
<td><strong>19.6</strong></td>
<td>36.5</td>
</tr>
<tr>
<td>NM MD</td>
<td>1.9</td>
<td>0.1</td>
<td>0.5</td>
<td>1.4</td>
<td>2.6</td>
<td>6.2</td>
<td>7.2</td>
<td>7.6</td>
</tr>
<tr>
<td>Research Radiochem</td>
<td>1.9</td>
<td>0.1</td>
<td>0.1</td>
<td>0.6</td>
<td>3.3</td>
<td>6.3</td>
<td>7.8</td>
<td>8.2</td>
</tr>
<tr>
<td>Commercial Radiochem</td>
<td>1.6</td>
<td>0.1</td>
<td>0.1</td>
<td>0.3</td>
<td>1.3</td>
<td>7.1</td>
<td><strong>23.5</strong></td>
<td>70.2</td>
</tr>
<tr>
<td>Radiation Safety</td>
<td>1.1</td>
<td>0.1</td>
<td>0.5</td>
<td>1.0</td>
<td>1.9</td>
<td>2.2</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Inpatient Nurse</td>
<td>0.4</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
<td>0.4</td>
<td>0.9</td>
<td>1.8</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Dauer: EPRI 2016  
Dauer: EPRI 2016
A guideline protocol has been drafted, to provide practical recommendations about when and how eye lens dose should be monitored in the framework of the implementation of the new dose limit for the lens of the eye, as well as guidance on use of protective devices depending on the exposure levels.
Guideline protocol for eye protection and eye dose monitoring of workers

- Workers for whom lens of the eyes monitoring might be needed
- Proposed dose levels for implementation of dose monitoring
- Eye lens monitoring procedures
- Guidance on use of eye protective devices
This guidance is based on the ICRP dose limit of 20 mSv/y

Hp(10) may be a reasonable substitute for imaging X-ray photons (including scatter).

Measured Hp(3) may be needed for other irradiations. Validity of collar measurements is irradiation geometry dependent.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Dosimeter position</th>
<th>Dose quantity*</th>
<th>Annual dose (mSv)</th>
<th>Monthly dose (mSv)</th>
<th>Protection / Dose monitoring recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes</td>
<td>Collar or headband</td>
<td>Hp(3)</td>
<td>1–6</td>
<td>0.2–0.5</td>
<td>Initial monitoring with collar or head dosimeter to establish dose levels. Regular monitoring recommended</td>
</tr>
<tr>
<td>Eyes</td>
<td>Collar or headband</td>
<td>Hp(3)</td>
<td>&gt; 6 (15)**</td>
<td>&gt; 0.5</td>
<td>Regular monitoring with collar or head dosimeter is required.</td>
</tr>
</tbody>
</table>
Work still has to be done

• Calibration method for Hp(3)
  – Test geometry is critical.

• Standards for defining the clinical protection factor for PPE
  – Irradiation geometry
  – Clinical task
- These values are prudent for either 20 or 50 mSv/y
- Individual monitoring results will demonstrate the (im)proper use of external devices such as ceiling-suspended screens.
- Even with proper use of external devices, the collar reading can exceed 10 mSv/y. Protective eyewear is also needed for these individuals.

### Table 2 Proposed dose levels for guidance on use of protective devices

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Annual unprotected dose (mSv)</th>
<th>Protection recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes</td>
<td>3–6</td>
<td>Ceiling suspended screens should be used where available. Protective eyewear may be considered where there is no other protective device.</td>
</tr>
<tr>
<td>Eyes</td>
<td>6–10</td>
<td>Training in use of ceiling-suspended screens recommended. Protective eyewear should be considered, particularly where no other protective devices are available.</td>
</tr>
<tr>
<td>Eyes</td>
<td>&gt; 10</td>
<td>Protection essential. Both ceiling suspended shield and protective eyewear should be considered and at least one form used.</td>
</tr>
</tbody>
</table>
Percent of 68,740 monthly (non ‘M’) 2014 collar badge readings on medical workers.

% of Collar Badges with monthly DDE reading (mrem)

Annualized Hp(10) mrem

Annualized Hp(10) mrem

\[ y = 20.409x^{-1.568} \]
\[ R^2 = 0.9822 \]
PPE for Eyes

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Reduction Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaded glasses</td>
<td>3-10</td>
</tr>
<tr>
<td>Shielded drape</td>
<td>25</td>
</tr>
<tr>
<td>Leaded glasses + drape</td>
<td>140</td>
</tr>
<tr>
<td>Ceiling shield</td>
<td>130</td>
</tr>
<tr>
<td>Rolling shield</td>
<td>1000</td>
</tr>
</tbody>
</table>

Thornton, Dauer et al 2010 JVIR

Dauer: EPRI 2016
Operator orientation matters
Orientation relative to the beam

Monte Carlo Assessment of Dose to the Lens
(Xu et al. 2016 AAPM meeting)
Protection factor for fluoro glasses?

- A minimum attenuation factor of three (3) for each eye is desirable.
- Dependent on device construction, geometry, operator’s height, operator’s motion, etc.
- Operational evaluation in a facility is possible.
- No available standard that accounts for known major variations in the orientation of the individual’s head in the scatter field.
IRPA (EPRI) Conclusions

• Lens of eye dose limits of 20 – 50 mSv/y.
• Open question: Should all observable opacities be treated as cataracts?
• For the USA (assuming eye 50mSv/y) protective glasses with a minimum factor of 3 are consistent with the allowance for protective aprons.
• Adjustment for eye PPE should be as routine as adjustment for body PPE.
Focht - 1961

No longer needed c 1940
Lens of Eye Guidance: European Status and Research

Liz Ainsbury and colleagues

NCRP/HPS Stakeholder Workshop on Implementation and Research, MSK, 29th August 2016
Introduction

Radiation induced cataracts

Basis for ICRP recommendations
   Mechanistic evidence -> mutational?
   Epidemiology -> reduced/no threshold?

New BSS/IRR – Implications for radiation protection
   Results of recent studies
   Who will be affected
   What to measure
   How to protect
Ionizing radiation induced cataracts: Recent biological and mechanistic developments and perspectives for future research

Cataracts are the most frequent cause of blindness worldwide.

**Multifactorial aetiology:** Age; Genetics (congenital cataracts); Also: Sunlight, alcohol intake, nicotine consumption, diabetes, persistent use of corticosteroids...
“Nuclear cataract”: http://2.bp.blogspot.com/_OkLnqwQYzEo/TAbWxDZp2DI/AAAAAAAABPQ/4ZOIHLXy11o/s1600/cataract1.jpg
Ionizing radiation is generally (but not exclusively) associated with cortical and posterior sub-capsular opacities.

Latency and severity dependent on:
- Age;
- Gender;
- Type of irradiation;
- Dose;
- Dose rate;
- Dose fractionation;
- LET…

Adapted from Beebe, 2008
Cataracts as a deterministic effect

**Merriam et al. 1950s:** Threshold ~ 1.3 Gy; *E. J. Hall, Radiobiology for the Radiologist, 1980s* – Cataracts are a deterministic, late, effect

**NRPB, 1996:** General advice document deterministic effects, included cataracts, based on previous work

**ICRP, 1990 (and 2007):** Thresholds for radiation induced cataracts: 2 Gy acute exposure; 4 Gy fractionated exposure; higher for chronic exposures
Ainsbury et al., 2016 (figure 2)
MEMORANDUM

Radiation-induced cataracts: the Health Protection Agency’s response to the ICRP statement on tissue reactions and recommendation on the dose limit for the eye lens

Simon Bouffler, Elizabeth Ainsbury, Phil Gilvin and John Harrison
Health Protection Agency Centre for Radiation, Chemical and Environmental Hazards, Chilton, Didcot, Oxon OX11 0RQ, UK

E-mail: Simon.Bouffler@HPA.org.uk
Summary - status of recent research

Mechanistic studies:
Lots of recent data has aided overall understanding, no definitive answer yet
Key point: Genetic component of cataract development - Subsection of the population genetically predisposed to cataract development?

Human (epidemiological) studies:
Strong evidence for link between radiation exposure at 1 Gy and development of various types, in various exposure situations (A-bomb survivors; Chernobyl; Clinical; Occupational; Commercial/space flight; Protracted exposures…)

Recent threshold reanalyses:
Threshold ~ 0 - 1 Gy
Research model

- IR
- UVB

Questions to be addressed experimentally

- <100 mGy IR exposure
- Stochastic vs deterministic (radiation protection)
- Acute vs. protracted exposure (dose rate)
- Identify markers of cataract initiation and progression (diagnosis/prognosis)
- Induction of impaired proliferation/differentiation by radiation exposure

Mechanistic targets

Identification of murine strains suitable for endpoints

Genetic/environmental conditions
- Diet
- Circadian rhythm
- Age/gender
- Epigenetic altered gene expression

Opacity monitoring
- Lens shape
- Standardized grading
- Epithelial cell density

In vivo (ex vivo) models

Ainsbury et al., 2016 (figure 3)
Exposed human cohorts
- Medical/occupational
- Accident survivors
- Head/neck RT patients
- Nuclear workers

Quality of dosimetry?

Accelerated aging
- Nuclear/cortical
- Latency period length

Monte Carlo modeling of dose deposition

Confounding factors
- Smoking
- Alcohol consumption
- Background IR exposure
- UV exposure
- Obesity
- Diabetes
- Hypertension
- Eye injury/inflammation
- Asthma
- Steroids
- COPD

Risk prediction

In vivo relevance

Ainsbury et al.,
2016 (figure 3)
Future work – remaining research Qs

**Mechanisms:** Biological and biochemical considerations for initiation and development of cataracts, especially at low doses
- What are the target cells (technological development needed)?
- What is the initiating event?
- How is latency determined (Hamada et al., 2014)?
- What is the effect of dose, LET, age, gender, genetics (Hamada et al., 2016)…
- Consideration of the lens as a bioindicator of global radiosensitivity (Worgul et al., 1996)
- Potential role of countermeasures (e.g. Lin et al., 2016)

**Epidemiology:**
- Development/implementation of a single classification scheme for cataracts
- Large scale reanalyses to be carried out to reduce statistical uncertainty
- Development of screening programs for occupational exposures
Cataracts as a deterministic effect?

**Phelps Brown, 1997:** Too little data? Especially at low doses – inaccurate dose estimation

**Smilenov et al., 2008:** Study timescales too short? Latent period, time from cataract initiation to manifestation, > years

**ICRP 2007:** Revised judgements needed? ‘*Lens of the eye may be more radiosensitive than previously thought*’
ICRP 2011 Statement/Publication 118:

- Absorbed dose threshold for induction of cataracts by ionising radiation now ~ 0.5 Gy

- Lens occupational exposure limit recommended to be reduced from 150 mSv y⁻¹ to 20 mSv y⁻¹, averaged over 5 years, with no 1 year > 50 mSv

- Rationale: weight of epidemiological evidence cataracts after v. low doses

http://www.icrp.org/images/P118.JPG
What happened next (UK perspective)?

SRP:
• Recommendations not justified
• Some published + anecdotal evidence that some UK workers will find compliance difficult…
• How best to measure lens dose?

ORAMED project:
• Categorical evidence (EU) that compliance will not be possible for some medical workers, e.g. interventional radiologists

EU Low Dose Research (e.g. MELODI):
• Radiation induced lens opacities are a priority non-cancer effect

For practical radiation protection:
• ICRP recommendations incorporated into new BSS…
II Non-legislative acts

DIRECTIVES

BSS – dose limits

“New scientific information on tissue reactions calls for the optimisation principle to be applied to equivalent doses as well, where appropriate, in order to keep doses as low as reasonably achievable. This Directive should also follow new ICRP guidance on the limit for equivalent dose for the lens of the eye in occupational exposure.”

Occupational exposures: “The limit on the equivalent dose for the lens of the eye shall be **20 mSv in a single year** or **100 mSv in any five consecutive years** subject to a maximum dose of **50 mSv in a single year**, as specified in national legislation.”

In addition, the lens dose limit for students and apprentices aged 16 – 18 and the general public: **15 mSv/year** (effective dose limit 6 mSv/year for students and 1 mSv/year for public)

UK Ionising Radiation Regulations


- Interpretation
- General principals and procedures (restriction, limitation, authorisation, notification, RP, training, risk assessment, PPE, contingency plans)
- Designated areas
- Classification and monitoring of persons
- Control of radioactive substances, articles and equipment
- Duties of employees
- Other (e.g. MOD modifications)
1999 No. 3232

HEALTH AND SAFETY

The Ionising Radiations Regulations 1999

Made - - - - - 3rd December 1999

Laid before Parliament 9th December 1999

Coming into force

All regulations except for regulation 5 - 1st January 2000

Regulation 5 - - - 13th May 2000
Basic Safety Standard – RP requirements

- Classified/category A workers: those with lens exposures > 15 mSv/year

- Specific arrangements need to be in place for all such workers including systematic monitoring based on individual measurements performed by a dosimetry service

- Where lens doses are likely to be ‘significant,’ specific lens based monitoring is indicated

- As previously, adequate justification for classification, recording and reporting of monitoring results and medical surveillance will be needed

***Member states have until February 2018 to comply with the BSS***
UK IRR vs BSS…

Overall responsibility: Department of Energy and Climate Change (DECC)

Next steps: Cross government group with input from Health and Safety Executive (HSE), based on ICRP and IAEA standards (http://www-ns.iaea.org/standards/review-of-the-bss.asp?s=11&l=88)

HSE: ‘Gap analysis’ between the current IRR 1999, REPPIR, and the BSS Directive requirements:

Who will be affected?

**Medical setting (published + anecdotal evidence):**
- Interventional medicine. UK: 166 radiology and cardiology centres, with ~600 interventional radiologists and 800 cardiologists;
- Also 35 PET centre sites
- Other nuclear medicine production/administration

**Nuclear setting:**
- Reactor vessel entry
- Fuel dismantling
- Industrial radiography

**Others?**
- E.g. MoD sites...
HSE gap analysis: key points

- Impact assessment for new lens occupational dose limit
- Small numbers of workers affected, but some work may be prohibited
- ‘Eye dose impact assessment’ (2012):
  - Immediate need for revised RA, PPE, training, RP advice
  - Ongoing need for health surveillance, dosimetry, monitoring and investigation, additional workers, ongoing training
  - Total one off costs (nuclear and medical sectors) ~ £8 million; 30 year costs ~ £24 million!

New regulations: Formal regulatory framework (revised IRR) still to be completed
Public Health England survey of eye lens doses in the UK medical sector

E A Ainsbury¹, S Bouffler¹, M Cocker², P Gilvin¹, E Holt³, S Peters¹, K Slack¹ and A Williamson⁴

- Small, targeted survey of UK lens doses to medical staff undertaking procedures involving the highest levels of ionising radiation

- 3 hospitals: Guy’s and St Thomas’ NHS Foundation Trust in Central London, the University Hospital of South Manchester Foundation Trust and the Oxford University Hospitals NHS Trust

- Full range of radiology services including computerised tomography (CT), fluoroscopy, mammography, MRI, nuclear medicine, ultrasound and X-ray; cardiologists and radiologists carrying out full range interventional procedures

- Active radiation protection departments
HSE lens dose survey - methods

- 68 PHE PDS lens dosemeters + headbands, instructions and questionnaires

- Participants asked to wear them for 4 full weeks in January 2013

- Questionnaire: questions about job title, procedures carried out during study period, PPE worn, whether dosemeter was worn according to instructions

- Dosemeters and questionnaires returned to PHE – data analysed and report produced by end February 2013
HSE lens dose survey - results

61 dosemeters returned:

- Median dose 0 mSv
- Only 13 > PDS minimum detectable dose of 0.15 mSv
- No correlation between type/No of procedures/PPE and dose…
- Maximum dose 1.60 mSv in 4 week period (2 individuals)*

* ~ just over 20 mSv in 1 year
HSE lens dose survey - conclusions

- Limited survey, but highest dose procedures in 3 busy radiology depts; > 1000 procedures over 4 week period
- Doses depend on a large number of factors and vary widely, however recorded doses similar or < other studies
- Total of 13/61 doses > 0; 2/61 doses >= 20 mSv y^{-1}
  - Without lead glasses
  - Assuming workload same, no holidays
- Excellent PPE use; only 9/58 participants used lead glasses
- DAP surrogate for operator dose?
But, in contrast:


- Interventional Radiologists at Edinburgh Royal Infirmary
- Eye-D dosemeters for 1 month monitoring period

**Results:** 1 scrub nurse and 2 consultants had average doses per procedure -> projected annual doses > 20 mSv
# REVIEW ARTICLE

Radiation protection of the eye lens in medical workers—basis and impact of the ICRP recommendations

1,2 STEPHEN GR BARNARD, BSc, 1 ELIZABETH A AINSBURY, PhD, 2 ROY A QUINLAN, PhD and 1 SIMON D BOUFFLER, PhD

## Table 1. Information from a selection of very recent studies of radiation dose specifically to the lens in medical scenarios

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Procedure</th>
<th>Average lens dose/ procedure</th>
<th>Min/max lens dose/ procedure</th>
<th>Dosemeter</th>
</tr>
</thead>
<tbody>
<tr>
<td>O'Connor et al</td>
<td>Ireland</td>
<td>ECRP</td>
<td></td>
<td></td>
<td>EYE-D™</td>
</tr>
<tr>
<td>Jacob et al</td>
<td>France</td>
<td>Various interventional cardiology</td>
<td></td>
<td>0.046/0.236 mSv</td>
<td>TLD</td>
</tr>
<tr>
<td>Vano et al</td>
<td>Spain</td>
<td>Catheterizations</td>
<td></td>
<td>0.044/0.067 mSv</td>
<td>APD</td>
</tr>
<tr>
<td>Al-Haj et al</td>
<td>Saudi Arabia</td>
<td>Cardiologists</td>
<td>0.02 mSv</td>
<td>0.005/0.08 mSv</td>
<td>TLD</td>
</tr>
<tr>
<td>Ainsbury et al</td>
<td>UK</td>
<td>Various radiologists</td>
<td>0.03–0.05 mSv</td>
<td></td>
<td>Eye lens</td>
</tr>
<tr>
<td>Romanova et al</td>
<td>Bulgaria</td>
<td>Fractura femoris</td>
<td>0.046 mSv</td>
<td>0.02/0.07 mSv</td>
<td>EDD30</td>
</tr>
<tr>
<td>Zagorska et al</td>
<td>Bulgaria</td>
<td>Fractura curvis</td>
<td>0.002 mSv (0.023 mSv with C-arm)</td>
<td>0.01/0.043 mSv</td>
<td>EDD30</td>
</tr>
<tr>
<td>Rathmann et al</td>
<td>Germany</td>
<td>Radiologists</td>
<td>0.018 mSv</td>
<td>0.012/0.029 mSv</td>
<td>TLD</td>
</tr>
<tr>
<td>Khoury et al</td>
<td>Brazil A</td>
<td>Hepatic chemoembolization</td>
<td>0.017 mSv</td>
<td>0.007/0.041 mSv</td>
<td>TLD</td>
</tr>
<tr>
<td></td>
<td>Brazil B</td>
<td>Hepatic chemoembolization</td>
<td>0.02 mSv</td>
<td>0.016/0.025 mSv</td>
<td>TLD</td>
</tr>
<tr>
<td></td>
<td>Brazil C</td>
<td>Hepatic chemoembolization</td>
<td>0.08 mSv</td>
<td>0.012/0.148 mSv</td>
<td>TLD</td>
</tr>
<tr>
<td>Cemusova et al</td>
<td>Czech Republic</td>
<td>Radiologists</td>
<td>0.013/0.070 mSv</td>
<td></td>
<td>EYE-D™</td>
</tr>
</tbody>
</table>

APD, active personal dosimeters; ECRP, endoscopic retrograde cholangiopancreatography; EDD, educational direct dosimeter; TLD, thermoluminescent dosimeter.
How to measure?

**Martin et al. 2011:**
- Collar measurements sufficient?
- Under or over lead apron?

-> Guidance including IAEA 1731 ‘flowcharts’

**ORAMED:**
- Hp(3) EYE-D™ dosimeter (Radcard)

**PHE PDS:**
- Thermoluminescent (TLD) dosimeters
  - Head band dosemeter (direct measurement of gamma, x and beta dose to lens)
  - Collar dosimeter (indicative measurement of gamma and x dose to lens)
### Technical Specification

<table>
<thead>
<tr>
<th>Material</th>
<th>$^7$LiF (Mg, Cu, P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change interval</td>
<td>Standard periods of 1, 2 or 3 months. Periods of 2, 4, 8 or 13 weeks also available.</td>
</tr>
</tbody>
</table>

#### Whole body TLD

- Radiation types: $\gamma$ (gamma) and X-radiations
- Dose range: 0.05 mSv to 10 Sv
- Energy range (photons): 16 keV to at least 662 keV
- Energy range (betas, $E_{max}$): NA
- Angle of incidence range: 0° to 60° from normal

#### Headband dosimeter

- $H_p(3)$ (body TLD on collar)
- $H_p(3)$ (headband)
How to protect?

- Cultural implications
- Practical implications
- Radiation protection:
  - Technological developments
  - Education and training

http://www.xrayleadaprons.com/images/products/Bubba.jpg

http://blog.universalmedicalinc.com/gallery/postimages/radiation-goggles.jpg
Take home messages

• ICRP recommendations based on weight of current scientific (epidemiological) evidence

• Although not lethal, cataracts can affect ability to work – surgery is not always effective in the long term (~5-10% complication rates)

• Recommendations incorporated into EU statutes; implementation by Feb 2018

• UK: Compliance should be possible (dosimetry and PPE)…

• More research needed in a number of areas, in particular mechanisms of cataract induction
Acknowledgements

Co-authors/collaborators:

  PHE colleagues, particularly S. Barnard, S. Bouffler, P. Gilvin, R. Tanner, S. Peters, K. Slack, J. Gillan, M. Coster, M. Ellender…


Health and Safety Executive
Department of Health, Public Health England
National Institutes for Health Research
Society for Radiation Protection
EU FP7 DoReMi project
NCRP SC1-23 Colleagues
Radiation Protection Week:

https://www.phe-protectionservices.org.uk/rpw/
Unique Biology of Lens

- Unlike the rest of the eye, the lens is derived from surface ectoderm (eye is derived from neural ectoderm).
- 90% of the proteins are water-soluble crystallins, they appear to have evolved from chaperone proteins.
- In mature lens fibers there are no light-scattering organelles such as nucleus, ER, or mitochondria. They have an extensive cytoskeleton.
- Glucose is the major nutrient for the lens; in the absence of mitochondria glucose is metabolized by anaerobic metabolism.
- Lens has lower energy demands than many other cells in the body.
The relationship of the lens and zonules to the other structures in the adult eye

from Adler’s Physiology of the Eye, 11th edition 2011
The early stages of lens formation. (A) The lens vesicle contacts the surface ectoderm. (B) The optic vesicle adheres to the surface ectoderm and the prospective lens cells elongate to form the lens placode. (C) The lens placode and the outer surface of the optic vesicle invaginate to form the lens pit and the optic cup, respectively. (D) The lens vesicle separates from the surface ectoderm. (E) The primary lens fibers elongate and begin to occlude the lumen of the vesicle. The posterior of the lens vesicle separates from the inner surface of the optic cup. Capillaries from the hyaloid artery invade the primary vitreous body. (F) The configuration of the lens as it begins to grow. Secondary fiber cells have not yet developed and organelles are still present in all fiber cells.

The expanded regions show the relationships between the elongating lens fiber cells and the posterior capsule as the basal ends of the fibers reach the posterior sutures and the changes in cell shape and orientation that occur as lens epithelial cells differentiate into lens fibers at the lens equator.

from Adler’s Physiology of the Eye, 11th edition 2011
The arrangement of lens fibers

Scanning electron micrograph showing the orderly arrangement of hexagonal lens fibers in the vertebrate lens. (Courtesy Dr. J. Kuszak.)

from Adler's Physiology of the Eye, 11th edition 2011
Mutations in genes that are expressed at high levels in the lens often underlie congenital cataracts

“Lens fiber cells accumulate high concentrations of lens-preferred crystallin proteins. Their plasma membranes also have large amounts of protein that form lens-specific gap junctions, water channels or cell–cell adhesions. Mutations in the genes encoding these abundant proteins are responsible for many of the hereditary congenital cataracts that have been identified over the past decade. Most mutations that cause hereditary congenital or juvenile cataracts show a dominant mode of inheritance. Experimental studies in animal models and study of the mutant proteins in cultured cells suggest that the defective proteins encoded by these genes cause cataracts by interfering with the normal function of lens fiber cells or by promoting their own aggregation and, perhaps, the aggregation of normal lens proteins. Therefore, these cataracts are not caused by loss of the normal function of the mutant proteins, but by the acquisition of an abnormal function. This conclusion is supported by studies in experimental animals in which complete removal of one copy of these genes has no effect on lens transparency. Interestingly, mutations in crystallin genes are sometimes associated with microcornea. Since most of these genes have not been detected in the cornea, it appears that defects that originate in the lens lead to alterations in the size of the cornea.”

(Adler’s Physiology of the Eye, 11th edition 2011)
Age-related cataract. (A) Posterior subcapsular; (B) posterior subcapsular on retroillumination, showing Wedl cells; (C) minimal and (D) moderate nuclear sclerosis. (from Clinical ophthalmology a systematic approach; 7th edition Jack J. Kanski, Brad Bowling; with contributions from Ken Nischal, Andrew Pearson.)
“Traumatic cataract” – posterior cataract caused by ionizing radiation

Tumors of the Lens: Not in Humans

- Examined 18,000 case studies from humans at Univ Wisconsin and Armed Forces Institute from 1975-2014: not one case of lens tumors in humans
- Veterinary studies: cats, 1 dog, rabbits, birds all were found to have a low incidence of lens tumors. Many had a history of ocular trauma.
- Some cases were induced in zebrafish, rainbow trout, hamsters and mice with carcinogenic agents (thioacetamide, methylcholanthrene, SV40, HPV-16)

Question: Stochastic or Deterministic?

- Is radiation-induced cataract formation a stochastic or deterministic (tissue) effect?

  Consider: All events are stochastic at the single cell level including cell death; deterministic effects can only be observed at the tissue level and hence are often called tissue effects. The concept is that when enough cells die then the effect is observed. Deterministic effects can have a threshold, but stochastic effects do not.

- If cataracts are deterministic, what is the threshold? If not, how can we regulate against cataracts?
Question: What is target of radiation damage?

- If lens cells have no DNA, what is the target for radiation-induced damage?

Consider: In most cells that are destroyed by radiation, the killing occurs by damaging the nuclear DNA. Lens cells have no organelles (including a nucleus) because it would interfere with the clarity of vision. How then do lens cells die following radiation exposure, if they do not have DNA to be damaged?

- Is the threshold for radiation damage to lens cells different than other cells because they have no DNA? Is protein damage (crystallins, for example) a major consequence of radiation exposure?
The connections between lens fiber cells

Visualization of the ball-and-socket interdigitations at the lateral surfaces of lens fiber cells. The tissue was fractured to show the surface morphology of the cells and viewed with a scanning electron microscope. (Courtesy Dr. J. Kuszak.)

from Adler’s Physiology of the Eye, 11th edition 2011
“The gap junctions of the lens are assembled from a unique set of subunits, or connexins. The cell-to-cell transport of small molecules (< 1 kDa) mediated by these gap junctions is likely to be important for the function of the lens, since most of the fiber cells are far from the nutrients supplied by the aqueous and vitreous humors. ...lens fiber cells have the highest concentration of gap junction plaques of any cells in the body.”
“The oxygen tension around the lens in the living eye is quite low, <15 mmHg (~2% O₂) just anterior to the lens and <9 mmHg (~1.3% O₂) near its posterior surface. Oxygen levels within the human lens are even lower (<2 mmHg). The low oxygen tension around and within the lens helps to protect lens proteins and lipids from oxidative damage. Even with this low level of oxygen, the lens normally derives a proportion of its ATP from oxidative phosphorylation, a process that, of necessity, generates free radicals.”
Diagrammatic representation of the distribution of reduced glutathione (GSH) and oxidized glutathione disulfide (GSSG) in the adult human lens. Deeper lens cells synthesize little glutathione – it arrives from superficial fibers. At the same time an increased fraction of “spent” glutathione (GSSG is the oxidized form) must diffuse from the center of the lens to the superficial layers for regeneration. This situation is often increased in the aging lens.

(Adler’s Physiology of the Eye, 11th edition 2011)
Diagram illustrating the role of the gel vitreous body and ascorbate in the vitreous fluid play in protecting the lens from excessive exposure to oxygen from the retinal vasculature. The gel state of the vitreous body prevents stirring of the contents of the vitreous chamber, allowing the uptake of oxygen by adjacent retinal cells. Increased mixing of the vitreous fluids after vitreous degeneration or vitrectomy increases exposure of the fluids to oxygen, which increases the degradation of ascorbate, allowing more oxygen to reach the lens. The chemical reactions summarized in the figure show the initial reactants (ascorbate and oxygen) and the end products (dehydroascorbate and water). Hydrogen peroxide is an intermediate product in this reaction, which is degraded to water and oxygen by the enzyme, catalase. If not taken up by cells, dehydroascorbate is rapidly hydrolyzed to yield several additional degradation products. (Adler’s Physiology of the Eye, 11th edition 2011)
Question: High LET?

- What is the basis for the extreme effect of high LET radiation on cataract induction?
  Consider: The RBE of neutrons at low doses is 50, at high doses is near 10. Why is this RBE at low doses so high? This would not be predicted based on standard radiobiological responses. This may not be relevant to the average worker, but much of the background in the US comes from alpha-particle exposures and for astronauts most of the exposures are high LET.

- This represents a major gap in understanding that probably relates to a lack of understanding of mechanisms of cataract induction.
Question: Low dose vs. high dose?

• Are radiation effects on the lens cells different after low dose exposure than after high dose exposure? Consider: There are many unique low dose responses that have been identified in non-lens cells—bystander effects, adaptive responses, induced repair, genomic instability, etc. These cells all have nuclei (DNA). Are there any unique responses that occur in the lens at low doses of radiation?

• Most high dose responses lead to cell death, while low dose responses may have other consequences that may be unique in lens cells because of their lack of organelles. This may impact the radiobiology of the lens.
Question: Dose Rate Effects?

• Dose-rate effects are in place for the lens cells, but what is the mechanism of these effects?
Consider: Most lens cells have no DNA and at least some mechanisms of improved survival following low dose rate exposure appears due to DNA repair; in the absence of DNA repair, other cellular recovery mechanisms must be in place. What are these mechanisms and pathways?
• Cataract induction decreases as the exposure is protracted, just as occurs in most normal tissues; nevertheless, unique aspects of the biology of the lens cells may help to identify mechanisms that are important in cellular recovery that are poorly understood.
Question: Males and Females?

- What is the difference between males and females in cataract induction?

Consider: There is some evidence in the literature that male rodents may be more susceptible to radiation-induced cataract formation than females, with steroid hormones being an important modulating factor. This sex difference is poorly defined in humans and again could relate significantly to mechanisms.

- Is this difference in rodents also apparent in humans? Astronaut data are too limited to conclude anything, but medical exposures could be helpful here.
Recent Data

- Some epidemiological work with interventional cardiology and radiology in mind
- Some re-evaluation of Japanese Atomic Bomb populations
- Radiobiology in PubMed: 1996-2016 total of 18 papers on ionizing radiation-induced cataracts and basic biology, mostly done by one group of investigators
- Yet…..radiation-induced cataracts are a true marker of radiation effects because they are PSC in origin, they occur with high frequency, and understanding basic mechanisms shed light on cataractogenesis in general.
Technology Changes Continuously

• Genomics: full sequences of genomes available
• Improved bioinformatics and computational methods
• New animal models
• Single cell methodologies, approaches to single gene knock-outs in many species
• Statistical methods to analyze subtle changes
• Stem cells, embryo/developmental studies possible
• New OMICS: metabolomics, elementalomics, transcriptomics, etc.
New Directions in Science as a Whole Lead to New Biology

Computing powers increased more than exponentially – completely new field(s) :

• ability to use large datasets
• new science: informatics
• renewal of statistics – e.g. use of machine learning
  ➔ new molecular biology, new cancer biology

Materials science – completely new fields :

• bionanotechnology
• microfluidics
  ➔ new cell biology, new cancer biology
OMICS = genomics

“Human genome project” ongoing – declared finished in 2003 with several human sequences (“averaged” for a given human being), NIH and DOE funded effort that lasted 13 years

2016

Many different OMICS = complete biological information on categories of molecules and their modifications:

- genomics (now thousands of human genomes, adjectives “functional genomics,” “personal genomics” are not empty)
- epigenomics
- transcriptomics
- proteomics
- metalomics
- Lipidomics
- metabolomics
- connectomics
Example: Use of X-ray Fluorescence to Study Elementalomics of Archival Tissues

**X-ray fluorescence Imaging at the APS synchrotron: Study of archival tissues from historic DOE and SUBI tissue archives**

ANL: Prostate hyperplasia in beagle dog ID 2752 [Dose rate 3.8 cGy/day (22 hrs/7 days), from 412 days until total dose 15 Gy. Death at 14+ years (5245 days).]

SUBI: Tritium in drinking water study. Mouse spleen showing normal overall and elemental morphology.

Studies of multi-cell/tissue/organ averages:

- Very few techniques allow collection and investigation of few hundreds of cells of a given type (e.g. laser capture micro-dissection)
- Material harvested from “captured” cells was “bulk proteins or bulk messenger RNAs (molecules encoding proteins)

Studies of single cells:

- Techniques to collect single cells based on cell behavior
- Single cell analysis can be done on every type of nucleic acid: DNA (complete genome sequence, methylation pattern) or RNA (every category messenger RNA, micro RNA, long noncoding RNA, piwi RNA circular RNA) can be fully investigated
Cancer Biology

1996

Old research tools
• 2D cell cultures or spheroids
• few animal models
• charting the “cancer roadmap” with a dozen stops

Old treatment and diagnostic tools going directly and only at cancer cells

2016

New research tools
• Stem cells are isolated and generated; organoids; 3D (and 3D printing
• abundance of animal models: PDX mice, CRISPR transgenic cells and animals, ...
• cancer roadmap includes whole organism as a milieu

New anti-cancer treatments capitalize on “holistic” approach, e.g.
modulation of immune system behavior (triggered by ionizing radiation)
Imaging of Cells, Tissues, Organisms

1996

Light microscopy (200nm max resolution)

X-ray diffraction for protein crystallography

Scanning and transmission electron microscopy

2016

New approaches to light microscopy – super-resolution (to 20nm), Raman spectroscopy...

X-ray microscopy – resolution from mm to nm on same sample at the same synchrotron; development of elementalomics

X-ray microscopy coupled to diffraction (coherent diffraction imaging, ptychography...
Cancer Biology: Cell Death

1996

Known mechanisms of cell death included
1) Necrosis
2) Apoptosis (programmed cell death)

Cancer induction and survival requires that a progenitor cancer cell avoids cell death

2016

New mechanisms of controlled cell death discovered:
3) Autophagy
4) Paraptosis
5) Pyroptosis
6) Necroptosis

New cancer protection and/or treatment agents can be investigated by their capacity to induce cell death in cells injured by radiation
New Ways of Reporting, Evaluating and Communicating Scientific Data

1996
Internet used to exchange finalized information

2016
Internet used as a data and technique repository and a hub for (informatics) research
Open access journals change speed of publishing
Virtual centers and international collaborations
New Knowledge Leads to New Understanding of Biology

- Concepts never before considered became “standard”
  - discoveries of new molecules and new means for “intracellular” control – subtle changes are detectable and understood as events occur in unison
  - discovery of qualitatively new types of cell to cell communication as means for “intercellular” control – subtle changes ripple through the whole organism (e.g., exosomes)
Key Biological Molecules 1996

DNA
- DNA modifications: histones, methylation...

*tRNA
* rRNA
* mRNA
- RNA modulation by degradation...

*proteins
- Protein modifications: ubiquitination, phosphorylation...

* "Full" information accessible (often through heroic efforts and only from POOLED cells)
Key Biological Molecules 2016

* DNA
  * DNA modifications: histones (acetlylation etc.), methylation...

* tRNA
* rRNA
* mRNA
  * RNA modulation by degradation... in dozens of ways

* proteins
  * protein modifications: ubiquitination, phosphorylation, SUMOylation, NEDylation, acetylation,...

* full information accessible and often from individual cells

* micro RNA
* long noncoding RNA
* circular RNA

RNA modulation by degradation... in dozens of ways
Radiation-induced Cataract Studies

- Almost non-existent now: NASA was a leader at one time, DOE had some studies
- Important questions remain and can be addressed with new biology that was not available 20y ago when most cataract-related radiation biology was eliminated.
- PSC cataracts are one of the few markers of radiation exposure and should represent a good model system.
- Some ongoing work in EU, Japan, China, Korea, others
Conclusions

• There have been few radiobiology studies of the lens that have been done in the past 20 years.
• Technology has changed drastically during this time; the initiation of new studies at this time could benefit from this technology revolution.
• Radiation-induced cataracts are risks of occupational and therapeutic exposures and affect a significant population of people. While effects might not be life-threatening, morbidity is significant.
• Understanding mechanisms will help us understand basic questions in radiobiology that will have a broader consequence.